The Impact of Optic Nerve Disorders on Sleep Wake

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Abstract

Background

Sleep is mediated by photic input from photosensitive retinal ganglion cells via the optic nerves which form part of the retinohypothalamic tract to the suprachiasmatic nuclei, which act as an endogenous circadian pacemaker. Previous studies have shown increased circadian dysfunction in ocular disorders and blindness; however, no large-scale studies demonstrating the impact of optic nerve disorders (OND) on sleep have been performed.

Hypothesis

It was hypothesised that individuals with OND would have poorer sleep quality and timing than individuals with normal visual function.

Aims

The aim of this research was to investigate the nature of the relationship between OND and sleep quality and timing.

Methods

A general literature review of the physiology of normal and abnormal human sleep and OND was undertaken. A systematic review of published research specific to sleep in OND was also carried out.

An observational study of sleep quality and timing in OND based on the SOMNUS study was conducted. In the prospective component of this study, participants were recruited from ophthalmology clinics and completed standardised questionnaires including the Pittsburgh Sleep Quality Index (PSQI); the Epworth Sleepiness Scale (ESS); The Morningness-Eveningness Questionnaire (MEQ) to evaluate chronotype; the SF-36 Questionnaire to evaluate quality of life (QOL); and the Hospital Anxiety and Depression Scale (HADS) to assess mood. A pool of normally sighted control subjects was also recruited. In the retrospective component, data from patients with autoimmune and demyelinating optic neuropathies was descriptively analysed.

Summary of Findings

In the prospective study, 122 participants with OND were compared to 302 control participants. Poor sleep was present in 65.6% of individuals with OND and in 39.7% of controls ($p<0.0001$). Sleep timing was worse in OND ($p=0.02$). Daytime sleepiness (ESS), chronotype and anxiety were comparable between groups, but HADS depression score was worse in OND ($p=0.04$). QOL scores for all parameters except for emotional wellbeing were worse in OND ($p<0.05$). Data were retrospectively analysed from 34 participants with neuromyelitis optica spectrum disorder, which revealed prevalence of poor sleep in the presence of depression, sphincter dysfunction, pain, psychiatric medication and glucocorticoid use.

Conclusions

In the prospective component of this study, participants with OND had poorer sleep quality and timing than those with normal visual function. In the retrospective component, subjects with autoimmune and demyelinating OND had systemic associations which may contribute to poor sleep. This supports the consideration of sleep quality and timing in the holistic management of patients with OND.

Declarations and Statements

Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed……  ……(candidate)

Date……27.09.2023……

Statement 1

This thesis is the result of my own investigation, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in footnotes.

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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Statement 2

I hereby give consent for my thesis to be available for photocopying and for inter-library loans and for the title and summary to be made available to outside organisations.

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Date……27.09.2023……

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Presentations

I presented findings from my thesis at the following meetings:

1. Association for Research in Vision and Ophthalmology and Ophthalmology Annual Meeting May 2018 (Poster): The Impact of Optic Nerve Disorders on Sleep Wake(1)

2. European Paediatric Ophthalmological Society Meeting August-September 2017 (Poster): The Impact of Optic Nerve Disorders on Sleep Wake(2)

3. Royal College of Ophthalmologists Annual Congress May 2017 (Poster): The Impact of Optic Nerve Disorders on Sleep Wake

4. Royal Society of Medicine Ophthalmology Section Trainee Meeting June 2018 (Poster): The Impact of Optic Nerve Disorders on Sleep Wake

5. South West Ophthalmological Society Meeting November 2019 (Oral Presentation): The Impact of Optic Nerve Disorders on Sleep Wake

List of Tables and Illustrations

Definitions of Abbreviations

AAION Arteritic anterior ischemic optic neuropathy

ACE Angiotensin converting enzyme

ACTH Adrenocorticotrophic hormone

AD Alzheimer disease

ADEM Acute disseminated encephalomyelitis

ADH Antidiuretic hormone

ADHD Attention-deficit hyperactivity disorder

AHI Apnoea/Hypopnoea index

AION Anterior ischaemic optic neuropathy

AIS Athens Insomnia Scale

ALDH Aldehyde dehydrogenase

A-POAG Advanced primary open angle glaucoma

APSD Advanced phase sleep disorder

AS Asperger syndrome

ASD Autism spectrum disorder

ATP Adenosine Triphosphate

BBB Blood-brain barrier

BCVA Best corrected visual acuity

BDI Beck Depression Inventory

BDI-II Beck Depression Inventory-II

BLT Bright light therapy

BMD Humphrey visual field mean deviation of the better eye

BMI Body mass index

BVA Best visual acuity of the better eye

BPD Bipolar disorder

BVF Visual field of the better eye

CBD Cannabidiol

CBT Core body temperature

CF Counting fingers

CFS Chronic fatigue syndrome

CHRRPE Combined hamartoma of the retina and retinal pigment epithelium

CI Confidence interval

CIS Clinically isolated syndrome

CNS Central nervous system

CP Craniopharyngioma

CRION Chronic relapsing inflammatory optic neuropathy

CRN Clinical Research Network

CSF Cerebrospinal fluid

csv Comma separated values

CT Computed tomography

CVI Certification of visual impairment

DCC Deleted in colorectal cancer, a netrin receptor

DI Diabetes insipidus

DLMO Dim light melatonin onset

DOA Dominant optic atrophy

DPSD Delayed phase sleep disorder

EBM Evidence-based medicine

ECG Electrocardiogram

EEG Electroencephalogram

EMG Electromyogram

ENT1 Equilibrative nucleoside transporter type 1

EOG Electrooculogram

EPR Electronic patient record

ERG Electroretinogram

ERGO Eye Research Group Oxford

ESS Epworth Sleepiness Scale

ETDRS Early Treatment Diabetic Retinopathy Study

FOSQ Functional Outcomes of Sleep Questionnaire

FR Free-running

FRD Free-running disorder

FQ Fatigue Questionnaire

GABA Gamma aminobutyric acid

GAD Generalised anxiety disorder

GCA Giant cell arteritis

GCL Ganglion cell layer

GH Growth hormone

GHQ General health questionnaire

GSII Glasgow Sleep Impact Index

GTP Guanosine triphosphate

GVF Goldmann visual field

HADS Hospital Anxiety and Depression Scale

HADS-A Hospital Anxiety and Depression Scale Anxiety Component

HADS-D Hospital Anxiety and Depression Scale Depression Component

HLA Human leukocytic antigen

HM Hand movements

HON Hereditary optic neuropathy

HPA-axis Hypothalamo-pituitary-adrenal axis

HRQOL Health-related quality of life

HVF Humphrey visual field

ICP Intracranial pressure

IFN-γ Gamma interferon

IIH Idiopathic intracranial hypertension

IOP Intraocular pressure

IOVS Investigative Ophthalmology and Vision Science (Journal)

IPL Inner plexiform layer

IVI Impact of Vision Impairment

JLD Jet lag disorder

LGN Lateral geniculate nucleus

LHON Leber hereditary optic neuropathy

MA Methamphetamine

MAOI Monoamine oxidase inhibitor

MAR Missing at random

MCTQ Munich ChronoType Questionnaire

MDD Major depressive disorder

MEN Multiple endocrine neoplasia

MEQ Morningness Eveningness Questionnaire

MeSH Medical Subject Headings

mfERG Multifocal electroretinogram

mfVEP Multifocal visual evoked potential

MNAR Missing not at random

MNST Melatonin suppression test

MON Monosymptomatic optic neuritis

MPFC Medial prefrontal cortex

MRI Magnetic resonance imaging

MS Multiple sclerosis

MSLT Multiple sleep latency test

mTBI Mild traumatic brain injury

MWT Maintenance of Wakefulness Test

nAChR Nicotinic acetylcholine receptor

NAION Non-arteritic anterior ischaemic optic neuropathy

NEI-VFQ-25 National Eye Institute 25-Item Visual Function Questionnaire

NEI-VFQ-25-NOS National Eye Institute 25-Item Visual Function Questionnaire 10-Item Neuro-Ophthalmic Supplement

Neuro-QOL Quality of Life in Neurological Disorders

NFMA Non-functioning pituitary macroadenoma

NMDA N-methyl D-aspartic acid

NMOSD Neuromyelitis optica spectrum disorder

NPL No perception of light

NOS Neuro-ophthalmic supplement

NREM Non rapid eye movement

NRM Nucleus raphe magnus

NSAID Non-steroidal anti-inflammatory drug

OA Optic atrophy

OCC Optic chiasm compression

OCD Obsessive compulsive disorder

OCT Optical coherence tomography

ODD Optic disc drusen

ON Optic neuritis

OND Optic nerve disorder

ONG Optic nerve glioma

ONH Optic nerve hypoplasia

ONSM Optic nerve sheath meningioma

OPN Olivary pretectal nucleus

OSA Obstructive sleep apnoea

PA Pituitary adenoma

PACG Primary angle closure glaucoma

PAG Periaqueductal grey matter

PD Parkinson disease

PERG Pattern electroretinogram

PFC Prefrontal cortex

PHQ Patient Health Questionnaire

PL Perception of light

PLM Periodic limb movement

PLR Pupillary light reflex

PNS Peripheral nervous system

POAG Primary open angle glaucoma

PPMS Primary progressive multiple sclerosis

pRGC Photosensitive retinal ganglion cell

PROM Patient-reported outcome measure

PSG Polysomnography

PSPS Post-stimulation pupil size

PSQI Pittsburgh Sleep Quality Index

PTSD Posttraumatic stress disorder

RAPD Relative afferent pupillary defect

RBD Rapid eye movement (REM) sleep behaviour disorder

REM Rapid eye movement

REML REM latency

RGC Retinal ganglion cells

RHT Retinohypothalamic tract

RLS Restless leg syndrome

RNFL Retinal nerve fibre layer

ROP Retinopathy of prematurity

RRMS Relapsing-remitting multiple sclerosis

SAD Seasonal affective disorder

SC Synthetic cannabinoid

SCN Suprachiasmatic nuclei

SCRD Sleep and circadian rhythm disorder

SDQ Sleep disorders questionnaire

SE Sleep efficiency

SF-36 The Medical Outcome Study 36-Item Short Form Health Survey

SI Sight impairment

SJL Social jetlag

SL Sleep latency

SMON Subacute myelo-optic neuropathy

SNP Single nucleotide polymorphism

SNRI Serotonin-noradrenaline reuptake inhibitor

SOD Septo-optic dysplasia

SPMS Secondary progressive multiple sclerosis

S-POAG Stable primary open angle glaucoma

SRQOL Sleep-related quality of life

SSI Severe sight impairment

SSRI Selective serotonin reuptake inhibitor

STAI State-Trait Anxiety Inventory

SWA Slow wave activity

SWS Slow wave sleep

T1DM Type 1 diabetes mellitus

TBI Traumatic brain injury

TCA Tricyclic antidepressant

THC Delta-9-tetrahydrocannabinol

TM Trabecular meshwork

TON Traumatic optic neuropathy

TSH Thyroid stimulating hormone

TST Total sleep time

VA Visual acuity

VEGF Vascular endothelial growth factor

VEP Visual evoked potential

VF Visual field

VFD Visual field defect

VI Visual impairment

VLPO Ventrolateral preoptic area

VRQOL Vision-related quality of life

WASO Wake after sleep onset

WS Wolfram syndrome

Chapter 1: Introduction

"You lack the season of all natures, sleep(3)."

So said Lady Macbeth to a sleepless and tormented Macbeth whose mental and physical health was growing worse(4). Most humans spend approximately one third of their lives asleep, and it provides a state that is essential for our physiological and psychological health and wellbeing. A lack of sleep can be detrimental to our physical and mental health, and published literature has shown that it is associated with an increased risk of cardiovascular and metabolic disease(5). Psychologically, poor sleep leads to increased depression, anxiety, and reduced concentration, resulting in an increased likelihood of accidental injury at home and at work, when driving vehicles and when operating machinery(6).

In ancient mythology, the Greek Hypnos, and his Roman counterpart Somnus are personifications of sleep. Hypnos lived in a cave at the meeting of night and day. The onset of dark typically coincides with sleep timing in humans, and this tends to occur at a predictable time, with waking also taking place at a regular expected time corresponding to light onset and the beginning of a new day.

The eye is known as "the light of the body"(7). In Ancient Egypt, the Eye of Horus was a representation of the most illuminated bodies in the skies: the sun and moon(8). In mammals, sleep is regulated by entrainment of the body's internal circadian pacemaker, the suprachiasmatic nuclei (SCN), which are located in the hypothalamus of the brain, by light(9). Photic input to the eyes is detected by photosensitive retinal ganglion cells (pRGCs) in the retina and relayed via the retinohypothalamic tract (RHT) to the SCN, which lies just superiorly to the optic chiasm(10). The optic nerves form part of this pathway. The hormone melatonin is a prime mediator of sleep and is produced by ocular structures and the pineal gland in the brain in low-light conditions(11, 12).

Circadian rhythms can be normally entrained to 24 hours, in which an individual's peak activity and low melatonin levels are concurrent with daylight hours. Some individuals, however can be abnormally entrained to a 24-hour cycle, exhibiting either an advanced phase, in which an individual has a tendency towards onset of daily activities and low melatonin levels beginning before daylight hours, and ending prior to the onset of darkness; or delayed phase, in which

there is a propensity for increased activity levels and onset of low melatonin several hours later than light onset, with increased melatonin levels and decreased activity levels several hours after the onset of darkness. A free-running (FR) circadian rhythm, or free-running disorder (FRD), is one in which the intrinsic circadian rhythm is no longer entrained to the 24-hour schedule. This occurs when there is loss of photic entrainment of the SCN, so that circadian regulation is largely internalised. In this instance, there is often a tendency for the internal body clock to operate at a period of longer than 24 hours, so that over a number of days, the internal pacemaker can become increasingly out of synchronisation with the light and dark cycle. Eventually, the internal circadian phase will continue to advance so that the circadian phase and day and night re-align, and this oscillatory cycle will then repeat itself. In some individuals with disordered sleep wake there is no discernible circadian period at all(13).

Published literature to date indicates that individuals with visual impairment (VI) are more likely to experience poor quality sleep in comparison to normally sighted people(14-16). However, there are few studies to date solely examining circadian dysfunction in relation to optic nerve disorders (OND), an essential component of the wiring of the circadian pathway circuitry in mammals.

Other contributors to sleep include anxiety and depression, particularly in cases of new or sudden onset profound visual loss, with associated loss of independence, reduction in social interaction, altered relationships, and impact on employment and career prospects. Loss of the ability to drive has been found to be particularly frustrating, as has increased dependence on friends and family and restriction of lifestyle choices preceding onset of visual loss(17-19). New-onset visual loss, in the setting of chronic disease has been found to have a measurable negative impact on vision-related quality of life (VRQOL)(20), and a new diagnosis of a chronic disease in itself, such as multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) can also contribute to additional anxiety and depression(21, 22). With increased time since diagnosis and increased disability, depression may predominate, although anxiety may still be prevalent(21, 22).

Age at onset of visual loss may determine psychological comorbidity and quality of life. Acquired and new-onset visual loss in adolescence and young adulthood may have a greater negative impact on self-esteem than in congenitally blind individuals, or in childhood onset, where adaptations and coping strategies have been consolidated(23), although in chronic

conditions leading to VI in childhood and early adulthood, such as in NMOSD, the psychological impact can be profound(24). Middle-aged adults can be negatively affected with new-onset visual loss, the burden encompassing social interaction, career prospects and psychological wellbeing(25). Low vision has been associated with worse self-esteem than blindness in young adults(26), although new-onset chronic disease in children has been found to have a marked impact on quality of life, anxiety and depression(27). In the elderly, depression has been found to correlate with visual loss, in conjunction with poorer quality of life (QOL)(28, 29). Some OND can present with sudden onset profound visual loss in otherwise healthy individuals, which is often the case in Leber hereditary optic neuropathy (LHON), which can cause marked psychological morbidity. Diagnostic uncertainty and the shock at receiving a new clinical diagnosis may contribute to anxiety and depression(30).

Sleep quality can depend on environmental setting, with sleep at home reported to be of better quality and duration than in a hospital, with multiple occupancy rooms, light, temperature and clinical interventions contributing to sleep disturbance(31, 32). Poor sleep quality has been found to correspond to poor immune function and increased length of hospital stay which in turn prolongs of sleep impairment(33).

1.1 Problem Statement

The consequences of poor sleep are manifold and impact the social, psychological and physical functioning of an individual. This may be heightened in individuals with visual impairment, as visual impairment itself has been shown to have a negative impact on these functions(34-36). It is important and relevant for clinicians and the public to have an awareness of potential sleep disruption in the visually impaired population. In this study, I investigated sleep quality and timing in individuals with visual impairment, specifically OND.

Due to the functional relevance of the SCN in circadian regulation of sleep and wake, and the fact that it receives input almost wholly from pRGCs via the optic nerves which forms the retinohypothalamic tract (RHT)(37), I have confined my study to disorders of the optic nerves (from the optic disc to the optic chiasm). Components of the visual pathways which lie posterior to the optic chiasm comprise the optic tracts, lateral geniculate nuclei (LGN), optic

radiations and visual cortices which are not primarily involved in circadian regulation and are beyond the scope of this study(37, 38).

1.2 Hypothesis

I hypothesised that individuals with damage to the optic nerves have poorer sleep quality and timing than individuals who have normal visual function and intact optic nerves.

1.3 Aims and Objectives

The aim of my research was to investigate the nature of the relationship between OND and sleep quality and timing.

My specific objectives were to:

1) Review published literature evaluating the relationship between OND and sleep quality and timing

2) Collect subjective sleep quality and timing, general health, QOL and mood data from individuals with OND (with details of ocular history, time since diagnosis and visual function) and from a normally sighted control group

3) Statistically analyse data collected from individuals with OND and controls to determine whether OND and other health and lifestyle factors have an impact on sleep quality and timing

4) Discuss the relevance of my findings to practice and policy with regard to holistic management of patients with OND, taking into consideration their general health, QOL, lifestyle and mood.

1.4 Materials and Methods

1.4.1 Study Design

1.4.1(a) General Literature Review

To couch this study, I undertook a general literature review of the structure and physiology of normal sleep, and the pathophysiology of sleep disorders. I also reviewed OND using the categories of congenital, autoimmune and inflammatory, demyelinating, those resulting from increased intracranial pressure, compressive, vascular, traumatic, toxic and glaucomatous. I discussed exogenous and endogenous influences on sleep wake, and how sleep wake is measured subjectively and objectively.

1.4.1(b) Systematic Literature Review

I conducted a systematic literature review of published research evaluating the subjective sleep wake in the context of OND. Glaucomatous pathologies, a prevalent form of optic neuropathy were included for context, although participants with glaucoma were not included my observational study, as they were recruited to a separate arm of the SOMNUS study.

1.4.1(c) Observational Study

My study is primary research, and can be classified as an epidemiological observational cross-sectional study(39). This design enabled me to appraise the prevalence of sleep disturbances in participants with OND in comparison to control participants as a snapshot in time, and also allowed me to measure multiple outcomes from questionnaire data, as described below(40).

All data in my observational study were anonymised for analysis and formal written consent was obtained from participants in accordance with Good Clinical Practice (GCP)(41). The study was conducted in accordance with the tenets of the Declaration of Helsinki(42). Participants were free to withdraw their consent at any time, with subsequent removal of their data from the study.

1.4.1(c)(i) Prospective Component

I prospectively collected subjective data to assess multiple aspects of sleep and general and psychological health in individuals with OND recruited from ophthalmology clinics across five sites. Participants with normal vision across seven sites were also recruited to form a control group. I gathered this data using a compilation of seven questionnaires. These included:

- The Pittsburgh Sleep Quality Index (PSQI), in which a score >5 indicates poor sleep, and PSQI>10 being a consensus for severe sleep disorder(43, 44);
- The Jupiter Medical Centre Questionnaire (JMCQ), which assesses the presence of other forms of sleep disturbance including Restless Leg Syndrome (RLS) and Obstructive Sleep Apnoea (OSA)(45)
- A General Health Questionnaire (GHQ), adapted from the Patient Health Questionnaire (PHQ) to collect demographic, socioeconomic and general health information including past medical history, drug history and psychiatric history(46);
- The Short-Form 36 Questionnaire (SF-36), to assess QOL, mood, physical, emotional and social functioning(47);
- The Morningness-Eveningness Questionnaire (MEQ), to evaluate chronotype(48);
- The Epworth Sleepiness Scale (ESS) to assess daytime sleepiness, with a score>10 indicating excessive daytime sleepiness(49); and
- The Hospital Anxiety and Depression Scale (HADS) to assess anxiety (HADS-A) and depression (HADS-D) in two separate subscores, with a subscore >7 indicating the presence of anxiety and depression, respectively(50).

1.4.1(c)(ii) Retrospective Component

I retrospectively collected data from participants with OND who had been recruited to my prospective study at Oxford University Hospital. I then analysed a subset of data from participants with autoimmune and demyelinating OND, which was of interest due to the prevalence of these conditions within the cohort and their predominantly systemic nature, which can also impact on sleep quality and timing.

1.5 Research Team Acknowledgements and Role in this Project

The SOMNUS study was set up by Professor Susan Downes, Chief Investigator, in collaboration with Professor Russell Foster of the University of Oxford. It was supported by a Wellcome Trust grant and National Institute for Health Research (NIHR) funding. Eye Research Group Oxford (ERGO) assisted in the data collection. ERGO is a research team which includes Ophthalmology Consultants, a Research Nurse Manager, Research Nurses, a Research Coordinator, a Clinical Research Analyst and Administration Staff. I analysed data generated by this study independently, but advice and support was available within the team as required, with further statistical consultation from Dr. Iona Alexander and Mr. Colm Andrews.

1.6 Impact

This study raises awareness of disorders of sleep quality and timing in patients with OND. Raising awareness of the presence of poor sleep in a population who have sight loss is extremely important: This group may already have considerable health issues due to systemic disease associated with OND impacting on their QOL. Increased understanding and prompt recognition of sleep disorders, including poor sleep quality and timing could effect early intervention and could markedly improve holistic health outcomes. Melatonin, light therapy, or a combination of the two, as well as other novel interventions may have a role to play in improving QOL in this group of patients, particularly in those in whom circadian dysfunction is identified.

Chapter 2: Background

2.1 Introduction

Sleep is defined as "a reversible behavioural state of perceptual disengagement from, and unresponsiveness to, the environment"(51), and is essential for wellbeing(6, 52, 53). Sleep duration of less than six hours per night increases the risk of cardiovascular and metabolic disease and can lead to accidental injury as a result of reduced concentration(5). Whilst excessive sleep, known as hypersomnolence, of nine hours' or more duration per night may also be related to disease(54-57), sufficient sleep may be neuroprotective(6). My aims in this chapter are to examine the physiological processes concerned with sleep quality and timing, with specific reference to circadian physiology. I describe pRGCs within the optic nerve and RHT, how optic nerve and RGC function and sleep can be measured, and influences other than OND and circadian physiology that impact on sleep in a real world setting.

I commence this chapter by discussing the structure of normal human sleep, followed by circadian physiology. Following this, I consider the structure and function of the optic nerve as a key component of the RHT and clinical assessment of its function. I then discuss circadian rhythm disorders and other non-circadian disorders of sleep. I then consider the pathophysiology of OND relevant to this study and my systematic literature review and exogenous influences on sleep wake (including caffeine, smoking, alcohol and prescribed medications). I then examine endogenous influences on sleep wake (including psychological factors, and factors relating to systemic neurological disease). I then discuss demographic and relational factors influencing sleep wake and how sleep is measured subjectively and objectively.

2.2 Normal Human Sleep

Normal human sleep occurs during the night. The average duration of a night's sleep is 7.6 hours, although variations in age and sex exist. Normal sleep tends to occur in a reclined position, with low muscle tone and the eyes closed, and during which an array of biological mechanisms occur, including immune modulation and restorative metabolic processes(51, 58,

59). Normal sleep is composed of cyclical episodes of rapid eye movement (REM) and non-rapid eye movement (NREM) as described below(51).

2.2.1 Structure of Normal Sleep

Aserinsky and Kleitman(60) in their seminal study of electrooculography (EOG) and electroencephalography (EEG) in sleeping subjects observed sleep intervals characterised by rapid, short-arc rotational eye movements (REM) and those where eye movements were slower and of a wider arc of rotation (NREM). Normal sleep commences with 80-100 minutes of NREM sleep followed by cycling through REM and NREM stages approximately every 90 minutes(51).

REM episodes are depicted by a low-voltage, sawtoothed EEG pattern(61), and have been accompanied by atonia of the rest of the body(62), although normal tonic activity has been reported(63). REM is strongly associated with vivid dreams, which can be recalled, whereas "hypnagogic reveries", with more abstract images and sensations are found in NREM sleep(64, 65) although a continuum of dreaming corresponding to mentation during sleep stages is likely to exist(66-68).

NREM sleep has been subdivided into four stages with regard to EEG findings(60, 61, 64), which correspond to the sleep states first described by Loomis et al(69). NREM stage 1 is characterised by irregular, low electrical voltage activity, and comprises alpha waves, and slow, large range horizontal eye movements. NREM stage 2 contains sleep spindles of 12-14c/sec and K complexes, which are biphasic waves with superimposed sleep spindles of high wavelength and amplitude(70). Delta waves, which characterise "slow wave sleep"(SWS) begin to appear in NREM stage 3, and NREM stage 4 classically contains large delta waves(66, 71).

NREM stage 0 depicts wakefulness with eye closed, and is typically composed of alpha waves(61). During wakefulness, increase in fatigue correlates with increase in power density of theta waves, which appear to be associated with waking intensity, in addition to alpha and delta waves(72-74). NREM stages are usually short duration of fewer than ten minutes, with REM lasting up to 40 minutes.

NREM and REM occur at different frequencies during the night between individuals(75), and have similar auditory awakening thresholds(76). EEG recordings of sleep have been found to be consistent between males and females(77), although there appears to be reduced consolidation of NREM sleep, particularly SWS, associated with ageing, possibly due to decreased circadian influences(78).

2.3 The Two-Process Model of Sleep

The two-process model of sleep (Figure 1) describes how the physiological processes involved in sleep are under both homeostatic and circadian control in mammals(79, 80). Sleep pressure, or "Process S", is a homeostatic drive for sleep that builds up during wake time(81). EEG changes have shown increase in theta wave activity during prolonged wake periods, followed by increased slow wave activity power and increased slow wave activity (SWA) in early sleep following prolonged waking(82), indicating that "the longer we are active, the deeper we sleep"(81). At a cellular level, accumulation of extracellular adenosine during waking hours or during sleep deprivation activates adenosine A1 receptors and drives the SWA needed for sleep homeostasis. Adenosine is then metabolised by adenosine kinase in glial cells, causing deterioration in SWA, and decay in Process S(81, 83). Caffeine, a widely used stimulant antagonises adenosine A1, A2A and A3 receptors and can reduce sleepiness, as will be discussed later in this chapter(84-86).

"Process C" refers to the circadian sleep timer(81), which describes a rhythmic fluctuation in sleep tendency(87), and is consistent with the paradigm "the longer we are active, the shorter we sleep"(81). Circadian function is influenced by photic input from the eyes and has an influence on the sleep-wake cycle via the optic nerves and RHT to the SCN, the internal circadian pacemaker of the body(11). Sleep timing is modulated by the hormone melatonin(79), which is produced by a number of structures, the principal being the pineal gland in response to low light conditions transmitted through the eye(12). Ocular structures including the retina, ciliary body and lens, also produce melatonin(88).

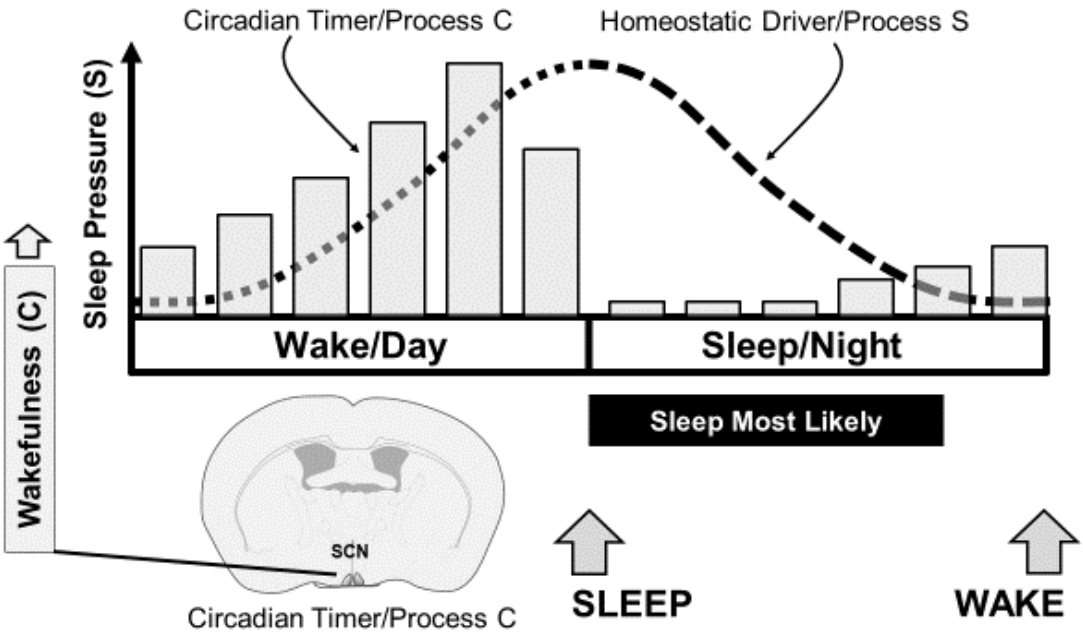


Figure 1: The Two-Process Model of Sleep Regulation for a Diurnal Mammal

A 24-hour signal (C, grey bars) arising from the SCN and a homeostatic driver (S, dotted line) interact to determine the timing, duration, and structure of sleep

Modified from: Russell G. Foster, Leon Kreitzman(2017)(79). Reproduced with kind permission.

2.4 Circadian and Homeostatic Misalignment

Misalignment of the circadian and homeostatic systems may occur in shift work and jet lag. In these instances, sleep and wake in relation to circadian phase is displaced and can impair physical and cognitive ability. The chronic effects of circadian misalignment as a result of frequent transmeridian travel and shift work which disrupt photic entrainment include dysfunction of lipid and glucose metabolism and regulation, insulin resistance, and disordered secretion of hormones including melatonin, growth hormone (GH), cortisol, and hunger- and appetite-regulating leptin and ghrelin, leading to a predisposition to diabetes, cardiovascular

disease and cancer(79, 89). I will discuss circadian rhythm disorders (SCRD) in more detail later in this chapter.

2.5 Circadian Physiology in the Animals and Humans

Photic entrainment of the endogenous circadian pacemaker is driven solely from light detected by the eyes in mammals(9). This is not the case in other species. For example, amphibians possess both circadian clocks and photoreceptors within extraretinal structures, such as a frontal organ, and lizards possess a parietal eye. Furthermore, birds possess photoreceptors deep within the hypothalamus that are used to regulate circadian timing through deep brain stimulation directly from ambient light(90). Within species, there may be heterogeneity of circadian patterns(91), which may be affected by factors such as sex, age, season and environment(92).

The key cell for non-visual (or non-image-forming) photoreception is the pRGC(93, 94). pRGCs are a small and distinct population of retinal ganglion cells (RGCs) which relay directly to the SCN via the RHT and contain the photopigment melanopsin(79, 95, 96). pRGCs are alternatively know as intrinsically photosensitive retinal ganglion cells (ipRGCs) and melanopsin retinal ganglion cells (mRGCs). For consistency, the term pRGC will be used throughout this review. Melanopsin (OPN4) is sensitive to blue light and was first proposed as an agent in circadian timing by Provencio et al(97) in which African clawed frogs were found to express melanopsin in directly photosensitive tissue, dermal melanophores; iris tissue, and brain tissue. In humans, pRGCs are found in greatest density 2mm eccentrically from the fovea, with decreasing density but increased proportion relative to the total ganglion cell population peripherally, and corresponding increase in size and overlap of dendritic field (98). PACAP, a neuropeptide co-stored with melanopsin in pRGCs has been found in the SCN, LGN, pregeniculate nucleus, pretectum, brachium of the superior colliculus and the superior colliculus in macaque monkeys(99). Similarly, studies of mice have found melanopsin projections through the optic nerves with dense SCN terminals bilaterally, and additional optic tract routes to the LGN and pretectum in the region of the olivary pretectal nucleus (OPN)(100).

Five morphologically distinct types of pRGC have been found in murine and human retinae, classed as M1-M5(101, 102). M1 and M2 pRGCs have been most widely studied, and project to

the SCN and OPN(101, 103). M1 are morphologically smaller with more dendrites, are acutely sensitive to light and lie in the outermost lamina of the inner plexiform layer (IPL), whilst M2 have lesser sensitivity to light, and are found in the innermost lamina of the IPL(101-103). M3 pRGCs are similar in size to M5, and are of intermediate light sensitivity, their dendrites being found in both inner and outer IPL laminae. M4 are the largest class of melanopsin pRGC, and are found with M5 in the inner IPL lamina, with both having a low response to light(101). M6 cells have been described in murine models by Quattrochi et al(2013)(104), which have projections to the OPN, which lies in the midbrain and forms part of the pupillary light response circuitry(105), and intergeniculate leaflet, which lies in the lateral thalamus, and is necessary for entrainment of the circadian rhythm to a skeleton photoperiod(106), although less known about M6 function(107). As yet the precise projections and physiological and light responses of melanopsin pRGCs are yet to be defined (see Figure 2).

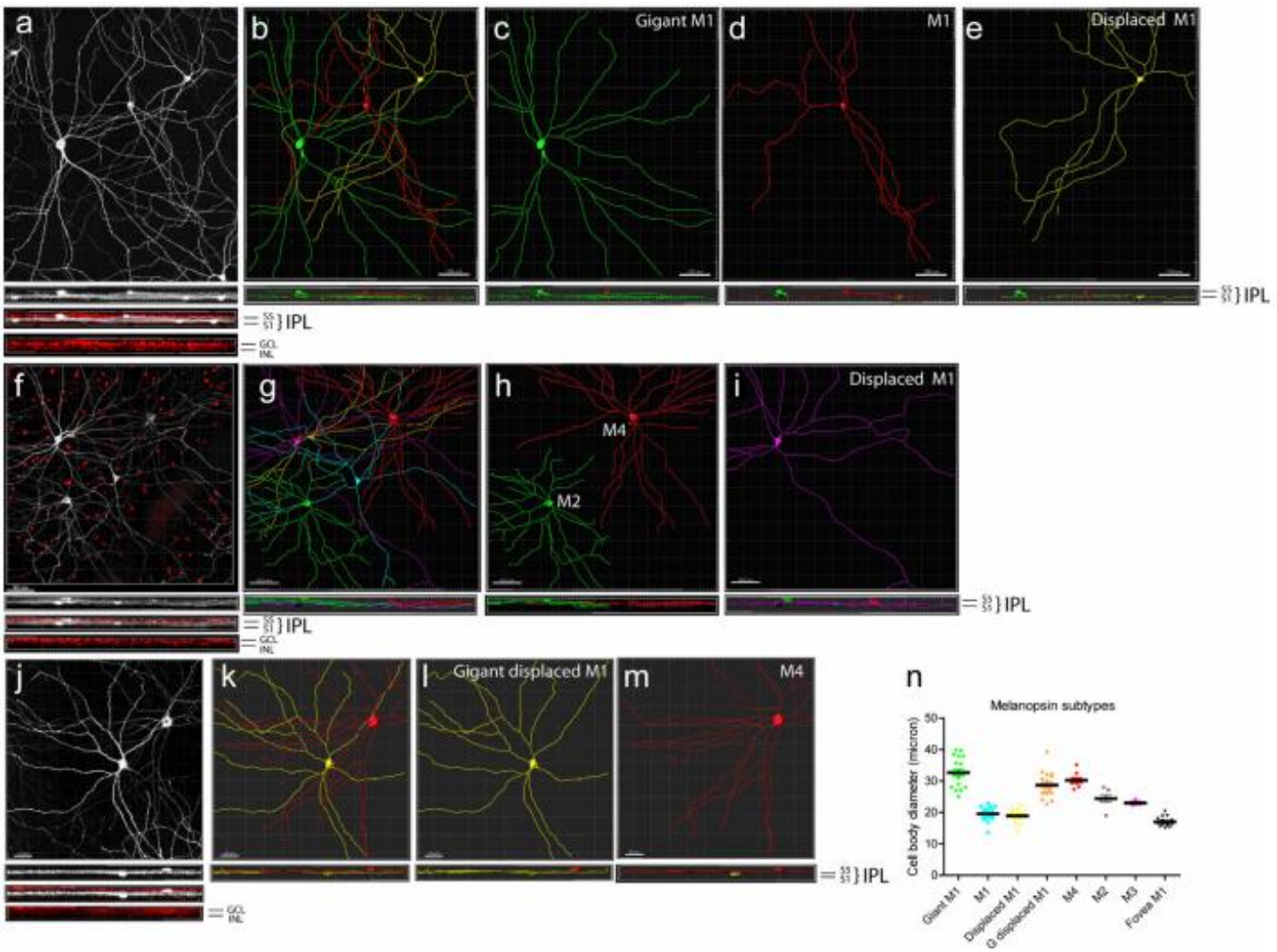

a
b
c
Gigant M1
d
M1
e
Displaced M1
IPL
GCL
INL
f
g
h
M4
M2
i
Displaced M1
IPL
GCL
INL
j
k
l
Gigant displaced M1
m
M4
IPL
GCL
INL
n
Melanopsin subtypes
Cell body diameter (micron)
0
10
20
30
40
50
Giant M1
M1
Displaced M1
G displaced M1
M4
M2
M3
Fovea M1

Figure 2: Melanopsin-Immunoreactive Retinal Ganglion Cells

Classification Based on Soma Localization and Dendritic Stratification

Images a, f and j: Melanopsin-ir subtypes was 3D-reconstructed from stacks of digital images which was costained red using ChAT immunoreactivity to identify localization of melanopsin-ir dendrites in the IPL. Each subtype of melanopsin-ir cells and dendritic processes was then identified using the tracing module in IMARIS® and pseudocoloured in the same program.

Images b–e: These illustrate in XY and XZ plane a gigantic M1 cell (green in b, c) and a classical M1 cell (red in b and d) and a displaced M1 cell (yellow in b and e). (g) shows a M2 (green), a M4 (red), and a displaced M1 cells (pink and yellow).

Image h: The M2 and M4 cells are for clarity illustrated alone, which also shows slightly deeper stratification of M4 dendrites in the IPL compared to M2 dendrites.

Images i-m: This illustrates a displaced M1 cell with dendrites in the outermost layer of the IPL. A gigantic displaced M1 cell (GDM1) with its relatively straight dendritic processes is illustrated (yellow) together with a large M4 cell (red) in (k). For clarity, the individual cell is also separate in (l) and (m). Note the relatively weak melanopsin immunostaining of M4 cells in (a) and in (j).

Image n: This illustrates the variation of soma diameter between the different subtypes of melanopsin-ir RGCs, the gigantic M1 cells and M4 cells being the largest.

Key: GCL=Ganglion cell layer; INL=Inner nuclear layer; IPL=Inner plexiform layer; ir=immunoreactive; RCGs=Retinal ganglion cells.

Scale bars: a–e; 100 mm, f–i; 80 mm, j–m; 50 mm.

Modified from: Jens Hannibal, A.T. Christiansen, S. Heegard, J. Fahrenkrug and J.F. Kiilgaard (2017)(108). Reproduced with kind permission.

Rods and cones (image-forming or visual photoreceptors) are not essential for photoentrainment in mammals but they do contribute to the system, and have demonstrated a weakened circadian response to light stimulation (94, 109). Similarly, there may be some overlap in conscious visual perception, with some evidence of retrograde transmission of visual stimuli via melanopsin-expressing cells(99, 110).

Individuals with VI or no vision have been reported to be more likely to experience poor quality sleep in comparison to sighted people(14, 15). However, these previous reports studied a heterogenous group and disease-specific information was not taken into consideration. Importantly, for studies in circadian biology in the visually blind, a non-recordable or flatline electroretinogram (ERG) is ideal as it indicates complete absence of rod, cone or ganglion cell responses(111), whereas individuals with no conscious perception of light, may still have functioning pRGCs and an ERG signal(112). Individuals who are registered blind must have a Snellen visual acuity (VA) of less than 3/60 with a full visual field (VF), or above 3/60 in the presence of severe visual field defects (VFD)(113), indicating the possibility of visual and non-visual photoreception. There is currently no standard way of assessing non-visual photoreception in humans, and whilst studies investigating the differential impact of disease severity on circadian biology are being carried out, sample sizes are often small, and there is no standardised way of comparing pRGC function across disease types. A further limitation is that factors unrelated to pRGC integrity, such as pre-existing sleep disorders or sleep modifying medications are rarely accounted for. In addition, results are often conflicting, and whilst the role of OND has been investigated in circadian disruption(114-116), to my knowledge there has been no overall review of this area.

2.6 The Optic Nerve

The optic nerves, which transmit sensory information from the retinae to the brain, are not histologically true cranial nerves but rather extensions of cerebral white matter tracts composed of oligodendrocyte-myelinated axons of RGCs (with the exception of their unmyelinated prelaminar portions)(117). Contents of the optic nerve additionally comprise astrocytes and microglia, blood vessels arising from the central retinal arterial and ciliary system, the central retinal vein and its tributaries(118). Each optic nerve carries 1.2 million

axons, which originate in the retina. RGCs, transmitting visual impulses that arise from rod and cone photoreceptors via bipolar cells, traverse the optic chiasm to the LGN of the thalamus, which then project to the visual cortices, where processing of visual information occurs(119). pRGCs are able to detect light, but are non-image forming, and form functional pathways involved in regulation of circadian rhythm, sleep and alertness, and pupillary responses. pRGCs conduct this photic information along the optic nerves, which are components of the RHT, and relay this to multiple intracranial nuclei, including the SCN(38, 120-126).

Each optic nerve is approximately 50mm long and has four anatomical segments, the most anterior being the intraocular portion, which is 1mm in length and forms the optic nerve head, which is visible on fundoscopy, and comprises the retinal nerve fibre layer (RNFL) at its most anterior followed by a prelaminar layer. It is then divided by the porous connective tissue septum, the lamina cribrosa, at the level of the sclera, posterior to which it forms the postlaminar portion, acquires a meningeal covering of pia and dura mater, is surrounded by CSF and is myelinated(38). This is followed by the intraorbital portion, which is the longest at 25mm and courses through the orbit; the intracanalicular portion of approximately 9mm length which traverses the optic canal, pierces the sphenoid bone and then becomes the intracranial portion, which is 16mm in length. Both intracranial optic nerves then unite to form the optic chiasm(119).

The optic chiasm lies superior to the sella turcica, the saddle-like concavity within the superior surface of the sphenoid that houses the pituitary gland, and its covering layer of dura, the diaphragma sellae. The optic chiasm is the site at which nasal fibres from each optic nerve decussate to join the contralateral optic tract and lies 2-6mm posterior to the tuberculum sellae, the bony prominence located at the front of the sella turcica. The posterior border of the optic chiasm forms the anterior wall of the third ventricle, which contains CSF, with the pituitary stalk passing posterior and inferior to the chiasm. The cavernous sinuses lie laterally and inferior to the chiasm and conduct the internal carotid arteries and internal carotid plexus, the cranial nerves involved in movement of the eye (oculomotor, trochlear and abducens nerves) and the ophthalmic and maxillary branches of the trigeminal nerve. The anterior cerebral arteries and anterior communicating artery lie

superior to the chiasm, the internal carotid arteries lie laterally, and the basilar artery posteroinferiorly(124, 127, 128).

The optic nerve lies within the subarachnoid space and is surrounded by CSF except for its most anterior prelaminar portion. The subarachnoid space may be compartmentalised rather than free-flowing as CSF concentration gradients along its length have been observed, which may explain apparent segmental compartment syndromes and asymmetric or unilateral optic nerve swelling(129, 130). Similar to the retia and brain, a blood-optic nerve barrier exists, formed by tight junctions and absence of fenestrations between endothelial cells(131). It has been postulated that CSF circulation around the optic nerve is via a glymphatic system, which is a system for removal of neurotoxic metabolites such as soluble proteins and β-amyloid, particularly during sleep, and dissemination of nutrients, hormones and neuromodulators(130, 132, 133).

Arterial supply of the optic nerve head is complex and anatomical configurations are highly variable. The lamina cribrosa is supplied by an abundant network of vessels known as the circles of Zinn and Haller, which are usually formed by the short posterior ciliary arteries, in addition to contributions from the short ciliary arteries, recurrent choroidal arteries, arteries of the pia mater and small intraneural branches of the central retinal artery, which arises from the internal carotid artery in most phenotypes(134). Anterior to the lamina cribrosa, the predominant arterial supply is typically from the choroid via the short posterior ciliary arteries and recurrent choroidal arteries, while posteriorly, arterial supply is from the pia mater complex externally and small branches of the central retinal artery internally(134). The intraorbital optic nerve is supplied by the ciliary arteries and central retinal artery, while the intracanalicular portion is supplied by a small network of branches of the superior hypophyseal arteries, which are extensions of the intracranial and intraorbital sections of the ophthalmic artery(135).

Venous drainage of the optic nerve is via the central retinal vein, with tributaries arising from the choroid and optociliary veins, with some drainage from pial veins. The central retinal vein lies in the subarachnoid space and empties into the cavernous sinus, either directly or via the superior ophthalmic vein(134, 136). Due to its position within the meningeal layers, the central retinal vein is vulnerable to fluctuations in intracranial pressure transmitted by the CSF. Venous valves are absent within the optic nerve and orbit,

and venous tributaries form a tortuous, anastamotic complex. The optic nerve is devoid of lymphatics, although they are present in the nerve sheath and lymphatic markers have been identified in macrophages of surrounding tissues(137, 138).

Postganglionic sympathetic fibres from the superior cervical ganglion supply the optic nerve vasculature, with vasoconstriction being protective against elevated blood pressure, while postganglionic parasympathetic contributions are relayed from the ciliary ganglion (oculomotor nerve) and pterygopalatine ganglion (facial nerve)(134).

2.6.1 Functional Relevance of the Optic Nerve

The optic nerve is a component of the RHT, and as such is a key feature of the relay system from the eye to the SCN. The optic nerves are therefore implicated in circadian regulation, and damage to the nerve could affect transmission of photic information from pRGCs to the SCN, leading to disrupted circadian function and impaired sleep quality and timing. In this chapter I discuss how different optic nerve pathologies, including glaucoma can affect pRGC function, and in Chapter 3 I present a systematic review of the published literature to determine what is currently known regarding the impact of OND and glaucomatous conditions on sleep quality and timing. As sleep is also affected by factors unrelated to the circadian system, it is important to differentiate between circadian rhythm sleep disorders and other sleep disorders, which are described in 2.7 and 2.9.

2.6.2 Measurement of Optic Nerve Function

There are several assessments of RGC and by implication optic nerve function available in the clinical and experimental setting, as described below. These all indirectly evaluate RGC transmission, although subjective input and compliance is required in most cases, and motor coordination is required for automated perimetry. The practicalities of performing these tests in the clinical setting vary, as several, including formal pupillary light reflexes (PLR) and ERG are time-consuming but provide useful objective data. All testing modalities for RGC function can be compromised by the presence of other ocular pathologies including

cataract and retinal disease, which should be assessed and taken into consideration for each patient(139).

2.6.2(a) Contrast Sensitivity

Contrast sensitivity can be measured by a simple letter chart with optotypes of reducing contrast, and has been found to be an early sign of RGC loss, preceding VFD and reduction in VA. It has been demonstrated to correlate with RGC count and thickness of the ganglion cell and inner plexiform layers of the retina and is related to the size and on-off reactivity of the RGC dendritic field in response to light and dark stimuli, which transmit impulses via magnocellular pathways(139-141).

2.6.2(b) Chromatic Vision

Colour, or chromatic vision is not consciously detected by RGCs, but relies on RGC function for transmission of impulses from light of differing wavelengths to the visual cortices via parvocellular routes. Midget RGCs are most prevalent in the fovea where cones provide direct input to RGCs regarding spectral reflectivity. RGCs are therefore implicated in determination of hue or saturation of red, green, blue and yellow wavelength light, and are also involved in edge detection and distinguishing the boundaries and form of objects. M1 pRGCS have also been found to respond to specific contrasts of blue and yellow light associated with sunrise and sunset, which may be implicated in circadian timing. In the clinical setting, colour plates can be used as a simple test of colour vision, in addition to panel tests of hue(139, 142, 143).

2.6.2(c) Pupillary Light Reflex

pRGCs mediate the PLR with projections to the lateral geniculate nuclei of the thalamus and Edinger-Westphal nuclei in the rostral midbrain. They are most responsive to blue light of wavelength 470-480nm, and are less sensitive than rods, which produce early, short-lasting pupil contraction, but are able to sustain pupil contraction, and do not display fatigue with repeated stimulation. The post-illumination pupil response is most specific to pRGC function, which evaluates pupil contraction at 1.7s post initiation of light. pRGCs are also

implicated in regulation of pupil size, and the presence of a relative afferent pupillary defect (RAPD) may denote damage to structures in the afferent arc of the pupil reflex, which comprises pRGCs. Clinically, pupil size and the presence of a RAPD are tests that can be swiftly carried out as part of a routine assessment(139, 144, 145). Automated bedside pupillometers can be used to evaluate pupil responses and size, however formal testing of full-field chromatic (red and blue light) PLR requires a protocol of several minutes of dark adaptation, and specialist equipment such as a Ganzfield screen and eye tracker(146).

2.6.2(d) Visual Fields

RGC dendritic fields cover the whole retina and overlap on average three-fold, with properties of size-selectivity and a balance of on- versus off-centre RGCs maximising the precision of spatial resolution, which gives rise to the field of vision(139, 147, 148). Damage to RGCs in OND and glaucoma cause VFDs, and assessment of visual field (VF) is a key part of assessment of RGC and optic nerve function, with standard automated perimetry (such as a Humphrey visual field (HVF)) being the gold standard for assessment of visual function in glaucoma, with correspondence to RNFL thickness(149, 150). VFs in neuro-ophthalmological conditions can also be measured using kinetic Goldmann perimetry, which requires interaction with a skilled perimetrist and has the advantage of evaluation of the peripheral visual field, defining the shape of scotomas with greater precision and reducing variability of repeat readings in patients with low vision, but has the disadvantage of being more dependent on the skill of the assessor, and a standardised method of numerical comparison of HVF and Goldmann visual field (GVF) in research studies has not been clearly defined(151, 152). Finally, confrontation VFs provide a rapid bedside test of central and peripheral vision, although this is less sensitive to smaller defects, and is more examiner-dependent(153).

2.6.2(e) Electroretinography

ERG produces a valuable objective measurement of RGC function. It is time-consuming and requires specialist equipment including corneal and skin electrodes, a curved screen and monitoring apparatus and in scotopic, or dark-adapted conditions, requires an adjustment period. The pattern electroretinogram (PERG) uses a reversing checkerboard grid to neutralise photoreceptor activity so that RGC function can be detected and has been found

to anticipate structural PRG damage on optical coherence tomography (OCT), with improved function detected following reduction in intraocular pressure (IOP) in glaucoma(154). The PERG N95 wave is a reflection of RGC function, and abnormalities can indicate the presence of OND; however the preceding p50 wave may be attenuated in the presence of macular or retinal atrophy(139, 155).

Photopic negative responses follow the ERG b wave. These are negative potentials that indicate peaks in RGC activity and correspond to findings on automated perimetry, with reliable correlations with extent of RGC damage found in compressive optic neuropathies and idiopathic intracranial hypertension (IIH)(156, 157). Visual evoked potentials (VEPs) can detect aberrant optic nerve conduction, with findings including slower peaking, reduction in amplitude and altered shape of the p100 waveform in optic nerve compression, with wider-field multifocal VEPs (mfVEPs) corresponding to VF loss(139, 156).

2.6.2(f) Visual Acuity

VA is not a sensitive test of RGC function, as it is an assessment of the function of neuronal integrity at the fovea, which comprises a tiny portion of the total RGC field, and peripheral damage can be missed(158). VA can also be spared in OND relative to other functions such as colour vision, contrast sensitivity and pupil reactions, and macular damage can exist in glaucoma in the absence of reduced VA(159, 160). Central RNFL loss does correspond to VA, and test reliability can be improved using ETDRS or LogMAR charts as Snellen charts do not have a uniform decrease in size of optotypes, leading to a skewed distribution of data. Low-contrast, high-pass optotypes have also been found to be more sensitive in identifying central RGC loss in glaucoma(158, 160-162).

2.7 Types of Circadian Rhythm Sleep Disorders

Normal circadian rhythms are entrained to 24 hours, with a corresponding alignment of sleep/wake to the light-dark cycle. Abnormal circadian rhythms, in their pathological state are known as sleep circadian rhythm disorders (SCRD) and are classified as entrained to 24-hours, or non-entrained to 24-hours, and have been frequently observed in individuals with low vision, including that associated with OND(13-15).

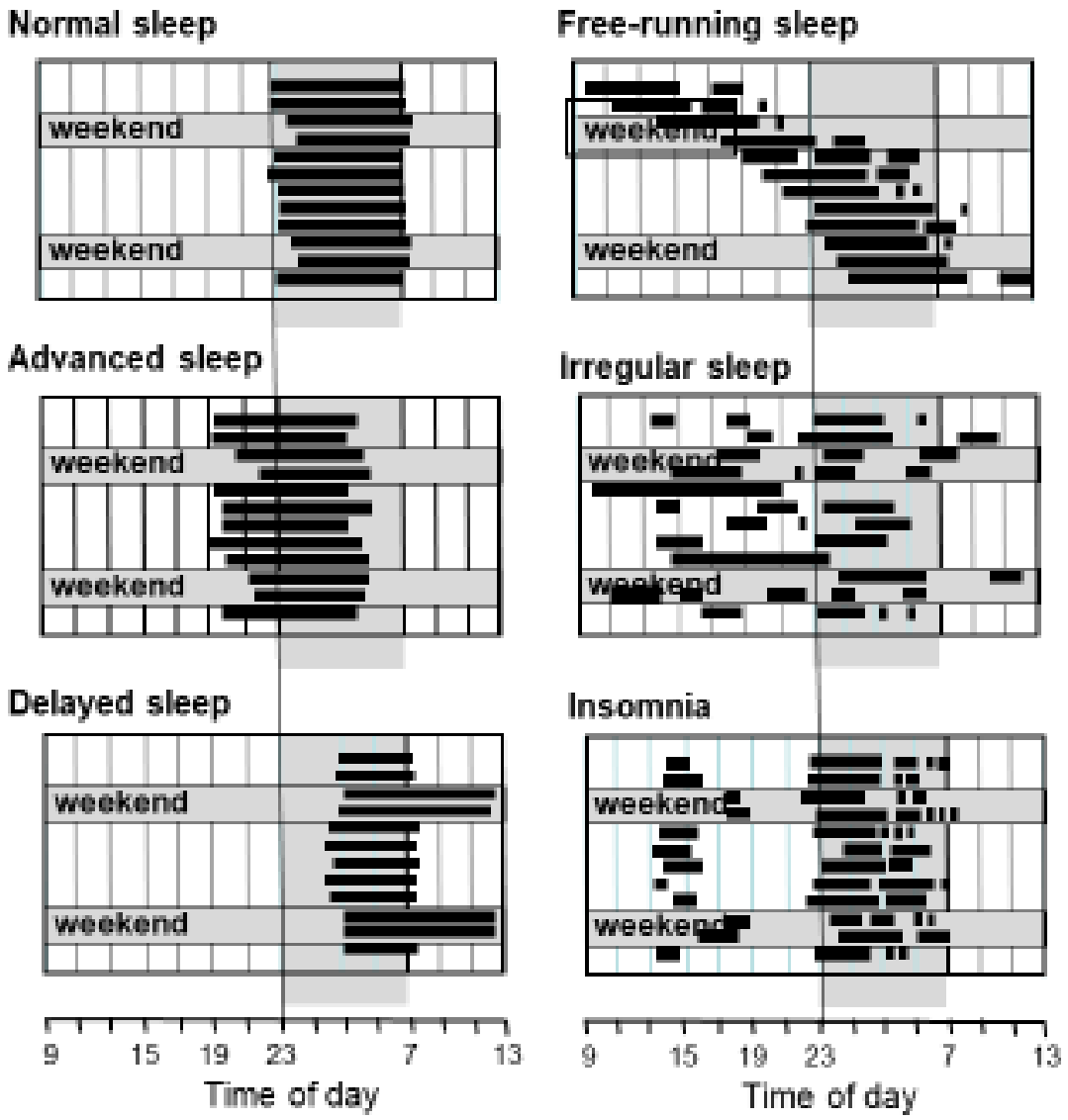
SCRDs entrained to 24 hours include advanced phase sleep disorder (APSD), which is characterised by sleep onset and melatonin peak occurring earlier than environmental night, leading to sleeping and waking several hours earlier than social norms. Delayed phase sleep disorder (DPSD), denotes sleep onset and wake time that occur several hours later than social norms, with peak melatonin levels occurring later into the night(163, 164).

Non-24-hour sleep wake disorders are those in which a stable, regular rhythm of sleep wake cannot be maintained and in which circadian rhythms are not entrained to a 24-hour period(165). Non-entrained SCRD includes the “free-running” disorder (FRD). A FR circadian rhythm is one in which photic entrainment is absent. Without photic input the endogenous rhythm of the SCN drives internal entrainment. This is typically longer than a 24-hour cycle(166), and means that over a number of days, the sleep period becomes increasingly out of synchronisation with the environmental light and dark cycle. Entrainment appears to occur when the internal day and external light-dark cycle temporarily attain a stable phase relationship.

In some cases, individuals exhibit an irregular sleep-wake rhythm with no discernible period. A fourth subset of SCRD, comprises individuals who have no discernible rhythm, known as irregular sleep wake disorder (ISWD), in which sleep episodes may be shortened (although total sleep time may be orthodox), and may occur at arbitrary intervals during the day and night. ISWD may also be classified as a non-24 hour sleep wake disorder(163, 164). (See Figure 3).

Figure 3: Normal versus Abnormal Patterns in Sleep Timing

Black horizontal bars represent periods of sleep on consecutive work days and at the weekend. Weekends and night time are indicated. From: Russell G. Foster, Leon Kreitzman (2017)(79). Reproduced with kind permission.



2.8 Jet Lag and Shift Work

There are multiple reasons for the occurrence of sleep wake disorders. In a 24-7 society, jet lag and shift work have been identified as major causes of circadian disruption. Jet lag disorder (JLD), is also known as “transmeridian desynchonisation”(167), and occurs

following rapid traversal of time zones, causing a self-limiting circadian misalignment. Shift work disorder (SWD) is induced by work done during standard sleeping hours, such as night shifts and irregular working hours. This results in difficulty sustaining sleep of sufficient duration, particularly when sleep must occur outside the endogenous sleep-wake timing (for example, during daylight hours), and increased sleepiness at work(167). Risk factors for SWD include age, sex, and inappropriately timed daylight and bright light exposure(168). Persistent insufficient sleep (of 4-5 hours total duration) can lead to a cumulative "sleep debt" and can affect mood, psychomotor vigilance, memory and cognitive and emotional processing(169) as well as lead to other health problems(4). Insufficient sleep has also been implicated in major industrial incidents and non-alcohol related road traffic accidents(170, 171), and advanced sleep phase, sleep fragmentation and early morning waking is predictive and characteristic of depressive conditions, and is associated with anxiety (172, 173).

Roenneberg et al(174) developed the Munich ChronoType Questionnaire (MCTQ), which explores the relationship between the solar clock, the social clock and the biological clock, calculating mid-sleep times and sleep duration of individuals with tendencies towards earliness (morning larks) and lateness (night owls). The results revealed that sleep timing changed over the lifetime, with a tendency for young adults toward lateness. They also showed that individuals with a tendency to lateness, irrespective of age, experienced loss of sleep during the working weeks, with compensation of the "sleep debt" during free days. By contrast, early types, who tend to lose less sleep during work days, may struggle to adapt to social pressures causing delayed sleep times on free days. This chronic difference between the biological circadian clock and social demands on work and free days is known as "social jetlag" SJL(175). SJL largely affects individuals with a late tendency, which is common in adolescence(176), in which the biological clock typically shifts to a later cycle, and may determine eating patterns, affecting educational outcomes as the school day does not shift back to reflect this biological delay(177). It may contribute to diabetes, psychiatric disturbances and mood disorders, taking up smoking, and caffeine and alcohol consumption (to compensate for difficulty waking and sleeping respectively)(175). Burnout has been associated with SJL in late-shift workers, and has been found to be more marked in late types, with expression of circadian genes NR1D1, NR1D2 and PER3 varying with social requirements of sleep and wake(178, 179).

2.9 Other Disorders of Sleep

There are multiple factors that can give rise to sleep disruption, which can be incorrectly categorised as a SCRD. Disorders of sleep which have the potential to be misdiagnosed as SCRD include OSA which is associated with glaucoma and optic neuropathy, periodic limb movement (PLM) and narcolepsy(180-182), among others(183).

2.9.1 Obstructive Sleep Apnoea

OSA is characterised by an upper airway obstruction occurring during sleep that is associated with increased tissue volume in the tongue, soft palate and pharyngeal walls, with consequential snoring, apnoeic episodes and daytime sleepiness. Obesity, increased neck girth, snoring, smoking, and alcohol consumption are risk factors due to their effect on the musculature of the throat and pharynx, and males are predominantly affected(184-186).

OSA classically comprises cyclical desaturation, arousals and re-oxygenation which has a negative impact on the cardiovascular system effected by oxidative stress, sympathetic activation, sudden-onset hypertension and widespread inflammatory changes. OSA is associated with coronary artery disease, cerebrovascular accidents and increased mortality, and may have corresponding ocular sequelae(185, 187). Individuals with OSA have been found to be at higher risk of non-arteritic ischaemic optic neuropathy (NAION), central serous retinopathy, floppy eyelid syndrome and retinal vein occlusion(188-190). OSA is also prevalent in normal tension glaucoma(191, 192), and primary open-angle glaucoma, although this may be due to common risk factors rather than the presence of a causal association(193, 194).

2.9.2 Restless Leg Syndrome

RLS is a neurological sensorimotor disorder which relies on clinical diagnosis, occurring in an estimated 2-3% of the population. It includes a cycle of unpleasant crawling sensations in

the legs, particularly during periods of rest, causing a compulsion to move the limbs, which provides some relief. RLS is common in pregnancy, and other associations include iron deficiency, renal failure, diabetes, myelopathy and Parkinson disease (PD)(195, 196). RLS generally presents in individuals over 35 years of age, is twice as common in women, and is not associated with increased daytime sleepiness(196). PLM is associated with 90% of RLS cases, and refers to sudden limb or bodily movements, which can occur at night, but also during the day. PLM is thought to be a manifestation of sympathetic hyperactivity, and together with RLS is linked to a common gene variant BTBD9(197).

2.9.3 Parasomnias

Parasomnias are atypical behaviours during sleep and transition between the states of sleep and wake that comprise abnormal motor, sensory and behavioural phenomena due to impaired dissociation of NREM sleep, REM sleep and waking states, with a prevalence of 2.2-4.2% in adults(198, 199). These include confusional arousals, night terrors, sleepwalking, bruxism (jaw grinding), motor agitations, hallucinations, and rarely, violent behaviours which put the individual and their bed partner at risk(200, 201).

REM sleep is typically characterised by muscle atonia and paralysis: however, in REM sleep behaviour disorder (RBD), abnormal muscle tone, motor activity, vocalisations and vivid nightmares are present, and may occur in combination with dream enactment. It is most common in males over 40years, and can be present idiopathically, or in association with cognitive impairment, Lewy body dementia and PD(202).

Sleep paralysis is a disorder of REM sleep in which there is inhibition of skeletal muscle movement, with continuance of respiratory functioning and ocular movements. It occurs most frequently at the beginning and end of sleep and may coincide with vivid hallucinations which are often frightening for the sufferer. Sleep paralysis has been found to occur more frequently in narcolepsy, hypertension and epilepsy, and in individuals with disordered circadian functioning, for example in shift work or jet lag(203). Psychiatric disorders and use of anxiolytic medication are also risk factors(204). Hypnagogic hallucinations usually occur in the REM sleep phase, and may comprise highly vivid

experiences of visual, auditory and tactile phenomena. They are frequently found in conjunction with sleep paralysis and have been found in association with narcolepsy(205).

Confusional arousals are a NREM parasomnia found in 4.2% of the population(198), and occur when there is a dissociation between sensorimotor function and other brain activities. Abnormal jerking movements of the limbs, talking, slow mental processing and amnesia after the event occur. They occur at higher incidence in individuals with psychiatric disorders and those taking psychiatric medications(199, 206, 207).

Sleepwalking, or somnambulism, is considered to be a disorder of unstable NREM sleep and occurs with a peak incidence of 13.5% in childhood, which decreases to 2-4% in adults. The sleepwalker has impaired consciousness and decision-making ability and tends to be in a SWS state, with no recollection of the episode. In children, this is generally benign, but in adulthood the sleepwalker can unconsciously put themselves or others in danger. Occasionally, violent behaviours can occur during sleepwalking episodes(208, 209). Somnambulism appears to have hereditary and environmental influences, and may be found in conjunction with sleep-disordered breathing, RLS or PLM(209, 210).

As in sleepwalking, sleep terrors, which are intense, fear-inducing dreams, occur during fragmented slow wave NREM sleep and are present in approximately 2.2% of people. There may be partial or total amnesia of dream content, and it is not uncommon for them to exist concurrently with sleepwalking. In comparison to RBD, dream content in sleep terrors is less aggressive, less complex and involves accidents and misfortunes, with varying degrees of dream enactment, which may be related to somnambulation activities. Night terrors can occur in association with psychiatric medication and psychiatric conditions(198, 211-213).

Somniloquy (sleep talking) is not classified as a parasomnia per se, but vocalisations and talking during low arousal states, with reduced recall, forms part of other parasomnia disorders, although it may also occur in normal, undisturbed sleep. It is most common in NREM sleep stages 1 and 2, and during REM sleep. Somniloquy has been reported to have a prevalence of 4.9% in Chinese children, and 5.3% in adults in the United States(199, 214-216).

2.9.4 Narcolepsy

Narcolepsy affects 1 in 2000 individuals, is a neurological disorder of rapid eye movement (REM) sleep, and is considered to have an autoimmune basis(180, 217). Narcolepsy can take the form of dramatic daytime cataplexic episodes with paralysis of voluntary (except respiratory) muscles, often despite good quality night-time sleep, leading to difficulties in school and work, and potential accidental injury. Type 1 narcolepsy is associated with loss of orexin A- and B- producing hypothalamic neurones, generally with a positive multiple sleep latency test (MSLT).

Type 2 narcolepsy clinically resembles Type 1, although it may be less severe, with normal orexin-A levels, absence of cataplexy, and more variable results on MSLT. Narcolepsy may be difficult to differentiate from other causes of daytime somnolence, such as OSA and PLM without further investigation(180).

Both genetic and environmental factors are thought to contribute to the development of narcolepsy; the presence of human leukocyte antigen (HLA) DR2(218) is confirmatory, and there is association of the chromosome 4p13-q21 locus(219). Similarly, polymorphisms at immunologic loci such as T-cell receptor alpha, the tumour necrosis factor superfamily 4(TNFS4), cathepsin H (CTSH), purinergic receptor genes (P2RY11), and DNA methyltransferase (DNMT1) are implicated(217). In combination with cataplexy, narcoplesy is linked to HLA DQB1*602(220, 221), and severity of symptoms has been found to increase with the number of HLA DQB1*0602 alleles inherited(222).

Further evidence for an immunogenic cause is provided by the increased incidence of narcolepsy in children and young people associated with the H1N1 Pandemrix vaccination(223-225). Symptoms of narcolepsy have been successfully managed with modafinil, a wake-promoting agent, and in the presence of cataplexy, sodium oxybate, a type B GABA agonist, has proven effective(226-229).

2.10 Optic Nerve Disorders

There are many causes of OND, but the underlying mechanisms all produce structural and functional impairment of the optic nerve. This section describes an array of mechanisms of

damage to the optic nerve and their aetiology, clinical presentations and systemic associations.

Optic neuropathy is defined as damage to the optic nerve that affects the structure and function of RGCs with resulting loss of visual function, which clinically may be identified as loss of VA and contrast sensitivity, decreased colour vision, visual field defects and altered pupillary responses. Optic atrophy may present one month following damage to the optic nerve, with depletion of RGC axons, which may be observable as sectoral or widespread pallor and cupping of the optic nerve head(230, 231).

Optic neuritis (ON) is defined as inflammation at any point along the length of the optic nerve, and may cause swelling of the optic disc, known as papillitis, or may spare the optic nerve head, producing a retrobulbar neuritis. Inflammation of the nerve may damage RGC structure and the integrity of the myelinated optic nerve sheath, resulting in slowed conduction of impulses, the development of optic neuropathy and subsequent optic atrophy(232, 233).

2.10.1 Optic Atrophy

Pathological loss of axons of the optic nerve, and insult to or aberrant development of the anterior or posterior visual pathways results in an OA which manifests as loss of VA, VFD, abnormal pupillary reflexes and loss of colour vision(234). Fundoscopically, OA can be observed as disc pallor and cupping, with OCT imaging revealing thinning of the peripapillary RNFL in addition to reduction in ganglion cell layer (GCL) and IPL thickness(120, 235). Underlying pathologies that lead to OA, include mitochondrial and other forms of inherited diseases, structural and neurological developmental disorders, impaired development of the optic nerve due to concurrent nystagmus, strabismus or refractive error, post-inflammatory or infectious end-stage ON, compression of the optic nerve or chiasm, papilloedema, ischaemic damage, trauma and neurodegeneration(234, 236, 237). OA can also be idiopathic in childhood in a small number of cases(238).

2.10.2 Congenital Optic Nerve Pathologies

Congenital optic nerve pathologies are disorders of the optic nerve which are present at birth. They are a heterogenous group of disorders with multiple underlying mechanisms and may be sporadic or inherited. Notable conditions include coloboma (incomplete closure of the embryonic cleft), staphyloma (excavation of the peripapillary area), optic nerve choristoma (a congenital ocular or periocular tumour), tumours of the optic nerve and sheath (glioma, meningioma, medulloepithelioma, oligodendroglioma), morning glory syndrome (an embryological malformation of the optic disc) and myelinated nerve fibres (optic nerve fibres at the level of the optic disc are typically unmyelinated)(239, 240). The following sections focus on OND relevant to my study population and systematic literature review, and as such describe optic nerve hypoplasia (ONH), septo-optic dysplasia (SOD), primary congenital glaucoma and buphthalmos, and optic neuropathy associated with retinopathy of prematurity (ROP).

2.10.2(a) Optic Nerve Hypoplasia

ONH has been found to have an incidence of 10.9 per 100,000 per year and 2.4 per 100,000 per year in a population under 19 years(241). It is a generally sporadic unilateral or bilateral congenital condition characterised by a reduction in RGC axonal fibres which may be as much as 90%(242, 243). ONH is thought to be the result of a higher rate of RGC axonal apoptosis during gestation, and animal studies have found an association with netrin-1 (an axonal guidance molecule in embryogenesis), and DCC (deleted in colorectal cancer, a netrin receptor) deficiency(241, 244, 245). Other associations are low maternal age, low socioeconomic status, maternal diabetes, prematurity and primiparity(244, 246).

The spectrum and severity of ONH and its associated conditions is variable, and clinical findings may include a reduced diameter of the optic disc (less than 1.4mm) and optic canal, disc pallor or greyness, nerve fibre layer thinning, and tortuous retinal vessels. Assessment of visual function may reveal reduced VA, nystagmus and strabismus. Reported associated systemic conditions comprise cerebral dysplasias, endocrinological dysfunction, developmental delay, obesity and ASD(241, 246, 247), with polymorphisms found in

transcription factor genes *HESX1*, *SOX2*, *PAX6*, *NR2F1*, *OTX2*, *VAX1* and *ATOH7* among others(244, 248, 249).

2.10.2(b) Septo-Optic Dysplasia

Septo-optic dysplasia (SOD), also known as de Morsier syndrome, has an incidence of one in 10,000 live births, is phenotypically heterogeneous and is characterised by at least two features from a classic triad of ONH, which is frequently bilateral; abnormal pituitary hormone production (which may be an isolated hormone insufficiency, multiple hormone insufficiencies, or panhypopituitarism); and midline brain anomalies, such as dysgenesis of the corpus callosum or septum pellucidum(249-251). Maternal and socioeconomic risk factors are consistent with those for ONH, as described above(246).

Most cases of SOD are sporadic, although associations with heterozygous mutations of the *HESX1* gene (located on chromosome 3 at position 3p14.3) which codes for the HESX1-S170L homeobox protein that is expressed during embryonic development of the forebrain and Rathke's pouch, and *SOX2*, a transcription factor that encodes for embryological development of the pituitary, forebrain and eyes (located on chromosome 3 at position 3q26.3-q27) have been found. Other genes implicated include *SOX3* (located on the X chromosome at position Xq27), which is associated with hypopituitarism; *OTX2* (orthodenticle homeobox 2, located on chromosome 14 at position 14q22), which codes for forebrain development; and a splice site mutation of *FLNA* (located on the X chromosome) which encodes for the filamin A protein and is pivotal in embryogenesis(252-256). Ocular presentation and visual assessment are similar to those found in ONH, as described above.

2.10.2(c) Primary Congenital Glaucoma and Buphthalmos

Buphthalmos, meaning "ox-eye" in Greek, is a most commonly consequence of congenital or infantile glaucoma, in which elevated IOP exerts an outward pressure on the elastic structural tissues of the eye, most frequently due to developmental irregularities of the trabecular meshwork and iridocorneal angle, which hampers drainage of aqueous humour, and has an incidence of 1 in 30,000 live births(257, 258). This leads to abnormal enlargement of the eye, including an increase in axial length and corneal diameter

(megalocornea) which is apparent at birth or during infancy. Juvenile onset glaucoma does not lead to buphthalmos, as it occurs later in childhood, by which time, the eyeball is less distensible(258), although both mechanisms lead to glaucomatous optic neuropathy and RGC damage.

Clinical presentation of buphthalmos comprises myopia and a deep anterior chamber due to increased axial length of the eye. Thinning of the anterior sclera and iris atrophy may also be present, and retinal rupture may occur in a minority of cases(257). Corneal clouding develops as a result of breaks in Descemet membrane, known as Haab striae, which evolve due to increased IOP. The Descemet membrane is the basement membrane of the corneal endothelium, which acts as a barrier to prevent passage of water from the aqueous into the cornea, maintaining corneal desiccation and thus its transparency, and can be breached in the presence of high IOP(259). On fundoscopy, glaucomatous optic neuropathy can be observed, which may comprise notches or pits in the optic disc, and a high cup: disc ratio due to compression and atrophy of RGC axons. VA and VF loss may be present, and signs associated with ocular surface exposure and incomplete lid coverage due to increased ocular size may also occur, which include photosensitivity, epiphora, eye swelling, conjunctival injection and blepharospasm(258, 260).

Genetic associations of buphthalmos tend to demonstrate autosomal recessive inheritance and include mutations in *CYP1B1*, a cytochrome P450 gene located at the GLC3A locus on chromosome 2 (position 2p21) which is also found in defects of the trabecular meshwork (TM), one of the principal drainage systems of the eye, and the ciliary body, which is involved in production of aqueous humour; consequently both the TM and the ciliary body contribute to the IOP(260). Other gene loci include GLC3B, located on chromosome 1 (position 1p36); GLC3C, located on chromosome 14 (position 14q24.3-q31.1) and GLC3D, where the *LTBP2* gene lies, which codes for latent transforming growth factor-beta binding protein 2(located on chromosome 14, position 14q24). *TEK*, tunica interna endothelial cell kinase, which codes for angiopoietin growth receptor and lies at the GLC3E locus on chromosome 9 (position 9p21.1) polymorphisms show an autosomal dominant inheritance pattern in primary congenital glaucoma and are also associated with buphthalmos(260-263).

Other conditions that may lead to increased IOP and manifest as buphthalmos include NF1, which, as described in Chapter 2 is characterised by Lisch nodules of the iris, and in which

there may be abnormalities of the iridocorneal angle which can impact on drainage of the aqueous humour(258). Sturge-Weber syndrome is a rare syndrome of incidence 1 in 20,000 to 50,000 live births and is a dermato-oculo-neural condition which occurs sporadically due to an intracranial vascular malformation. This can be observed as a facial port-wine naevus in the distribution of the ophthalmic and maxillary divisions of the trigeminal nerve ipsilateral to the malformation. Headaches, seizures and focal neurology may be present. Venous backpressure from episcleral vessels can increase IOP as can abnormalities of the iridocorneal angle, which may be present(264).

2.10.2(d) Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a visually-threatening condition associated with preterm births, particularly when this occurs before vascularisation of the retina is complete, with the highest risk in preterms born before 31 weeks' gestation(265). Retinal vascularisation commences at 12 weeks, and angiogenesis of the deep retinal vasculature is present at 25-26 weeks gestation, with vessels reaching the peripheral retina just prior to term(266, 267). In premature babies, the abrupt transition from in-utero development and loss of placental support leads to hypoxia and an arrest of circulating growth factors, such as insulin-like growth factor-1 (IGF-1), causing interruption of retinal vascularisation(268). The metabolic demand of the retina continues, however, and this stimulates neovascularisation at the border of between the normally vascularised retina and the peripheral retina at which angiogenesis has been arrested. Persistence of neovascular growth leads to formation of retinal scarring and fibrosis, which then precipitates tractional retinal detachment and loss of vision(268, 269). Glaucoma is a notable consequence of ROP(269, 270) and ROP has been associated with features ONH(271), while ONH itself has been found to potentiate ROP(272). Polymorphisms of the genes *LRP5*, *FZD4*, *TSPAN12* and *NDP* (Norrie disease protein) have been found concomitantly with ROP(273).

2.10.3 Hereditary Optic Nerve Conditions

HON typically results in permanent, sometimes progressive, bilateral central visual loss, (274), with the two most common forms being Leber hereditary optic neuropathy (LHON)

and dominant optic atrophy (DOA), which are termed mitochondrial optic neuropathies(275). Wolfram syndrome (WS) is not defined as a mitochondrial optic neuropathy, but has some similarities with LHON and DOA, and some markedly different features(276, 277). This section describes presenting features of LHON, DOA and WS in addition to comparing their similarities and differences.

2.10.3(a) Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy (LHON) typically presents in young adulthood as a subacute simultaneous or sequential bilateral painless visual loss with progression of a dense central scotoma over weeks or months(278, 279), with preservation of pRGCs demonstrated by preserved PLR(280). LHON is caused by one of three main mitochondrial DNA mutations (G11778A mutation at codon 340 resulting in an arginine to histidine substitution in the ND4 amino acid subunit; G3460A mutation with a theonine for alanine substitution at position 52 in the ND1 subunit; T14484C mutation with methionine-64 to valine substitution of the ND6 subunit). LHON displays incomplete penetrance, with phenotypic presentation in 50% of males and 10% of females, and LHON mutations being found to have a population prevalence of 5.92 per 10,000(281-283). Risk factors for phenotypic manifestation of LHON include smoking and heavy drinking, with penetrance increasing to 93% in male smokers(284). LHON is primarily mediated by oxidative stress and degeneration of RGCs particularly within the papillomacular bundle, which are highly sensitive to dysfunctions in ATP synthesis and mitochondrial malfunction(285, 286).

Although LHON tends to present with isolated visual signs and symptoms, other systemic manifestations can occur. In females with the G11778A mutation, 45% have been found to have an associated MS-like condition(287), a combination known as “Harding disease”, which has a more aggressive course(288). Nikoskelainen et al (1995)(289) described “Leber plus”, in which patients with LHON on closer examination also had neurological movement disorders, including postural tremor, motor ticks, Parkinsonism, dystonia, peripheral neuropathy, MS-like features, thoracic kyphosis and brainstem involvement. At least one of these phenomena were present in 59% of patients examined.

2.10.3(b) Dominant Optic Atrophy

Dominant optic atrophy (DOA), also known as Kjer-type, is characterised by an unpredictable severity and progression of bilateral temporal optic atrophy of insidious onset in the first or second decades as a result of heterozygous inheritance of a mutated *OPA1* gene (in 75% of cases), located on chromosome 3 at position 3q28-q29(290), of which a prevalence of 2.9 per 100,000 has been reported in the North of England(290). As *OPA1* codes for dynamin-related guanosine triphosphate (GTP)ase in the inner mitochondrial membrane, a mutation results in dysfunctional mitochondrial maintenance and biogenesis, and induction of apoptosis, which predominantly affects RGCs, hence its classification as a mitochondrial optic neuropathy(279, 291). Mutations in *OPA3*, which also codes for an inner mitochondrial membrane protein, and is located at 19q13.2-q13.3, have been implicated in a small number of patients with DOA, as have polymorphisms in *SSBP1*, a single-stranded DNA binding protein located at 7q33-q35, which was also associated with variable retinal degeneration(290, 292). Other genes producing the DOA phenotype include *OPA4* (18q12.2-q12.3), *OPA5* (22q12.1-q13,1) and *OPA8* (16q21-q22)(293).

Other clinical features of DOA include deficit of colour vision, with blue-yellow colours commonly affected, and a centrocaecal VFD, with preservation of pupil responses(294). High resolution OCT has revealed a reduction in retinal vascular density in DOA(295), and the presence of microcystoid lacunae in the macular GCL and IPL in approximately one quarter of patients, who tended to be younger(296). Like LHON, DOA demonstrates variable penetrance, with reports of 43-88%, although penetrance was previously considered to be near-complete(293). VEPs may be delayed or absent, and PERG may display reduction in magnitude of the N95 wave and abnormality of the N95:p50 ratio. Associated musculoskeletal and neurological irregularities are commonly associated with DOA, and muscle biopsy is sometimes required to confirm a DOA mitochondriopathy as opposed to other neuromusculoskeletal conditions(293). Systemic sequelae of DOA include ophthalmoplegia, myopathy, ptosis and gait abnormalities, sensorimotor peripheral neuropathy, ataxia and sensorineural hearing loss. Occasionally, endocrine, gastrointestinal, psychiatric and haematological conditions may co-exist(297).

2.10.3(c) Wolfram Syndrome

WS is a progressive neurodegenerative disorder, with a prevalence of 1 in 770,000 in the United Kingdom, which typically presents within the first two decades of life(298). WS is strongly associated with consanguinuity(299, 300) and is most frequently caused by homozygous (autosomal recessive) inheritance of a missense mutation of the *WFS1* gene. *WFS1* codes for the *wolframin* protein, a hydrophobic transmembranous glycoprotein found on the endoplasmic reticulum, which functions as a protector against endoplasmic reticulum stress(298), with autosomal dominant missense manifestations less frequently reported in WS(299, 301). The *WFS1* codon lies at position 4p16 on chromosome four, covering 8 exons and in which over 170 different mutations have been identified(298). *Wolframin* is found in high concentrations in the hippocampus, amygdala, olfactory bulb, brainstem nuclei, thalamic reticular nuclei and β cells of the islets of Langerhans in the pancreas, heart and muscle tissue, with *WFS1*-mediated pathways intrinsic to β cell functionality and survival via endoplasmic reticulum equilibrium(302, 303). Loss of function of *WFS1* may lead to defective calcium transport between the endoplasmic reticula and mitochondria, causing dysfunctional mitochondrial calcium ingress(276). Deficiencies in *WFS1* function result in central diabetes insipidus (DI), diabetes mellitus (DM), OA and sensorineural deafness (DIDMOAD), and additionally psychiatric, urinary tract and PNS symptoms(304, 305). Olfactory dysfunction, which is an indicator of neurodegeneration in early AD and PD may be present in WS, specifically smell identification, a qualitative central process, in contrast to smell sensitivity which is a process of the PNS(306, 307). Similarly, individuals with heterozygous mutations in *CISD2*, which codes for *ERIS* (endoplasmic reticulum intermembrane small protein) located at 4q22-24, display early OA, type 1 diabetes mellitus (T1DM) and deafness, with absence of DI, in a presentation known as “WS2”(298, 308). WS has been found to primarily affect the RGCs and glial cells of the optic nerves, which contain the *wolframin* protein, with demyelination of the optic chiasm, tracts and radiations being reported in MRI studies(303, 309).

Ophthalmic manifestations of WS include OA with optic disc pallor in almost all cases, with reduced VA and colour vision also characteristic. VF testing has demonstrated a range of defects, including generalised constriction or diffuse reductions in sensitivity, arcuate defects, and central or centrocaecal scotomas, and OCT frequently shows peripapillary RNFL and macular ganglion cell complex and IPL atrophy with measurements in the lowest 1% of

normal distribution(300, 310, 311). A generalised reduction in overall retinal vessel density has been reported on OCT angiography in addition to retinal microvascular impairment at the optic nerve head and macular superficial capillary plexus, with mild retinal degeneration also present, usually in the absence of diabetic retinopathy. OCT imaging has also demonstrated anomalies in lamination at of the outer plexiform layer and microcystoid oedema in the inner nuclear layer in autosomal dominant cases(312-314). Normal pupillary responses have been described, although and Adie's tonic pupil has been reported in some presentations(300, 310, 311). Recent publications describe keratoconus-like changes in corneal morphology and a reduction in corneal sensitivity corresponding to disease progression in WS, and other ocular manifestations include cataract and pendular, elliptical and horizontal conjugate jerk nystagmus and strabismus including exotropias and esotropias(299, 315, 316).

In addition to DM (23-100% prevalence), DI (39-77%), sensorineural deafness(40%) and impaired olfaction, systemic manifestations of WS comprise neurological disorders in 23-61% of cases which include ataxia, tremor, lower limb weakness, cerebellar and brainstem atrophy, pituitary adenoma (PA), cognitive impairment and severe headaches. Psychological manifestations found in 31% of cases include obsessive-compulsive disorder (OCD) and depression. Urological presentations such as hydroureteronephrosis and an atonic bladder have also been reported(299, 300).

2.10.3(c)(i) Comparison of Hereditary Optic Neuropathies

All HON appear to have selective preservation of pupillary responses against a background of severe VI(275). WS had been documented as having a more rapid loss of VA and VF than DOA, which progresses with more stability. Onset of OA in WS is also at an earlier age than in both DOA and LHON, with more marked loss of RNFL and GCL on OCT. Additionally, MRI shows more marked and extensive degeneration of the anterior and posterior visual pathways in WS, which may point to active degeneration rather than dysfunctional growth. Patterns of RGC injury in WS are dissimilar to those in mitochondrial optic neuropathies, with degeneration commencing with axons rather than at the cell body, and increased tendency for loss of neurones at the papillomacular bundle compared to LHON and DOA(277). Abnormalities of optic disc and retinal vasculature also vary between WS and

LHON, with increased vessel tortuosity at the optic disc, deep peripapillary plexus and outer retinal telangiectasia, and depletion of other peripapillary vasculature in LHON, resulting in an overall loss of blood supply to the optic nerve, with subsequent axonal loss and OA(317), whereas in WS there is a generalised reduction in microvascular density in the absence of telangiectasia or vessel tortuosity(317).

Electrophysiological evaluation in LHON has been found to shown reduction in N95/P50 ratio and reduction in P50 peak time on PERG, with reduction in amplitude density in central rings on multifocal ERG (mfERG). PVEP have found to demonstrate minimal responsiveness, with delay and reduction in peak times, although standard full-field ERG has been found to be normal(318). This is in contrast to DOA, in which standard ERG is suggestive of inner retinal layer damage, and RGC degeneration is implied from reduction in N95 amplitude on PERG and atypical photopic negative responses prior to altered VEPs, which progress to show aberrant waveforms on PVEP, attenuation of P50 and reduction of peak time on PERG(319). In WS, normal ERG and flash VEP has been described, although reduction in amplitude and increased latency of P100 waves have been detected on VEP, and barely detectable PVEP responses with marked delay have been recorded(310-312).

Mean life expectancy is 35 years in WS, with death due to brainstem atrophy. Life expectancy is normal in DOA and LHON in the absence of systemic involvement, which occurs less frequently(320); however WS presents with a range of phenotypes, including the absence of DM, DI, hearing loss or neurological sequelae, with clinical appearance characteristic of mitochondrial optic neuropathy(299, 312).

2.10.4 Autoimmune and Inflammatory Optic Neuropathies

Autoimmune disorders usually arise due to the inability of the body's immune system to discriminate between autogenous or "self" tissues and foreign, or "non-self" material. This may occur due to a genetic predisposition, epigenetic modifications in immune responses, viral insult affecting protein expression, or exposure of tissue that is usually concealed from the immune system(321, 322). Autoimmune disorders of the optic nerve manifest as an ON, which may be isolated, relapsing-remitting, or chronic, and may occur as part of NMOSD or MS(323). As NMOSD is primarily an autoimmune disorder, I will discuss it in relation to OND

in this section and discuss demyelinating disorders in relation to OND (MS) in the next section. This section also describes chronic relapsing inflammatory optic neuropathy (CRION) and OND related to sarcoidosis, an inflammatory condition.

2.10.4(a) Neuromyelitis Optica Spectrum Disorder

NMOSD, also known as Devic disease has a prevalence of 0.8 per million in the United Kingdom and is a rare autoimmune disease that primarily attacks the optic nerves (optic neuritis) and spinal cord(myelitis)(324, 325). The majority of cases present at age 35-45 years, albeit initial manifestations in children and the elderly do exist. A female to male preponderance of 2.3:1 has been observed(325, 326). Although demyelination is present in its pathophysiology, NMOSD is primarily an autoimmune disorder, and therefore distinct from MS, with seropositivity for antibodies against aquaporin-4 (AQP4), the most abundant water channel protein in the central nervous system (CNS), which regulates water homeostasis, present in 80% of patients(325, 327, 328). Antibodies against myelin oligodendrocyte glycoprotein (MOG), which is involved in the attachment of the myelin sheath, its immune relationships, and oligodendrocyte structure(329) are present in a further 9.8% of cases(330). Neuronal damage within the optic nerves and CNS is caused by depletion of astrocytes, aggregation of auto-antibodies and complement proteins and subsequent incursion of granulocytes and mononuclear phagocytes, with inflammation disturbing the integrity of the blood-brain barrier (BBB), allowing further infiltration of immunoglobulins and further immune dysregulation(331). Other immune mediators implicated in NMOSD include the pro-inflammatory cytokine IL-6, which may induce Th17-helper lymphocytes, B-cell activation, and elements of the innate immune response including degranulation of eosinophils and neutrophils, and macrophages(324, 325). An association of the haplotypes HLA-DRB1*03 and HLA-DRB1*01 has been reported, which is different from MS(332). Clinical diagnosis of NMOSD is made by the presence of AQP4 or MOG antibodies, a spinal cord lesion extending over at least three vertebral segments, and findings on magnetic resonance imaging (MRI) of the CNS that do not meet the criteria for MS(324, 328), and may reveal optic nerve enhancement in isolation(327, 328).

NMOSD is characterised by an inflammatory autoimmune optic neuropathy, which can produce sequential attacks of painful ON and transverse myelitis. The course of NMOSD in

90% of cases is relapsing, and within five years 60% of sufferers lose functional vision in at least one eye and development of severe disability, as a result of motor and sensory loss and autonomic impairment which may comprise paraparesis or tetraparesis, and bladder and bowel dysfunction. In the case of brainstem involvement, intransigent hiccups and vomiting may be present, with mortality due respiratory failure caused by brainstem or cervical lesions in approximately one-third of patients(328, 333).

2.10.4(b) Chronic Relapsing Inflammatory Optic Neuropathy

CRION was first described by Kidd et al in 2003(334) and is a rare, although likely underreported condition that is characterised by an optic neuropathy that demonstrates a marked response to high dose glucocorticoid therapy which has a high potential for relapse following their tapering or discontinuation. It is frequently bilateral and painful, is more common in females, affecting a wide spectrum of ages, with mean age of presentation reported to be 35.7years(335). CRION appears to affect races and ethnicities equally, and case series and reports have been published worldwide. Presentation includes reduction in VA, colour vision, contrast sensitivity, VFD and RAPD (in unilateral or asymmetric cases). Initially, an oedematous optic disc may be seen on fundoscopy, with progressing to a pale, cupped disc in the absence of effective intervention. OCT of the peripapillary RNFL has shown reduced thickness. MRI brain demonstrates high optic nerve signal and enhancement with no associated brain abnormalities, in contrast to NMOSD and MS. VEPs have been found to be abnormal with reduction in N95 amplitude. No disease-specific biomarkers of CRION have yet been identified, although an overlap with MOG-associated disorder and/or the presence MOG antibodies have been found in a subset of patients with CRION. AQP4 antibodies have been found to be positive in less than one-fifth of cases(336, 337).

Current recommendations for management of CRION include early intervention with high-dose intravenous glucocorticoids such as methylprednisolone, sometimes accompanied by intravenous immunoglobulins or plasmapheresis, with transfer to oral glucocorticoids and gradual tapering and regular monitoring of visual function in the intermediate phase to ascertain the minimum effective dose for prevention of relapse, with transition to steroid-sparing immunosuppressants (azathioprine, methotrexate, cyclophosphamide, mycophenolate, cyclosporine) in the long term, in addition to monoclonal antibodies (such

as rituximab or the anti-TNFα infliximab), intravenous immunoglobulins and plasma exchange(335), with delay in treatment and misdiagnosis of MS-related ON potentially leading to poorer outcomes(335, 337, 338).

2.10.4(c) Sarcoid Optic Neuropathy

Sarcoidosis is an idiopathic granulomatous systemic disorder that most commonly affects the lungs and mediastinum (in 90% of cases) but can affect many other tissues. Its onset is typically between 20 to 40 years of age, and it is more prevalent in females and is four times more common in African Americans than in Caucasians and Asians, with prevalence 11 to 36 per 100,000 in the United States(339, 340). Non-caseating granulomas, which are clusters of epitheloid cells, giant cells, T lymphocytes and activated macrophages(341) are pathognomonic of sarcoidosis, and other markers include a raised CD4:CD8 ratio, raised serum calcium and angiotensin converting enzyme (ACE), and elevated immunoglobulins, protein and pleocytosis, in addition to decreased glucose on cerebrospinal fluid (CSF) analysis(339). Neurosarcoidosis is sarcoidosis of the nervous system, and accounts for 5-15% of sarcoidosis patients. Neurosarcoidosis can affect the CNS (brain and spinal cord) and the PNS, including the peripheral nerves and muscles. The most frequent presentation of neurosarcoidosis (23-73% of cases) is cranial nerve infiltration. Damage to the facial nerve (cranial nerve VII) and optic nerve (cranial nerve II) are most common, with VII damage presenting as unilateral facial weakness, and II infiltration causing loss of VA and VF, distorted colour vision and papilloedema(339, 340). Other neurological sequelae include hearing loss (VIII cranial nerve damage), diplopia, limb weakness, sensory abnormalities, gait disorders, ataxia, speech disorders, intracranial masses, hypothalamic and pituitary dysfunction, aseptic meningitis, hydrocephalus, seizures, cognitive disturbance and psychiatric symptoms, myelopathy, peripheral neuropathy and myopathy(341-343). Prognosis in sarcoidosis is poor, with a mortality rate of 10-18%, and seizures being a predictor of poor outlook(343, 344). The mainstay of treatment is glucocorticoid therapy, with second-line treatment including immunosuppressive agents such as methotrexate, cyclosporine, chlorambucil and azathioprine, and a minority of patients requiring anti-TNF therapy(340, 342, 345).

2.10.5 Demyelinating Optic Neuropathies

Demyelination is a T-cell mediated process, to which leukocytes and microglia contribute, with inflammatory activity causing disintegration of oligodendrocytes and other myelin-producing cells. RGC axonal dysfunction and formation of scar tissue following inflammation can cause delay in neural transmission, which is characteristic of MS(346) and other demyelinating disorders, including acute disseminated acute disseminated encephalomyelitis (ADEM)(347). This section discusses OND disorders where the primary process is demyelination, which include OND associated with MS, ON due to a clinically isolated syndrome (CIS) and ADEM.

2.10.5(a) Multiple Sclerosis

MS affects 2.5 million people worldwide and is a chronic progressive condition which is caused by demyelination within the CNS, mediated by inflammatory and immune processes. The development of MS is considered to be the result of a complex interplay between genetic and environmental factors, evidenced by a 20-40 times greater risk of development in a first-degree relative, inheritance of the HLA-DRB1*1501 haplotype, female:male ratio of 2:1, temporal geographic latitude, and exposure to Epstein Barr and other viruses(348, 349). Demyelination is visible on neuroimaging as focal white matter plaques, and produces a range of neurological manifestations including ON, bladder dysfunction, motor and sensory impairment (weakness, spasticity, gait abnormalities, sensory loss and dysaesthesiae) and difficulties with balance and coordination, euphoria, personality changes and overwhelming fatigue(349, 350). MS generally follows a relapsing-remitting (RRMS) or progressive course. RRMS describes a course of acute episodes of neurological impairment, followed by phases of remission and full or partial recovery. In progressive MS, remissions do not occur, and the condition follows a course of increasing morbidity over time. RRMS may transform into progressive MS at a later stage in the disease process(351). Clinically definite MS is diagnosed using the McDonald criteria, which were updated in 2017(352), and specify dissemination in space and time, i.e. two distinct episodes of clinical symptoms which relate to lesions at different locations within the CNS, with a requirement for MRI confirmation or the presence of CSF oligoclonal bands depending on clinical certainty.

Typical, demyelinating ON classically presents as an acute, painful, unilateral visual loss in young adults aged 15-45 years, affecting both sexes with female predominance. Wakakura et al (1999) published an epidemiological study with estimated incidence of 1.6 per 100,000 per year in Japan(353), while reported incidence in the United States is 5.1 per 100,000 annually(354). Complete or partial resolution of symptoms occurs within 6 weeks of onset, with a 25% lifetime risk of development of multiple sclerosis (MS)(355). Following penetration of the BBB by CD8+ and to a lesser extent CD4+ T-lymphocytes, and via mediation of CD20+ B-cells, a delayed hypersensitivity reaction is thought to occur in MS-associated ON, with antibodies secreted against myelin contributing to oligodendrocyte apoptosis and axonal depletion(356, 357). Loss of RGCs is caused by axonal transection in acute ON, and has been found in eyes of patients with RRMS without ON, in additional to reduction in amplitude and latency delay in mfVEPs and delayed b-wave latency on ERG(358).

2.10.5(b) Clinically Isolated Syndrome

A monophasic typical ON with duration at least 24 hours is known as a CIS, which is an episode of CNS demyelination with features analogous to an attack of MS, but which fails to fulfil the McDonald criteria of dissemination in space and time for MS(352). A CIS may transpire to be an isolated event or may progress to RRMS(359), and may present with unilateral or bilateral ON(360, 361). The CSF biomarker homebox protein HOXB3 has been found to be associated with progression of CIS to MS within 5 years(362), and diffusion tensor imaging of the brain combined with brain volumetry has been found to be predictive for development into clinically definite MS within 2 years(363).

2.10.5(c) Acute Disseminated Encephalomyelitis

ADEM is a post-infectious(50-85%) or post-vaccination demyelinating disorder that affects the CNS, and is more common in children and adolescents, though a second peak aged 50-59years has also been reported, with an overall incidence of 0.07-0.6 per 100,000 per year(364, 365). Neurological symptoms appear approximately four weeks following the initial illness or insult and develop subacutely over the course of several days. These may be polyfocal or diffuse and may include lethargy (progressing to coma in severe cases),

hemiplegia or diplegia, cranial nerve palsies, ON, seizures, disordered gait and movement and ataxia(366, 367). Distinct from MS, ADEM has a monophasic course, with serial MRI findings demonstrating a lack of progression or resolution of CNS lesions in comparison to the appearance of new lesions in MS, although ON may recur(366). Thalamic involvement is more common in ADEM, and lesions of the corpus callosum are less likely(368). CNS lesions in ADEM typically show invasion of tissues surrounding blood vessels with T-cells and macrophages, with demyelination generally confined to these regions, although astrocyte proliferation and gliosis may evolve in advanced disease(369, 370). Elevated cerebrospinal fluid albumin and pleocytosis is present, usually with absence of oligoclonal bands(366) The mortality rate of ADEM is 1-3%, although partial or complete recovery occurs in most cases(371, 372).

2.10.6 Raised Intracranial Pressure

2.10.6(a) Idiopathic Intracranial Hypertension

The worldwide incidence and prevalence of IIH is increasing in association with age-standardised body mass index (BMI), the prevalence of childhood and adult obesity being of particular concern(373). In Wales, the incidence of IIH between 2003 and 2017 has more than tripled from 2.3 per 100,000 in 2003 to 7.8 per 100,000 in 2017(374). IIH is most common in young obese women and in social deprivation. It can lead to an increase in unscheduled hospital admissions and marked visual and systemic morbidity(373, 374). Typical presenting features of IIH include headache, which may be associated with neck and back pain, nausea, pulsatile tinnitus and diplopia (which can be associated with cranial nerve palsies, particulary of the abducens nerve), with vision loss often being in the form of transient obscurations initially. Diagnostic features include the presence of papilloedema, and the absence of any focal neurology other than cranial nerve signs, with normal brain parenchymal and meningeal structures, and no evidence of space-occupying lesion or hydrocephalus on MRI, although an empty sella, optic nerve head protrusion and tortuous optic nerves with distended sheaths may be present(375, 376). On lumbar puncture, CSF opening pressure is usually found to be elevated above 25mmH_2O, although papilloedema may be apparent at lower pressures. Perimetry can identify subtle VFD, with enlargement of the physiological blind spot being common(377). Pathophysiological mechanisms include

altered CSF dynamics, with increased cerebral venous sinus pressure reducing the pressure gradients and CSF drainage, which may be exacerbated by venous sinus stenoses and diminished CSF absorption. Metabolic and hormonal influences in IIH comprise adipose secretion of inflammatory mediators, with an array of interleukins, γ-interferon and leptin (a lipid storage hormone) found on CSF and serum analysis, and upregulation of androgens(376). Transmission of elevated CSF pressure to the subarachnoid space of the optic nerve sheath causes compression and downstream oedema of RGC axons, leading to optic disc swelling that is visible on fundoscopy, and obstruction of blood flow within the optic nerve vasculature, leading to observable vessel tortuosity and curling of capillaries at the optic disc(377). With continuing elevated pressure within the optic nerve sheath, destruction of optic nerve axons ensues, with the development of OA, loss of VA and colour vision, worsening VFD, and development of an afferent pupillary defect(378-380). OCT and OCTA studies have shown elevated optic nerve head volume, increased peripapillary RPE and Bruch's membrane volume, the presence of retinal (Patton lines) and choroidal folds, atrophy of macular RGC cell bodies, and dilation and tangling f vessels at the optic disc(377). Reduction in amplitude of full-field photopic negative responses and correlation of PERG with HVF and ganglion cell complex volume have also been found(381). In animal studies, RGC cell body and axonal loss has been demonstrated in the retina and optic nerve, respectively, with reduction in electronic transmission and worse contrast sensitivity observed, and production of hypoxaemia-inducible factor -1α by the GCL(382). Management of IIH aims to reduce intracranial pressure (ICP) via measures to reduce BMI, oral carbonic anhydrase inhibitors, or in refractory cases surgical venous sinus shunting to redirect CSF or optic nerve sheath fenestration(376).

2.10.7 Optic Nerve Compression

Compression of the optic nerve can occur at any point from the optic disc the chiasm and can lead to both reversible and irreversible visual sequelae, including loss of VA and VFD, atrophy of the optic radiations, reduced activity at the visual cortex and apoptosis of RGCs leading to reduced RNFL thickness(383-385). In this section, I will discuss intracranial

(affecting the optic chiasm and intracranial portions of the optic nerves) and intraorbital causes of optic nerve compression.

2.10.7(a) Intracranial Compression of the Optic Nerve

Structures surrounding the optic chiasm include the pituitary gland and cavernous sinus. Compression of the optic chiasm often occurs in the presence of endocrine dysfunction, ocular motility and pupil dysfunction and facial sensation disorders as a result of damage to the gland itself and structures which pass through the cavernous sinus such as the 3rd-6th cranial nerves and ocular sympathetic nerves. Chiasmal lesions often present initially as blurred vision and some VF loss, progressing to a bitemporal hemianopia with loss of near depth perception. A gradual reduction of monocular or binocular vision is common, but acute worsening or fluctuation in vision may resemble an ON, due to swelling of RGC axons and surrounding structures, progressing to RGC apoptosis and OA over time. The axons of RGCs lie in the optic chiasm and long-term chiasm compression can lead to defective nerve fibre layer function, with poorer visual recovery post-resection(121). Intracranial causes of compressive optic neuropathies include infectious, inflammatory, vascular, traumatic, neoplastic and bony tumours(385); in this section I will focus on primary lesions such as PA, meningiomas and craniopharyngiomas (CP).

2.10.7(a)(i) Pituitary Adenomas

PA are slow-growing benign growths of the pituitary gland and comprise 12-15% of symptomatic intracranial neoplasms, with incidence increasing with age. They are present in approximately 16.7% of the population, and some can be invasive with progression to the optic chiasm, which lies 10mm above the pituitary gland. Sudden enlargement of the adenoma can be precipitated by haemorrhage or infarction (pituitary apoplexy), resulting in acute visual loss, ophthalmoplegia, headache, and facial dysaesthesiae(121). Many adenomas, however, are asymptomatic and are detected incidentally on neuroimaging or at postmortem(386). A PA is defined as a microadenoma if it is less than 10mm in diameter, and a macroadenoma if 10mm or greate, with microadenomas being more prevalent (approximately 80% of PA)(387). Endocrine dysfunction may be present, with hypopituitarism (undersecretion of hormones produced by the pituitary) or

hyperpituitarism (excessive pituitary hormone secretion). Prolactinomas are the most common form of PA, with prevalence 76 per 100,000(388). If symptomatic, lactotrophic cells within the prolactinoma replicate and secrete excessive prolactin, leading to symptoms such as gynaecomastia, hypogonadism and impotence in men, galactorrhoea, breast shrinkage and amenorrhoea in women, and reduced libido, infertility, hair loss and osteoporosis in both sexes(389); similarly excessive secretion of adrenocorticotrophic hormone (ACTH) from a corticotrophic tumour can produce Cushing disease, while gonadotrophic tumours may over-secrete excessive LH or FSH, which tends to result in hypogonadism. Somatotrophic tumours, which may oversecrete GH can demonstrate signs and symptoms of acromegaly; and thyrotrophic tumours which hypersecrete TSH show features of hyperthyroidism(389). Haemorrhage or infarction of a pituitary tumour can cause pituitary apoplexy in which there may be sudden onset of visual loss and increased ICP with accompanying nausea, vomiting and headache, with vision- and life-threatening consequences(390).

Anatomically, the pituitary gland lies inferior to the optic chiasm and intracranial portions of the optic nerves, and medially to the cavernous sinus, which conducts the third (oculomotor), fourth (trochlear) and sixth (abducens) cranial nerves, meaning that a large pituitary tumour producing a mass effect can cause compression of the optic chiasm or the nerves controlling the extraocular muscles(389). Signs of optic nerve or chiasm compression include a VFD, most commonly in a bitemporal hemianopia pattern on Goldmann or Humphrey perimetry; reduction in VA, abnormal pupillary responses to direct or consensual light stimulation, reduced colour vision, and the presence of optic disc swelling or OA with loss of RNFL on fundoscopy. Cranial nerve compression may manifest as ptosis, abnormal oculomotor movements, and a fixed dilated pupil(156, 391, 392). Prior to detectable changes in perimetry, VA or RNFL thickness on OCT, dysfunction of pRGCs has been demonstrated in the early clinical stages of tumour development, which has been observed on electrophysiological testing, including mfVEPs and PERGs, indicating that without rigorous ophthalmological assessment, compromised visual function may be missed(156).

Multiple endocrine neoplasia (MEN) type 1 is a dominantly inherited condition in which a group of endocrine tumours occur simultaneously. These tumours affect the anterior pituitary gland in 95% of cases, in addition to insulin-secreting islet cell tumours of the pancreas, duodenal gastrin-secreting tumours and parathyroid neoplasia(393). Pituitary

tumours associated with MEN type 1 are often larger in size and are more likely to secrete multiple hormones, for example a somatotrophic tumour or prolactinoma associated with increased LH or FSH secretion(394).

2.10.7(a)(ii) Meningiomas

Meningiomas have an incidence of 2 per 100,000 per year(395) and make up 13-18% of primary intracranial tumours. Incidence of meningioma increases with advancing age. They are formed from meningothelial cap cells of the arachnoid villi(396). Compression of the chiasm is generally from below (sphenoid planum or tuberculum sella meningiomas), with a small percentage causing posterior (diaphragma sellae meningiomas) or lateral (medial sphenoid ridge meningiomas) or superior compression (olfactory groove subfrontal meningiomas, suprasellar meningioma). Multiple meningiomas and familial meningiomas may be associated with NF1. Examination may reveal bitemporal and incongruous VFD and OA, with some patterns of optic nerve cupping and altitudinal VFD being mistaken for glaucomatous optic neuropathy(121, 397).

2.10.7(a)(iv) Craniopharyngiomas

CP are embryological epithelial tumours of the sellar and suprasellar region formed in the craniopharyngeal duct from the vestigial residue of Rathke's pouch between the anterior and posterior pituitary(121, 398). CP are relatively rare, comprising 2-4% of intracranial neoplasms, with incidence of 1.3 cases per million person years(399). CP presentation displays a bimodal distribution with peaks of incidence at 5-15 years and 45-60 years(400).

Although benign and slow-growing, CP present a delicate problem due to the morbidity of their presenting symptoms. In view of their proximity to the hypothalamus, pituitary gland and optic chiasm, complete or partial surgical removal or radiation therapy can be precipitous and cause lasting or lethal damage, either as a result of endocrine deficiency or seizures(399). Visual symptoms are present in 50.3% of children with CP, and tumour location relative to the optic chiasm can vary, with the highest proportion of CP being suprasellar, compressing the chiasm from above and leading to bitemporal inferior visual loss. Other common visual manifestations include loss of VA, central VFD, OA and

strabismus. Signs of increased ICP, including papilloedema, are frequent, and involvement of CNS endocrine regulation (pituitary and hypothalamus) can produce an array of effects(398). Endocrine sequelae of CP and surgical removal can cause marked morbidity and can have fatal consequences. Decreased ACTH production can produce symptoms of weight loss, fatigue and hypoglycaemia, and can lead to hypotension and death due to a deficiency in cortisol secretion(401). GH and gonadotrophin (luteinising hormone (LH) and follicle stimulating hormone (FSH)) deficiency can lead to pubertal delay in children; reduction in thyroid stimulating hormone (TSH) can produce signs and symptoms of hypothyroidism including fatigue, weight gain and bradycardia. Antidiuretic hormone (ADH) depletion can induce the Syndrome of Inappropriate ADH Secretion (SIADH), DI, polydipsia or adipsia, while prolactin deficiency can cause amenorrhoea in females. Melatonin dysregulation can also occur, resulting in daytime somnolence and obesity(402-404).

2.10.7(b) Intraorbital and Intracanalicular Compression of the Optic Nerve

Compression of the optic nerve and RGCs within the orbital cavity can lead to loss of VA and colour vision, VFD, abnormal pupillary responses and swelling of the optic nerve head and subsequent OA, either due to direct compression of the optic nerve or interruption of its blood supply(385). Alterations in VEPs may be present in the early stages of optic nerve compression, with reduced P100 and N160 amplitudes and peak times, and OCT RNFL thickness may be reduced(405). The presence of damaged myelin within the CNS following neural injury had been found to induce apoptosis and inhibit axonal growth, limiting the capacity for regeneration(406). As for intracranial optic nerve and chiasm compression, intraorbital and intracanalicucular aetiologies can encompass a wide range of disease processes, including infectious, inflammatory, vascular, traumatic, neoplastic and bony tumours(385). This section focuses on intraorbital and intracanalicular optic nerve compression due to the neurofibromatoses, including optic nerve gliomas (ONG) and optic nerve sheath meningiomas.

2.10.7(b)(i) Neurofibromatosis

The neurofibromatoses are a spectrum of hereditary tumour-suppressor syndromes characterised by growth and pause phases of benign and malignant tumours which arise

from the neural tissue of the CNS and PNS. They comprise neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis(407). In contrast to NF1 and NF2, involvement of the visual system in schwannomatosis is rare; instead it involves the peripheral and spinal nerves in the majority of cases(408-412). In the sections below I will discuss NF1 and NF2 as they can give rise to OND.

2.10.7(b)(i)(i) Neurofibromatosis Type 1

NF1, known as von Recklinghausen disease, displays autosomal dominant inheritance with an incidence of 1 in 3000 births. Mutations are present in NF1, a tumour suppressor gene located at 17q11.2 that codes for the neurofibromin protein, a GTPase activity cytoplasmic protein present in Schwann cells, oligodendrocytes, CNS tissues, neural crest melanocytes, leukocytes and adrenal glands, with ocular, neural and cutaneous manifestations prevalent, although any organ system can be affected(413-416). Mutations in the NF1 gene lead to deficient neurofibramin which results impaired control of cellular growth and development of tumours(414). Benign peripheral nerve sheath tumours, or neurofibromas, are characteristic and present in 78% of patients, with malignant transformation occurring in a minority of cases (2-5%). Neurofibromas may be cutaneous, subcutaneous, or associated with peripheral nerves (plexiform), and frequently appear in the head and neck, but can arise in any location, with plexiform neurofibromas ranging from asymptomatic to causing severe pain and compression of surrounding structures. Common cutaneous presentations include café-au-lait spots in 97%, axillary and inguinal freckling in 90%, lipomas in 6.3%, with melanoma found in 0.7% of cases (Miraglia). Other systemic manifestations include macrocephaly, short stature, learning disabilities, seizure disorders, peripheral neuropathies and musculoskeletal abnormalities such as bony dysplasia, pseudoarthrosis and scoliosis(417, 418). Cardiovascular and pulmonary disorders can also occur, such as congenital heart defects, hypertension, cerebrovascular disease, bullous and interstitial lung disease, and pulmonary hypertension(407, 417, 419, 420).

Ocular manifestations of NF1 include iris Lisch nodules, which are pigmented hamartomas present in 78% of cases and often contribute to a clinical diagnosis, and iris ectropion(421, 422). Gliomas of the optic nerve are present in 15-20% of confirmed cases of NF1, which can cause compression, damage and apoptosis of RGCs leading to loss of VA and VFD, with

possible endocrine dysfunction and mass effects if there is chiasmal or intracranial involvement. CNS gliomas can also affect the optic tracts and radiaions(423). Glaucoma has been reported in 1 in 300 patients with NF1, and can present as buphthalmos in children, with increased prevalence in patients with orbital and facial and anterior chamber involvement, or where fibrovascular thickening of the ciliary body or choroid is present(422, 424, 425). Retinal vascular tortuosity has been reported in 74% of patients with NF1, with microvascular abnormalities present in 31%. Choroidal abnormalities have been observed in up to 100% of patients with NF1, with choroidal nodules and reduction in RNFL thickness described(415, 420, 426). Other ocular findings include neurofibromas of the eyelid, orbit and uvea, retinal astrocytic hamartomas and combined hamartomas of the retina and retinal pigment epithelium (CHRRPE)(422, 427-429).

In addition to RGC dysfunction in the presence of ONG or optic nerve compression due to neurofibromas, soft tissue, vascular or bony abnormalities, NF1 can disrupt oligodendrocyte function in the optic nerve leading to reduction in myelin production with subsequent delayed conduction of RGCs. PVEPs have been found to show increased latency and diminished amplitude in patients with NF1(416).

2.10.7(b)(i)(ii) Neurofibromatosis Type 2

NF2 is less prevalent than NF1, but carries a higher morbidity and mortality than other neurofibromatoses due to the development of tumours of the CNS. NF2 has a prevalence of 1 in 33,000 and demonstrates autosomal dominant inheritance, with anomalies present in the *NF2* gene, located at 22q12.2, which codes for the merlin protein, a structural component of nerve and Schwann cells, and fibre cells of the lens and meninges(410, 422, 430, 431). CNS features are more common than in NF1, and may predominate, comprising unilateral or bilateral vestibular schwannomas, which can affect hearing and balance, and may produce tinnitus, vertigo and facial nerve palsies. CNS astrocytomas and ependymomas (neuroectodermal tumours), spinal schwannomas and meningiomas may also arise, while peripherally, nodular schwannomas, cutaneous neurofibromas, and café-au-lait spots may present(430).

Cataract is the most common ocular manifestation of NF2 and presents in up to 80% of cases, and can lead to amblyopia and strabismus in childhood(432). Retinal abnormalities have been found in 48% of a population of adults with NF2, including retinal tufts in 43%, retinal hamartomas in 35% and epiretinal membranes in 13%. Gliomas of the optic disc have been observed in 14%, and optic nerve sheath meningiomas in 4.1-28% of patients with NF2(432-434). Optic nerve dysplasia can present with a morning glory disc abnormality. Optic disc swelling due to RGC axonal oedema can develop as a result of intrinsic infiltration or compression of the optic nerve by gliomas or optic nerve sheath meningiomas but can also appear as a result of increased ICP due to cranial masses. Chronic RGC compression may lead to OA, with loss of VA, colour vision, VFD and pupillary abnormalities. Intraorbital involvement may present as proptosis, and compression of cranial nerves by tumours can cause restricted ocular motility, diplopia, reduced corneal sensation and lid dysfunction(435, 436).

2.10.7(b)(ii) Optic Nerve Gliomas

Of patients diagnosed with ONG, 10-70% have NF1, although less than half of ONG identified are asymptomatic. ONG have an equal prevalence in males and females, and 90% occur within the first two decades of life, with highest incidence in children under 10 years(437). ONG arise from the neuroglia and infiltrate the intraorbital optic nerve in almost half of cases but can also affect the intracranial optic nerve and optic chiasm. In cases of NF1, ONG can be associated with aberrant tumour suppression at 17q, with induction of the retrovirus associated sequence (RAS) oncogene. In NF1, characteristic radiologic findings of ONG include increased tortuosity and diffuse enlargement of the optic nerve, although alternatively it may have a fusiform appearance. 95% of symptomatic cases present with proptosis and associated abnormalities of oculomotor movements. Other clinical findings of reduced vision (either unilateral or bilateral, depending on location), dyschromatopsia, RAPD, nystagmus, headache or pain may be present, and the optic disc may appear normal, oedematous or atrophic. Chiasmal gliomas may involve the hypothalamus, with disruption of endocrine function, and elevated intracranial pressure may accompany intracranial gliomas. ONG associated with NF1 tend to progress with a more benign course, but are

more likely to be malignant in older patients, and rapid, painful visual loss and death may occur(396, 437, 438).

2.10.7(b)(ii) Optic Nerve Sheath Meningiomas

Optic nerve sheath meningiomas (ONSM) account for 2% of orbital tumours, of which 25% have been found in association with NF2 in childhood(395, 439). They are most prevalent in females aged 45-55 years, and tend to be unilateral, with bilateral cases more likely to demonstrate intracranial extension and association with NF2(440). Many forms of ONSM are indolent, although the most frequent histology type is transitional in 50% of cases, and more rapid growth has been observed in pregnancy, which may be associated with the density of oestrogen and progesterone receptors in meningioma tissue(440).

Clinical presentation of ONSM classically shows progressive loss of vision, OA and collateral retinociliary vessels(441); however in most cases the picture is more varied, and misdiagnosis or delayed diagnosis is common due to their low prevalence. Findings indicating RGC dysfunction include the presence of a RAPD, reduced colour vision and an oedematous optic disc which may be related to proximal compression of the optic nerve causing downstream dilation of the anterior subarachnoid space(440), with vision loss more frequent in intracanalicular and orbital apex ONSMs. OCT has shown reduced peripapillary RNFL, while OCTA has indicated impaired flow in the superficial capillary plexus of the retina, particularly superiorly(442). PVEP have been found to pre-empt loss of VF, with reduction in amplitude and altered waveform morphology presenting prior to other clinical findings, with mfVEP mirroring changes seen on perimetry. PERG has shown reduction in N95 waves, and photopic negative responses are attenuated, mirroring changes in RNFL thickness(443). In unilateral cases, abnormalities on PVEP with low-normal amplitudes and reduced fMRI responses to stimulation have also been observed in the fellow eye, although the pathophysiological explanation for this is yet to be determined(444).

2.10.8 Vascular Optic Neuropathies

Vascular optic neuropathies are characterised by ischaemic damage to the optic nerve, resulting in sudden onset of visual loss and VFD, a RAPD and optic disc swelling. Anterior

ischaemic optic neuropathy (AION) can be divided into arteritic anterior ischaemic optic neuropathy (AAION), and non-arteritic anterior ischaemic optic neuropathy (NAION) which is often associated with crowding of the optic disc. Posterior ischaemic optic neuropathy (PION), is rare, and can also be arteritic, non-arteritic, or perioperative(445, 446). The sections below describe anterior vascular, or ischaemic, optic neuropathies as they are relevant to my study population and systematic literature review.

2.10.8(a) Anterior Ischaemic Optic Neuropathies

Anterior ischaemic optic neuropathy (AION) most commonly presents in older adults with hypertension and/or diabetes as acute visual loss, altitudinal, sectoral or complete VFD and optic disc oedema as a result of impaired perfusion with associated disc haemorrhage, progressing to OA, which may be segmental(447). Disruption of axoplasmic flow and swelling can cause a compartment syndrome and leads to segmental degeneration of RGCs, and impaired optic nerve function, and optic disc swelling may be visible in some cases. Presentation includes a episode of transient visual loss preceding onset of achromatopsia, an afferent pupillary defect, reduction in VA, arcuate or central scotomas or altitudinal VFD, with visual function tending to be irreversibly impaired following the insult. AION can also occur in association with optic disc drusen (ODD), which are present in 2% of the population and contribute to the prevalence of AION in patients under 50 years. ODD can cause a compartment syndrome due to crowding of the optic nerve head, leading to ischaemic damage to RGCs, with the presence of bilateral drusen increasing the risk of second eye involvement, which has been reported in 22% of cases(448, 449).

2.10.8(a)(i) Arteritic Anterior Ischaemic Optic Neuropathy

Arteritic anterior ischaemic optic neuropathy (AAION) has been reported to have an incidence of 1.0 per 10,000 person years, with increased incidence in females aged 70-79 years, and a 95% risk of involvement of the fellow eye if untreated(447, 450). AAION is associated with vascular inflammation due to giant cell arteritis (GCA), which can affect the short posterior ciliary arteries, and large and medium sized systemic vessels, including the temporal artery and aorta(451, 452), with subsequent narrowing or occlusion of the vessel lumen and ischaemic damage to the optic nerve and RGC injury(452). AAION is less common

than NAION in which vascular pathology is implicated, but not proven(447). Systemic manifestations of GCA include pyrexia, scalp tenderness, jaw claudication, headaches, malaise and generalised aches and pains, and it is closely related to polymyalgia rheumatica. Permanent visual loss may be heralded by episodes of amaurosis fugax due intermittent ischaemia of the optic nerve head. Interruption of blood supply to cranial nerves III, IV and VI may cause diplopia, and central retinal artery occlusion has been reported in 20% of cases(446, 453). Axonal ischaemia may cause hyperaemia and oedema of the optic disc, or there may be disc pallor, with preserved vascular clarity on fundoscopic examination(447, 454).

2.10.8(a)(ii) Non-Arteritic Anterior Ischaemic Optic Neuropathy

Non-arteritic anterior ischaemic optic neuropathy (NAION) has been found to have an incidence of 2.3 to 10.2 per 100,000 per year in the United States(455). It is thought to have a vascular cause, often due to crowding of axons at the lamina cribrosa, which may produce stasis, thrombosis or insufficiency in the short posterior ciliary arteries and subsequent ischaemic damage to the optic nerve, with axonal oedema, degeneration and apoptosis of RGCs(454, 456). Smaller optic nerve head morphology with absent or smaller disc cups and crowding of the disc contents are frequently found, and segmental disc swelling with peripapillary haemorrhages is also common(457). Systemic risk factors for NAION include diabetes, hypertension, nocturnal hypotension, elevated homocysteine in younger patients, Factor V Leiden and other coagulopathies, vasospasm and impaired autoregulation(458, 459). Presentation is characteristically an acute, painless visual loss which occurs over hours or days, which may remain stable, or may progress with time until it reaches a plateau. Altitudinal VFD, deficiency of colour vision and segmental disc swelling and RAPD are also typical(455). Dilation of the carotid arteries have also been reported to cause a compression optic neuropathy, and can also have a traction and ischaemic component, due to vascular occlusion, presenting as a NAION(460, 461).

2.10.9 Traumatic Optic Neuropathy

A direct or indirect injury to the optic nerve is seen in 0.5-2% of head injuries, and can result in permanent or temporary disruption of visual function(462). Optic nerve trauma most frequently occurs due to head injuries sustained in road traffic accidents or falls but may be missed on initial survey due to the presence of life-threatening injuries and altered conscious level of the patient. Direct trauma to the optic nerve may be caused by penetrating injuries, notably midfacial fractures and orbital trauma, with resulting avulsion or transection of the optic nerve or haemorrhage of the nerve sheath, retrobulbar haemorrhage and orbital emphysema (creation of a one-way valve between the sinuses causing tension within the orbital compartment)(463, 464). Indirect optic neuropathy is caused by compression or haemorrhage within the optic nerve sheath, which is particularly vulnerable in the optic canal, and shearing forces transmitted to the optic nerve in non-penetrating head trauma. The mechanisms of traumatic damage to the optic nerve are both mechanical and circulatory, with an inflammatory response produced by lymphocytic incursion, antibody secretion, proinflammatory cytokine and TNF release with demyelination mediated by macrophages. Cell membrane damage occurs via lipid peroxidation and axonal damage causes Wallerian degeneration of RGCs, which manifests as visual loss, VFD, RAPD, RNFL loss and development of OA. There may be partial recovery from crush or compression injuries of the optic nerve, although in many cases of trauma, permanent loss of vision may ensue. The effects of orbital emphysema, optic nerve sheath and retrobulbar haemorrhage can be reduced with decompression treatments; however, avulsion and transection are untreatable(462, 463, 465). Subclinical TON has been identified in traumatic brain injury (TBI) and mild traumatic brain injury (mTBI) with reduced RNFL and GCL thickness found on OCT, and histology showing depletion of neurones within the optic tracts, which is considered to be mediated by neuroinflammation and astrocyte proliferation in the acute phases following the insult(463, 466, 467). Other physiological and psychological sequelae of TBI and mTBI can be confounders in the assessment of pRGC damage in TON and its impact on sleep wake, as discussed in Section 2.12.7, as can an associated direct injury to the SCN(468).

2.10.10 Toxic Optic Neuropathy

Toxic damage to the optic nerves is caused by a wide range of substances, which can also affect the optic chiasm and anterior visual pathways due to continuation of histology. Cyanide in tobacco smoke, methanol, antituberculous drugs, antibiotics, quinine and cobalt among many others can injure neurones and myelin leading to visual dysfunction(469, 470). Nutrient deficiencies may create a similar picture, and there can be overlap between toxic and nutritional processes, for example excessive alcohol consumption can lead to direct damage to RGCs but is also associated thiamine and B12 deficiencies which also contribute to RGC injury. In the developed world, nutritional optic neuropathies are rare, however, they can arise secondary to bariatric, gastric or small bowel surgery, inflammatory bowel disease or severe diarrhoea due to a reduction in absorption of thiamine, B12, folate and copper, and behave similarly to toxic optic neuropathies(469-471). A similar pathophysiological pathway of mitochondrial oxidative stress leading to RGC damage and subsequent apoptosis exists between toxic optic neuropathy and HON, and there may be genetic susceptibility. Screening for LHON has been advised in cases of toxic optic neuropathy(472, 473).

Clinical presentation in toxic optic neuropathy is commonly bilateral painless reduction in vision, with a generally symmetrical symptom progression. Marked dyschromatopsia is an early feature, and reduced afferent PLR may be present, with discs initially oedematous and hyperaemic followed by atrophic changes. Similarly, RNFL thickness may be increased initially as a result of neuronal swelling, with long-term atrophic changes ensuing(474). PERG changes appear early and include a reduced P50 implicit time and attenuated N95 wave, with mfERG being less sensitive(475).

2.10.11 Glaucomatous Optic Neuropathies

Participants with glaucoma were not included in the population of this study, as glaucoma was considered as a separate arm of SOMNUS (see Appendices D and E). Glaucoma is a common ocular pathology and non-glaucomatous optic neuropathies are less prevalent. As a form of optic neuropathy, it is relevant to consider glaucoma. In this section, I will discuss the pathophysiology of glaucoma, and two of its major subtypes, POAG and PACG.

It has been predicted that by 2040, the global prevalence of all forms of glaucoma will be 111.8 million. Glaucoma accounts for 11% of blindness in adults aged over 50 years worldwide and is the primary cause of irreversible VI(476-478). Glaucoma is an umbrella term used to describe a heterogeneous group of clinical conditions, all of which comprise progressive degeneration of RGCs and a characteristic optic neuropathy with a distinctive excavated appearance of the optic nerve head and VFD(479). Elevated IOP is often present but is classified as a risk factor rather than an essential for diagnosis(231). Glaucoma is considered to be a neurodegenerative condition, with the mechanism of neuronal loss showing similarities with that of Alzheimer disease (AD) and PD(480-482).

Mechanical damage to the axonal cytoskeleton of RGCs at the level of the lamina cribrosa, in addition to metabolic and biochemical injury, may impair axonal transport in glaucomatous disorders. Anterograde degeneration of long axons and prevention of retrograde transport of neurotrophic factors, chronic hypoxia or ischaemia of the optic nerve head are thought to play a role in pathogenesis(483). Excessive glutamate causing excitotoxicity, mitochondrial dysfunction-related or cellular-mediated destruction, and inflammatory cytokines such as TNF-α and nitric oxide may lead to loss of RGCs in a progressive, degenerative process. This may occur alongside natural apoptosis, resulting in depletion of RGCs at a more rapid rate than expected in normal ageing(481, 484-489). Remodelling and excavation of the optic nerve head with an enlarged cup, notching and pallor of the neuroretinal rim are features on fundoscopy, although the mechanism of glaucomatous OA is not fully understood(490, 491). Glaucomatous OA is associated with early loss of peripheral visual sensitivity(486). Arcuate scotomas are characteristic VFDs, and thinning of the RNFL is a common finding on OCT(492). The adenosinergic system, which is also of interest in the regulation sleep wake, is implicated in the production and outflow of aqueous humour, which has implications for increased IOP in glaucoma. Agonism of A1 adenosine receptors enhances aqueous outflow, and A3 receptor antagonism can prevent opening of channels in the non-pigmented ciliary epithelium and can counter calcium-induced RGC death. A2A antagonism (for example, by caffeine) is protective against retinal ischaemia, as is A1 agonism(493).

2.10.12(a) Primary Open Angle Glaucoma

75% of individuals with glaucoma have POAG, with 55% of cases occurring in females(480). POAG is considered to be a disorder of aqueous humour drainage, leading to an increase in IOP, although exact pathophysiology is unknown. Aqueous humour is produced by the ciliary body and flows into the posterior chamber behind the iris. It then flows into the anterior chamber via the pupil, is drained via the TM and the uveoscleral system and enters the venous system(494). In POAG, the iridotrabecular angle is open and allows movement of the aqueous humour from the posterior chamber to the anterior chamber without impedance. Resistance to drainage of the aqueous humour is thought to be the cause of increased IOP, possibly due to increased collagen and fibrillar substances creating a blockage at the TM(495). Continued pressure on nerve axons causes destruction of RGCs and loss of the peripapillary RNFL(489). POAG tends to be associated with increasing age, high myopia, steroid use and a positive family history, and has a proportionately higher prevalence in ethnic Africans. It has an uncertain, and likely complex genetic basis, with identified gene mutations for *myocilin*, *optineurin*, *WDR36* and *neurotrophin-4* only accounting for a small percentage of all POAG sufferers(492, 495, 496). The nitric oxide-guanylate cylase-cyclic guanosine monophosphate pathway is involved in IOP control and glaucomatous retinal degeneration. Cyclic guanosine monophosphate and nitrite levels have been found to be reduced in POAG, which is hypothesised to affect ocular perfusion pressure, with implications for choroidal and optic nerve head blood flow(497).

2.10.12(b) Primary Angle Closure Glaucoma

PACG has a worldwide prevalence of 0.6% and accounts for 17 million glaucoma cases globally, with 70% of these in Asia(498). Prevalence of PACG is 1.0% in Asian populations and 0.4% in European-derived populations(499, 500). PACG is most common in Inuit, Chinese and Indian ethnicities, and is associated with hyperopia and a positive family history, with a female preponderance in 70% of cases(480). PACG is defined as glaucomatous optic neuropathy in the presence of iridotrabecular contact, or the obstruction of the TM by the iris root of 180˚ circumference or greater. As drainage of the aqueous humour via the TM is disrupted, a build-up of aqueous humour and subsequent increase in IOP occurs(492). Pupillary block can also be responsible for elevated IOP. In this

case, contact between the posterior iris and anterior surface of the lens can prevent aqueous humour moving from the posterior chamber to the anterior chamber via the pupil. Obstruction of flow at this point causes a pressure differential between the posterior and anterior chambers, which causes the iris to billow forwards, at which point, it may obstruct the TM, increasing resistance to aqueous drainage(501). Elevated pressure on axons of the retina and optic nerve over a sustained period results in loss of RGCs and optic neuropathy, with a higher proportion of blindness in PACG than POAG(480, 498). *NNO1*, located on chromosome 11, is the only human gene known to cause PACG, and is also associated with nanophthalmos(502).

2.11 Exogenous Influences of Sleep Wake

An exogenous substance is one that is produced by sources external to the body and then introduced to the body(503). Exogenous substances include anything that is consumed as food or drink, any chemical taken recreationally, any medication administered via any route, and any substance that is natural to the body which has been produced outside of the body, such as synthetic hormones, for example insulin and progesterone. The aim of this section is to discuss common substances which may influence sleep and wake, with particular note to those relevant to individuals participating in this study, either as lifestyle choices, or as part of the management of their conditions, including caffeine, smoking and nicotine, alcohol and prescribed medications.

2.11.1 Caffeine

1,3,7-trimethylxanthine, commonly known as caffeine is likely to be the most commonly used stimulant worldwide due to its ubiquitousness, primarily in beverages(504). It is a competitive antagonist of adenosine receptors throughout the body, and primarily acts at A1 (located in all brain areas) and A2A receptors (located in dopamine-rich regions of the CNS), with A2B and A3 receptors affected to a lesser degree(505). Caffeine disables the adenosinergic drive towards sleep propensity(506), and is able to counteract the effects of sleep inertia following sleep deprivation, leading to short-term improvements in cognitive

and motor performance(504, 507). Concerns exist that caffeine-induced gains in psychomotor function may be offset by rebound sleepiness, over-confidence and a lack of self-awareness, leading to increased operational risks(505, 508). Caffeine has a half-life of 3-7 hours and has been found to lead to sleep disturbance when taken 6 hours before sleep onset, with demonstrable effects on sleep latency (SL) (the time in bed prior to sleep onset) lasting at least 24 hours. Caffeine clearance can be reduced with chronic use, due to a build-up of its major metabolite, paraxanthine (its other metabolites being theobromine and theophylline)(509, 510). Caffeine is largely hepatically metabolised by the cytochrome P450 enzymes CYP1A2 and CYP2A6(511), and factors that inhibit caffeine clearance include liver disease, alcohol intake, grapefruit juice, pregnancy, and the oral contraceptive pill, while smoking induces its breakdown(512). Caffeine intake may have a greater effect in the elderly compared to younger adults(513), and males have been reported to be more susceptible to caffeine-induced anxiety(514). Oestrogen may impact on caffeine metabolism in females, with slowed metabolism in the second half of the menstrual cycle(515).

EEG findings following caffeine administration include increased SL, increased alpha wave spectral power and NREM stage 2 sleep, increased wake episodes in early sleep, and reduced total sleep time(TST) and delta wave spectral power and SWS(516, 517). Caffeine has not been reported to impact on night time REM activity, but has been associated with reduced REM duration following night time sleep deprivation(365, 518).

Polymorphisms in genes coding for CYP1A2 and CYP2A6 (located on chromosomes 15 and 19, respectively(519, 520)), the enzymes responsible for caffeine metabolism, can reduce caffeine clearance, as can variations in the adenosine deaminase (*ADA*) gene (located on chromosome 20(521)), which removes extracellular adenosine(512). Alterations in the *ADORA2A* gene, which is located on chromosome 22 and codes for adenosine A2A receptors(522) can heighten sleep disruption, and an intergenic single nucleotide polymorphism(SNP) near the GBP4 gene (a guanylate binding protein that hydrolyses guanosine triphosphate, an adenosine-like molecule(523)) locus on chromosome 1(524) and an intronic SNP in *PRIMA1* (an organisational protein and neurone membrane anchor for acetylcholinesterase located on chromosome 14(525)) may also linked to caffeine-related sleep disturbance(511, 512, 517).

Caffeine consumption can generate expectancy, such that its anticipated effects augment or occur without its metabolic effects(505). Chronic high doses of caffeine have been reported to lead to tolerance and dependence(526, 527). Acute caffeine withdrawal can lead to fatigue, reduced alertness, concentration difficulties, headache, low mood and irritability(528), which could create a complex picture when assessing sleep wake.

2.11.2 Smoking and Nicotine

Nicotine is the primary addictive chemical found in tobacco in cigarettes, pipes and cigars, and is a major worldwide behavioural health concern. The constituents of smoked tobacco, such as tar, cause an estimated 4 million premature deaths globally(529-531).

In low doses, nicotine has a sedative effect, but in higher concentrations produces heightened arousal and agitation(532). Together with acetylcholine, nicotine inhibits sleep-promoting GABA neurones in the ventrolateral preoptic area (VLPO) by inducing presynaptic noradrenergic terminals and muscarinic postsynaptic activity, and instead promotes wakefulness(533) Activation of nicotinic receptors in the CNS can decrease TST and REM sleep, and induce circadian wake times(534).

The hypothalamus and SCN contain predominantly α7 nicotinic acetylcholine receptors (nAChRs) in adults(535). In mammals, there appears to be a circadian entrainment effect of nicotine on rest and activity(535), with administration generally reported to phase advance the circadian clock, although phase delays have been observed in night-time exposure(536, 537) and an overall suppression of circadian locomotor activity has also been noted(538).

Nicotine consumption is associated with increased alertness and wakefulness, increased SL, reduced TST, reduced REM sleep, increased REM latency (REML), increased NREM stage 2 sleep, reduced SWS, sleep fragmentation and early morning waking, which is dose-dependent(539-542). There is a higher likelihood of sleep disturbances on polysomnography (PSG) and poorer subjective sleep quality in chronic smokers compared to non-smokers, which has also been replicated in studies of transdermal nicotine(539, 543, 544). Increased severity of nicotine addiction is associated with reduced sleep duration, impaired sleep quality, early morning awakening, and increased daytime sleepiness(545), and individuals

who smoke at night are reported to have greater sleep disturbances(546). Withdrawal from nicotine tends to produce a collection of effects, including elevated daytime arousal, cravings, increased night-time awakenings and REM sleep, reduction in subjective sleep quality and depressed mood, which may last over several weeks, meaning those who have recently quit smoking are also likely experience altered sleep(535, 539, 540, 545, 547). Smoking-related respiratory disorders (reflected by an increased apnoea/hypopnoea index (AHI)), also have an adverse impact on sleep quality and quantity, in addition to associated increased parasomnias including PLM(540, 541, 548, 549).

Nicotine may have a beneficial effect on sleep and mood in severe depression, as it may reduce wakefulness and improve SWS, which can be impaired in depressed individuals(530, 540, 550). In addition, there appears to be a greater susceptibility to nicotine dependence in individuals with psychiatric conditions, including depression, anxiety, attention deficit disorders and schizophrenia(534, 551). Depressed mood, irritability restlessness and fear can also be factors in acute and subacute nicotine withdrawal(534, 540). Caffeine consumption has been associated with a temporary increase in smoking urge(552), with increased α4β2 nAChR availability demonstrated in smokers with heavy caffeine use(553).

2.11.2(a) Effects of Smoking on RGC and Optic Nerve Function

Smoking tobacco has been found to reduce orbital and ocular blood flow via vasoconstriction and atherosclerosis, increase local hypoxia and increase oxidative stress to RGCs. This causes DNA and mitochondrial damage and structural changes, and cellular injury via free radicals and caspases, exacerbated by cyanide present in tobacco. Increased induction of apoptosis and autophagy in the presence of nicotine has been found in RCG populations in vitro, with attrition in proportion to intake(554-556). Healthy smokers have been reported to have asymptomatic scotomas on perimetry, poorer retinal sensitivity, thinner RNFL and ganglion cell complexes, and abnormal photopic negative responses and PERG in a dose-dependent manner(557, 558). Smoking can be directly harmful to the optic nerve, resulting in demyelination and toxic optic neuropathy due to the toxic effects of cyanide, reduction in arterial oxygen concentration and restriction of blood flow. Reduction in vitamin B12 levels in smokers has also been reported(556). Presentation with a centrocaecal VFD and corresponding RNFL loss is typical, although optic nerve oedema may

also be present(469, 557, 559). In tissues that are already vulnerable to degeneration, such as in mitochondrial optic neuropathies, mitochondrial DNA replication, oxidative phosphorylation and scavenging of reactive oxygen species can be further reduced, increasing the risk of phenotypic penetrance and visual loss(560, 561).

2.11.3 Alcohol

Alcohol in common terms refers to a drink containing ethanol, and is widely available substance that has been used for millennia due its effects on mood, relaxation, social functioning and sleep(562). Through its sedative effects, alcohol can reduce anxiety, which can drive further consumption, although its impairment of motor and cognitive function may be undesirable. Additionally, the stimulant properties of alcohol include euphoria, and aggressive behaviour, risk taking and sexual arousal can also be precipitated(563). In adult humans, low alcohol intake (1-2 standard drinks) is defined as 0.15-0.49mg/kg. Moderate intake is classified as 0.5-0.4mg/kg (2-4 standard drinks) and high intake (more than four standard drinks) as 0.75mg/kg or greater(564).

The likely mechanism for the stimulatory effects of alcohol is via induction of dopamine release in the striatum(563). Soporific effects may be caused by facilitation of the GABA inhibitory system in the basal forebrain, thalamus, hypothalamus and brainstem reticular activating system, which may account for the association of alcohol with SWS. Specifically, $GABA_A$-receptors in the thalamus, which has a major role in sleep regulation, may be activated extrasynaptically via tonic inhibition, leading to sedation(565). In contrast, alcohol antagonises the glutaminergic system, including NMDA receptors, which has a dominant excitatory role in the CNS, and is implicated in REM sleep induction(566).

Animal studies have found that alcohol increases extracellular adenosine and inhibits cholinergic wake-promoting neurones in the basal forebrain via adenosine A1 receptors (A1R)(562), with in-vitro studies isolating blockade of the equilibrative nucleoside transporter type 1 (ENT1) as a key factor in the build-up of extracellular adenosine(567, 568). Fronto-thalamic damage in individuals with alcohol use disorder and Korsakoff syndrome has been found to be associated with fewer subjective complaints regarding sleep

quality(569). Combined use of alcohol with nicotine is common, the mesocorticolimbic dopamine reward system, which projects from the ventral tegmental area to the nucleus accumbens, being a probable pathway for reinforcement(570, 571), with animal studies demonstrating that a dose of nicotine prior to alcohol administration counters alcohol sedation, maintains wakefulness and normalises NREM sleep, implicating the basal forebrain(572, 573). Similarly, caffeine can also attenuate the hypnotic properties of alcohol, including its effects on SL, and impede its diminution of psychomotor capability and memory(574, 575). However, caffeine has been found to have no effect on human inhibitory behavioural control in the presence of alcohol, and did not efface learning deficiencies caused by alcohol in animals(576-578).

2.11.3(a) Effect of Alcohol on Sleep Structure and Timing

High-dose alcohol was found by Mullin et al in 1933 to reduce SL, body temperature and motility during the first half of sleep, and to increase body temperature and motility during the second half of the night(579). Gresham et al in 1963(580) found that high alcohol intake reduced REM sleep in normal subjects. An increase in SWS during the first half of the night has also been found, as has suppression of REM in the first half of the night and REM rebound in the second half of the night(566).

Following alcohol intoxication with dose 1.1-1.2g/kg and peak breath alcohol concentration 0.11 ± .01 g% in young healthy adults, women have been reported to have higher subjective bedtime sleepiness, and more disrupted sleep on PSG, with reduced TST and increased wake after sleep onset (WASO), although SWS and stage 2 sleep have been found to be higher(581). A moderate dose of 0.45g/kg in women has been found to increase initial sleep intensity, reduce REM sleep and increase stage 4 sleep in the first 2 hours, with no changes in SL or SWS found(582). Animal studies have shown that females of reproductive age have faster alcohol metabolism. Other factors including body composition (women have a higher percentage of body fat, in which alcohol is insoluble), the speed and location of alcohol absorption (women have less gastric metabolism of alcohol, meaning that more is rapidly absorbed via the duodenum), enzyme activity and availability, and genetic factors may be responsible for the disparity in alcohol breakdown and elimination in males and females(583, 584).

A contrasting picture emerges in cases of alcohol tolerance, dependence, addiction and withdrawal when compared to the literature above. Tolerance to the sedative effect of alcohol, including its effect on NREM sleep can develop within a week of repeated exposure, which can contribute to increased alcohol-seeking behaviour to alleviate sleep disturbances and promote alcohol dependence(585, 586). Reinstatement of the original sleep pattern may occur with chronic alcohol exposure, with further disturbance of sleep suggesting dependence(585, 587). PLM have been reported to be higher in alcohol dependence, which can also impact on sleep quality(588). Chronic alcohol use downregulates the inhibition mediated by $GABA_A$, which may increase tolerance to its hypnotic action. It can cause locomotor and homeostatic circadian dyssynchrony, with altered melatonin and GH levels, disrupted NREM and REM sleep, increased SL and reduced TST and SWS(587, 589, 590).

In Brower and Hall's(591) study of recently-abstinent alcohol-dependent subjects, older subjects were found to have increased sleep disturbance. Reduced SWS and dampened REM cadences, sleep fragmentation, disordered timing of sleep onset and wake times, increased somnolence and daytime napping have also been found during acute alcohol withdrawal(592, 593), with reduction in expression of ENT1 and A1R as possible contributors to this process(589). Sleep disturbance may be a risk factor in precipitating relapse in drinking behaviours during acute and chronic withdrawal, and is a necessary consideration in rehabilitation programmes(594, 595).

2.11.3(b) Effect of Alcohol on Obstructive Sleep Apnoea and Periodic Limb Movements

Vinson and colleagues (2010)(596) reported lower risk of OSA in moderate drinkers compared to non-drinkers, and no association of alcohol intake with RLS or sleep quality in a population of primary care patients. However, data was self-reported so the presence of OSA could not be confirmed by PSG and AHI or blood alcohol levels. Simou et al (2018)(597) in their systematic review found that diurnal patterns and habituation of alcohol intake were likely to affect its relationship with OSA, although a positive association was found in studies using objective OSA assessments. It appears that alcohol consumption may increase symptoms of sleep-disordered breathing and alter sleep architecture in individuals who are predisposed to it, as reported in Burgos-Sanchez et al's (2020)(598) systematic review of the effect of alcohol on snoring and sleep apnoea; Scanlan et al (2000)(599) also found that

moderate intake with a blood alcohol level of 0.07g/dL in adult males who snored regularly increased the mean AHI on overnight PSG, with similar results reported in Izumi et al's (2005)(600) study of modest alcohol consumption in healthy adult males, which was also confirmed by Kolla et al's (2018)(601) systematic review.

Aldrich and Shipley (1993)(602) noted a higher incidence of PLM in drinkers, although this may be mitigated by the use of alcohol to reduce sleep disturbances caused by PLM. This does not appear to be the case in younger subjects, in whom difficulty initiating and maintaining sleep have been reported with increased consumption of alcohol(603), with a propensity to an evening chronotype and SJL reported in adolescent exposure(604, 605). A subjective reduction in sleep duration and increased next-day tiredness following an elevated intake of alcohol has been found to affect younger adults to a greater extent than the elderly(606).

2.11.3(c) Effects of Alcohol on RGC and Optic Nerve Function

Alcohol in sufficient quantities can be neurotoxic, and its effects are thought to be due to downregulation of inhibitory GABA neurotransmitter functionality, which affects many neurones within the CNS, including RGCs. Exposure to alcohol in-utero is teratogenic and can alter retinoic acid activity, products of oxygen and nitrogen-based reactions and production and function of PAX6 and OTX2 leading to optic nerve hypoplasia with abnormal flicker ERG. Alcohol exposure during early life has been found to lead to deficiencies in visual function, with altered RGC morphology, including reduction of soma size and dendritic field, and increased dendritic tortuosity, in addition to depletion of the GCL and dorsal LGN, to which RGCs project. This may be associated with dysfunctional expression, behaviour and quantities of neurotrophins(607-609).

Habitual alcohol intake is thought to stimulate apoptosis of RGCs via induction of p53 and suppression of vascular endothelial growth factor (VEGF), which may be dependent on angiotensin II type 1 receptor induction(610). It increases oxidative stress in the mitochondria of RGCs and photoreceptors(556), increasing the risk of visual dysfunction in individuals with susceptible genotypes(611-613). Clinical presentations of longstanding high alcohol consumption comprise loss of RGCs, depletion of RNFL and GCL, macular atrophy

and cognitive deterioration(614). An relationship between chronic alcohol use and POAG has been described, which can also lead to secondary damage to RGCs(608).

Acute alcohol intoxication can lead to disordered mitochondrial electron transport and ATP generation, accumulation of formate and metabolic acidosis. Formic acid impedes cytochrome C oxidase within mitochondria and along with other reactive oxygen species can cause irreversible injury and lysis of neurones, including RGCs. It also restricts axoplasmic transport due to defective ATPase ion channels, causing oedema of neurones and inflammation of the optic nerve. Clinical manifestations include impaired contrast sensitivity and colour vision and altered saccadic eye movements and fixation.

Alcohol optic neuropathy has also been found to be associated with vitamin B12 and folate deficiency and is characterised by demyelination of the retrobulbar optic nerve, retrograde degeneration of RGC axons, reduced VA and colour vision, centrocaecal scotomata and pale, cupped optic discs, and a relationship with deficiencies in cognition have also been reported(556, 608, 615).

2.11.4 Effects of Prescribed Medications on Sleep

2.11.4(a) Glucocorticoids

Endogenous glucocorticoid hormones are produced by the adrenal cortex and have two main classes: mineralocorticoids, such as aldosterone, which is involved in blood pressure and electrolyte modulation; and glucocorticoids, such as cortisol and cortisone that regulate protein, lipid and carbohydrate metabolism and storage, and have anti-inflammatory and immunosuppressive qualities(616-618). Endogenous glucocorticoids are derived from cholesterol and are four-ringed structures containing 17 carbon atoms and a cyclopentanoperhydrophenanthrene framework, and have a pivotal role in the physiological response to stress(618). Endogenous cortisol is secreted in a circadian manner and is regulated via the SCN of the hypothalamus with distal effects on corticotrophin releasing factor (CRF), ACTH and adrenal secretion. Trough levels of cortisol tend to lie between 12am and 2am in normal entrained individuals, with peaks around usual morning wake times(619). Synthetic steroids are used largely due to their anti-inflammatory and

immunosuppressive qualities, with modulation of responses of pro-inflammatory macrophages, mast cells, dendritic cells, eosinophils and lymphocytes, suppression of the pro-inflammatory mediator phospholipase A2, and impedance of the actions of cyclooxygenase A2, interleukins and TNF-α(620). Long-term use of high-dose steroids can cause central adrenal insufficiency due to downregulation of the hypothalamo-pituitary-adrenal (HPA)-axis, so doses need to be tapered cautiously when terminating treatment, with other adverse effects comprising development of the metabolic syndrome, predisposition to type II diabetes, hypertension, obesity, osteoporosis, skin fragility, acne, risk of infection, ocular hypertension, and mood changes, in addition to insomnia, which is likely to be due to HPA-axis interference(619-621).

Chronic conditions relevant to my study which may be treated with high dose systemic glucocorticoids in their acute phases include MS, NMOSD, space-occupying lesions of the CNS, and ADEM(622-626). High-dose glucocorticoid therapy during acute relapses in MS has been found to reduce SWS and REML and increase REM density(627), and glucocorticoid-induced suppression of melatonin has been reported in animal models of MS(628). Glucocorticoid therapy in space-occupying CNS lesions has been observed to worsen subjective insomnia(623, 629). In general, sleep disturbance, including reduction in REM sleep and increased night-time waking has been reported with systemic administration of the synthetic glucocorticoids methylprednisolone, dexamethasone and hydrocortisone(630-632). These sleep disturbances are postulated to precipitate or contribute to the known psychostimulatory side effects of synthetic glucocorticoids(633).

2.11.4(a)(i) Glucocorticoids and Cataract

The association of long-term glucocorticoids and cataract is well-documented and is thought to be due to activation of lens glucocorticoid receptors leading to modified genetic expression within lens epithelial cells. This causes epithelial cell migration and alterations in growth factors including IGF-1, lens epithelium-derived growth factor and transforming growth factor-β. The resulting signal changes lead to reduced differentiation and apoptosis, increased cell proliferation, alterations in sodium-water ion channels and subsequent lens hydration, reduced glutathione and increased reactive oxygen species(634). Several routes of glucocorticoid administration including oral, inhaled, topical and periocular and

intravitreal have been associated with increased prevalence of posterior subcapsular and nuclear sclerotic cataracts(635-639).

2.11.4(b) Opioids

Opioids are commonly used as analgesic agents for severe pain, which itself can cause marked sleep disturbance(640). However, opioids themselves can impact on sleep quality. Animal studies have found that opioids affect mu receptors and dampen sleep driving circuitry in the VLPO, reducing deep sleep and instead promoting wakefulness(641).

Opioids have been reported to increase light sleep (stage 2) and reduce deep sleep (stages 2 and 3) in healthy subjects(642). An acute dose of morphine has been found to reduce SWS and REM sleep in humans, with reduced delta wave power, while increasing alpha wave light sleep(643, 644).

In individuals with opiate addiction, an administration of heroin has been found to reduce measures of TST and sleep efficiency (SE), in addition to delta sleep and REM sleep, with increased muscle tension, wakefulness and number of transitions between sleep stages(645). Methadone has been found to increase electromyogram (EMG) activity, reduce delta wave activity and NREM stages 2-4, and reduce REM sleep, with morphine producing a reduction in NREM stage 2 and increased EMG activity(646). In post-addicts, administration of morphine has been reported to reduce deep sleep (NREM stages 3 and 4), and increase light sleep (NREM stages 1 and 2), with reduction of REM, increased arousal and increased EMG activity(647).

With chronic methadone use and methadone dependence, EEG SWA has been found to increase, and subjects have reported an increase in sleep time, implying adaptation of the CNS to long-term use(648). With chronic use of morphine, there appears to be less adaptation of sleep circuitry, as EEG and subjective measurements of wakefulness do not return to normal levels, implying partial, rather than full tolerance(649, 650).

Opioids can have adverse effects in individuals with sleep-disordered breathing including OSA and central sleep apnoea, as they can cause respiratory suppression and hypo-oxygenation(640).

2.11.4(b)(i) Effect of Opioid Use on the Optic Nerve

Three major types of opioid receptors are present in the CNS: δ, κ and μ(651). δ-Opioid receptors are implicated in neuronal protection against ischaemia-reperfusion injuries and damage due to increased IOP, and are located in high concentrations in the RNFL, RGCs and astrocytes of the optic nerve head(652). δ-Opioid receptors protect against neuronal, and specifically RGC death caused by ischaemic injury by inhibiting key points along the apoptotic pathway. Processes include directly suppressing neuronal injury, reducing sodium-potassium influx, depolarisation and mitochondrial dysfunction, and inhibiting glial activation, free radical release and TNF-α secretion. δ-Opioid receptors also activate survival kinases such as mitogen-activated protein (MAP) kinase, the phosphoinositide (PI)-3/protein kinase B (AKT) pathway, and signal transducer and activator of transcription (STAT) proteins, which in turn prevent glutamate release and neuronal injury due to excitotoxicity(653). In-vivo studies have found reduced production of TNF-α after ischaemia-reperfusion injuries, which has implications for RGC damage in central retinal arterial occlusion; and suppression of TNF-α-mediated matrix metalloproteinase-2 secretion from optic nerve head astrocytes, which are implicated in glaucoma and protection of RGCs, with prevention of TNF-α induction of p-38 MAP and resulting preservation of PERG responses(654-656).

RNFL thickness measurements in opiate misuse have yielded varied results, with some showing increased RNFL thickness compared to healthy controls(657), some reporting comparable results(658), and some finding superior quadrant thinning(659). In-utero exposure to opiates has been associated with ONH(660), and a case of OA subsequent to chronic heroin intoxication has also been reported(651).

2.11.4(c) Psychiatric Medications

There are numerous categories of psychiatric medications, including antidepressants, anxiolytics, antipsychotics, mood stabilisers, antiepileptics, Z-drugs and stimulants(661). It is important to note that sleep can be affected by the underlying affective or psychotic conditions, which are discussed later in this chapter. Administering a particular drug may

have a different affect in healthy subjects compared to those whose sleep may be altered at baseline as a result of their disorder.

Selective serotonin reuptake inhibitors (SSRIs) such as sertraline, citalopram, fluoxetine and paroxetine, are a widely used form of antidepressant, their primary mechanism of action being prevention of serotonin uptake in postsynaptic and pre-synaptic nerve terminals. Serotonergic neurones can be found within frontal cortical, striatal, thalamic, amygdalal, hypothalamic, and hippocampal projections from ascending pathways originating in the medial and dorsal raphe nuclei, and in descending pathways from the raphe nuclei to the spinal cord(662). This increase in usable serotonin alongside a reduction in dopamine-driven activity may be responsible for the association of SSRIs with prolonged REM suppression and PLM, although an increased percentage of REM sleep has also been reported(661, 663, 664). Paroxetine and fluvoxamine have been found to increase subjective dream intensity, and sertraline has been found to increase delta wave sleep and REML in individuals with major depressive disorder (MDD), which may indicate serotonin-related REM suppression followed by cholinergic rebound(665, 666).

Amongst other antidepressant classes, serotonin-noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine, inhibit the reuptake of noradrenaline and dopamine in addition to serotonin(667), and have been found to suppress REM sleep and increase PLM(668). Similarly, mono-amine oxidase inhibitors (MAOIs) such as pargyline and clorgyline have been observed to suppress REM sleep in patients with affective disorder(669), while tricyclic antidepressants (TCAs), such as amitriptyline inhibit serotonin, noradrenaline and dopamine reuptake and have been found to suppress REM sleep and increase REML, but overall improve TST, reduce awakenings and improve SE(667, 670). Nefazadone, a serotonin-2 receptor antagonist and SSRI has been found to have no effect on REM sleep(671).

Benzodiazepines have an anxiolytic and hypnotic action and can be used to reduce anxiety in the short term. However, long-term use can be complicated by the development of dependence and withdrawal symptoms including increased anxiety and depression(672). Benzodiazepines influence GABA-ergic fibres and can reduce the processing of adrenaline, noradrenaline, dopamine, serotonin and acetylcholine, with their impact on sleep being REM suppression, reduced SWS and theta activity, and increased stage 2 sleep(673-675).

Both typical and atypical antipsychotic medications act via dopamine(D_1-D_4), serotonin($5HT_{2A}$, $5HT_{2C}$, $5HT_6$, $5HT_7$), α-adrenergic (α_1,α_2), histamine (H_1) and acetylcholine muscarinic receptor blockade, with antagonism of D_2, α_1 and H_1 receptors hypothesised to contribute to improvement of sleep in patients with schizophrenia(676, 677). Sleep architecture is altered with both classes of medication: typical antipsychotics including haloperidol, thiothixene and flupentixol have been reported to increase TST and SE with reduction in stage 2 latency, while atypical antipsychotics have been observed to increase TST and SE, reduce WASO and stage 2 latency, reduce REM sleep and increase REML. More problematic side effects of typical, and to a lesser extent atypical antipsychotics include sedation, which can have negative social consequences. Atypical antipsychotics can increase the risk of sleep-disordered breathing, unrelated to their effects of weight gain(676, 678-681).

Mood stabilisers are frequently used in the treatment of bipolar disorder, which in both depressive and manic states can profoundly affect sleep(682). Lithium carbonate is the typical mood stabiliser, with carbamazepine, valproic acid, lamotrigine, gabapentin, topiramate and olanzapine having combined mood stabiliser and anti-convulsant properties(661). Lithium has a neuroprotective function, stabilises the balance of neural excitation and antagonism, and facilitates neuroplasticity(683). It has been found to increase delta wave and suppress REM sleep and harmonise circadian rhythms(684, 685).

In epilepsy, good quality sleep of sufficient duration is protective against seizures, and several antiepileptic medications impact on sleep quality and structure. Carbamazepine is of similar structure to TCAs(686), and has been found to improve SWS and SE, and reduce WASO and REM sleep, although increased daytime drowsiness has been reported. Valproic acid produces a general reduction in neuronal excitability, with suppression of glutaminergic activity and increased GABA-ergic activity(687). Valproate can steady circadian rhythm, although it also increases stage 1 sleep and daytime somnolence. Lamotrigine, which blockades sodium channels and has antiglutaminergic and neuroprotective qualities(688), has been observed to reduce the number of transitions between sleep stages and may increase REM but reduce SWS. Gabapentin is of complementary structure to GABA(689), and can increase SWS and REM sleep, reduce stage 1 sleep and night-time awakenings, and attenuate sleep disturbance caused by discomfort in RLS and neurogenic pain(690).

Topiramate causes blockade of voltage-gated sodium and calcium channels, enhances GABA receptors and antagonises kainite/AMPA glutamate receptors(691), with no impact on PSG or subjective sleep parameters reported(692-694).

Z-drugs, for example, zopiclone, zolpidem and zaleplon, are hypnotics intended for the short-term treatment of insomnia, and are short acting GABA agonists that work on the same receptors as benzodiazepines. They have been found to reduce subjective and objective SL without disrupting sleep architecture. However, side effects include daytime sleepiness and there is a low risk of addiction and rebound insomnia on withdrawal(695-698).

2.12 Effects of Endogenous and Internal Factors on Sleep Wake

Endogenous refers to a substance or factor that originates internally or is naturally produced by the body. Endogenous factors may influence an individual's sleep and wake. In this section, I will discuss the endogenous influences that are most relevant to my study population.

2.12.1 Pain

There is a complex, bidirectional interrelationship between sleep and pain(640, 699). Pain is described as "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components"(700). With repeated activation of nociceptive relay systems, mild nociception, a non-nociceptive stimulus, or the absence of a stimulus can invoke a painful response, with development of hyperalgesia (sensitisation of nociceptors through the action of bradykinin, histamine, serotonin, substance P, prostaglandins and acetylcholine), allodynia and central sensitisation (modulation of NMDA fibres at the dorsal horn of the spinal cord, thalamus and cerebral cortex) respectively(701, 702).

Sleep disturbance is a notable feature of acute and chronic pain(702). Acute pain can have a temporary influence on sleep and can cause reduced SWS and REM sleep, with reduced TST

and irregular sleep patterns on PSG(702). It tends to be unpredictable, associated with stress, and caused by a nociceptive response to a recent injury such as surgery(702).

In contrast the impact of chronic pain on sleep is variable: the pathway from bodily insult to a person's experience of pain is less certain, with reduced sleep exacerbating perceived discomfort, and disruption of SWS found to be hyperalgesic(699, 702). Frequently, back pain, muscle pain, headaches and muscle aches can impact during or on transition to REM sleep(699). Call-Schmidt and Richardson found that adults with chronic pain are twice as likely to suffer from sleep disturbance as healthy adults, although subjective sleep quality improved in adults who had experienced chronic pain for longer durations(703). To add complexity, use of analgesic medications for pain can also affect sleep. Non-steroidal anti-inflammatory drugs (NSAIDs) can increase night-time awakenings, reduce SE and delay SWS onset(704). Medications for neuropathic pain such as gabapentin can increase SWS, improve sleep quality and SE and reduce arousal after sleep onset(690, 705). TCAs can increase TST and sleep continuity, suppress REM sleep, and predispose towards PLM(706, 707). Muscle relaxants such as baclofen can affect respiratory function in sleep when taken orally, increase TST, increase NREM and REM duration, improve sleep continuity and reduce WASO(708, 709). Opiate medications, as previously discussed can also reduce SWS, increase arousal in increase muscle tone in sleep(647).

Excessive, insufficient and disturbed sleep have been found in individuals with multiple sclerosis (MS), which may exist in a complex interrelationship with fatigue, depression and anxiety, resulting in a deleterious effect on QOL, although no differences in PSG data have been found between good sleepers and poor sleepers with MS(710-712). In NMOSD, pain is highly prevalent, and has been found to have a greater impact on daily living than in MS(713, 714). Neuropathic, headache, spasticity-associated, arthralgia, connective tissue and vasculitis pain have been reported in NMOSD . There is a positive correlation of pain fatigue and use of NSAID, anticonvulsant and muscle relaxant analgesia (which may also influence sleep as previously described)(713, 715).

There is overlap of arousal and nociceptive function of areas of the CNS, including the mesencephalic periaqueductal grey (PAG) matter, which is theorised to be involved in the "pain gate" mechanism, and the thalamus, which acts as a relay centre of pain information to the sensory cortex(699, 716). Plasticity in cells in the nucleus raphe magnus which

regulate wakefulness and pain has been demonstrated in persistent pain(699). In addition, the HPA-axis stress response is excited by pain and also influences REM sleep through the effects of adrenaline, cortisol, dihydrosphenylglycol and dihyroxyphenylacetic acid. The neurotransmitters serotonin and acetylcholine, and endogenous opioid peptides are also involved in the modulation of both pain and sleep(717, 718), with serotonin affecting mood, which itself may impact on pain, and facilitating REM sleep(699, 718, 719).

Idiopathic intracranial hypertension (IIH) often presents with a nonspecific headache, although it may be characterised by more specific features including aggravation with eye movement and valsalva, retrobulbar pain, unilateral pain, dermatomal distribution, nausea, and vomiting, and of note night time waking(720), with headaches being one of the most frequent types of pain experienced at night along with back pain and muscle aches(699).

2.12.2 Sphincter Dysfunction

Bladder and bowel dysfunction can contribute to poor sleep quality, particularly in the elderly and patients with neurological disorders, such as MS and NMOSD. Bowel symptoms in neurological conditions include constipation and faecal incontinence, while urinary symptoms of detrusor overactivity and detrusor-sphincter dyssynergia may be present. With increasing age, outflow obstruction due to prostatic enlargement is common, with OSA increasing the risk of developing lower urinary tract dysfunction in males(721). Bladder and bowel symptoms are associated with anxiety and depression, which can also affect sleep(722, 723), with depression and symptoms of overactive bladder found to negatively impact on each other(724). Combined bladder and bowel dysfunction has been reported in 87% of patients with NMOSD, while lower urinary tract dysfunction has been found in 74% and bowel problems in 39-73% of patients with MS(725-727). A negative association between nocturia, sleep quality and daytime dysfunction has been described(728), and in a population-wide study, sleep disturbance was found to be positively associated with nocturia and the presence of urinary tract symptoms(729).

2.12.4 Fatigue

Fatigue is prevalent in chronic systemic conditions(730) and has been found to be present in up to 83% of patients with MS and 58-77% of patients with NMOSD(731, 732). Fatigue has been found to correlate with poor sleep quality, in addition to anxiety, depression and worse QOL in MS, with poor mood known to further exacerbate sleep quality and duration(173, 733, 734). Fatigue has also been found to be a predictor of poor sleep quality in NMOSD(735).

2.12.5 Physical Exercise

Zeitgebers are external cues that can modulate biological circadian rhythms. In addition to the light and dark cycle, these can include working times, mealtimes, and other regular tasks, activities or social requirements(736). Physical exercise is a weak zeitgeber, and has been used to modify circadian rhythms in subjects with sleep and mood disorders(737, 738). In general, exercise has been found to increase TST and SWS, as well as reducing REM sleep and increasing REML(739).

Exercise has been hypothesised to impact on sleep via its thermoregulatory effects and the metabolic requirements for body restoration and energy conservation following an episode of physical activity(739). Governance of exercise and sleep involves coordination of the cardiovascular, endocrine and immune systems, of which the cytokine system, particularly the pro-inflammatory IL-1, IL-6 and TNF-α play a prominent role. Each is instrumental in modulating NREM sleep via thermoregulatory and systemic influences and is released with a diurnal rhythm. IL-1 and IL-6 are produced in skeletal muscle in correlation with exercise duration and intensity, and TNF-α released in plasma with sustained activity durations. IL-1 bidirectionally induces serotonin in the hypothalamus, amongst other areas of the CNS, and altering GABAergic transmission(740).

Low physical activity in adults has been associated with poor sleep quality(741, 742), delayed sleep timing(743), and excessively short or long sleep duration(744). Participation in exercise programmes at least weekly has been found to reduce the risk of sleep disorders in middle aged and elderly subjects(745). In aerobically fit males over 60years, reduced SL and

stage 1 sleep, higher SE and SWS with reduced WASO and stage shifts have been found compared to sedentary subjects, though an intense bout of physical exercise in all participants produced an episode of sleep fragmentation(746). Similarly, physically active women over 60 years have been found to have longer TST and better sleep quality compared to those who were sedentary(747). Physical activity has been observed to have a more profound effect on sleep in individuals who lead a more sedentary lifestyle and poorer sleep quality at baseline(738). In comparison, in a study of elite cyclists, no differences in sleep quality and TST were found during rest days compared to intense training, although training increased excretion of adrenaline and noradrenaline, increased REML and reduced REM sleep in the first half of the night(748). This may suggest that at higher baseline fitness, sleep patterns may be more consistent, with less scope for notable improvement.

Resistance training in young adults has been found to improve sleep quality and reduce night-time awakenings with no effect on sleep architecture. Exercise taken in the morning has been observed to have a greater impact on sleep quality than that taken in the afternoon or evening(749, 750). Exercise in dim light conditions has been found to phase delay melatonin rhythms(751), although high-intensity evening exercise in young male adults is reported to prompt a hike in melatonin secretion leading to phase advance, which is postulated to coincide with the homeostatic drive for sleep, and the steepest rise in subjective sleepiness, or the “sleep gate”(752).

2.12.6 Psychological Factors

2.12.6(a) Stress

Stress is defined as “a nonspecific response of the body to any demand”(753). It has cognitive, behavioural and neuroendocrine responses, and can be evaluated through its impact on arousal, perception of aversiveness and uncontrollability(754). The physiological adaptation to non-specific stress responses is termed the General Adaptation Syndrome, in which an initial alarm reaction causes cellular catabolism, adrenal cortex secretion, hypoglycaemia, gastroduodenal erosions, and increased blood viscosity. This is followed by systemic resistance and reversal of these changes, and a further reversal to the alarm reaction in systemic exhaustion(755). The HPA axis and the sympathetic systems are major

protagonists in the human stress response and are also closely involved in sleep wake, with dysregulation found in elderly subjects in response to life trauma, burnout and chronic fatigue, with associated sleep disruption. Similarly, there is a correspondence of immune response in stress and arousal: natural killer (NK) cell activity is upregulated in acute stress and suppressed (along with B and T lymphocyte activity) with chronicity, with alteration of cytokines IL-1β, TNF and interferon reported in fluctuations in stress response and sleep(756-758).

Acute experimental stress has been observed to reduce SWS, REM sleep and SE and increase night-time awakenings in healthy subjects(759), while intensely stressful lived experiences such as bereavement can affect REM sleep for up to two years. Following severe trauma, as in post-traumatic stress disorder (PTSD), nightmares and altered REM sleep are characteristic(757). Cognitive stress has been found to increase SL in subjects with normal sleep and to increase heart rate in individuals with insomnia(760). Individuals with a genetic susceptibility to insomnia have augmented sleep disruption in response to acute stress(758), as do those with an emotion-orientated coping strategy to stress(761). There also appears to be an interrelationship between chronic emotional stress, insomnia and obesity, which may be consistent with diminished leptin and ghrelin levels leading to increased appetite in sleep deprivation(762, 763).

2.12.6(b) Anxiety Disorders

Anxiety disorders are characterised by experiences of disproportionate fear and evasion of particular objects or circumstances in the absence of a real threat. Anxiety disorders are present in a large proportion of the population and have been found to have a lifetime prevalence of 28.8% in the United States(764), and comprise PTSD, panic disorder, social anxiety disorder, specific phobias, OCD and generalised anxiety disorder (GAD)(765). The neural fear wiring system comprises the nucleus accumbens, hippocampus, amygdala, ventrolateral hypothalamus, PAG, brainstem and thalamic nuclei, insular cortex and the prefrontal cortex, suggesting an overlap with the circuitry that regulates sleep wake(765). Anxiety, like depression, has a higher prevalence in individuals with chronic disease and may be interrelated with it(766, 767). Reduced sleep quality has been found in most anxiety disorders, in addition to associated poor daytime functioning(768), with progressive

relaxation and anxiety management training found to improve sleep satisfaction, reduce anxiety symptoms and increase SWS(769).

2.12.6(b)(i) Generalised Anxiety Disorder

GAD, which has a lifetime prevalence of 5.7%(764), is an unshakable state of anxiety of at least 6 months' duration, and occurs in response to a range of events along with a cluster of physical tension symptoms including restlessness, easy tiring, muscle tension, and increased intolerance of uncertainty(765, 770). Exaggeration of responses within the amygdala have been observed, as have those of the medial prefrontal cortex, with increased fear activity demonstrated in the dorsal and rostral anterior cingulate cortex(765). Sleep-maintenance insomnia is a frequent finding, and sleep-onset insomnia is present in some cases. Increased SL and nocturnal awakenings, WASO and stage 1 sleep have been reported, in addition to reduced TST, SWS, REM density and REML(771, 772). Emotional dysregulation in GAD has been found to be associated with sleep disturbance, including reduced sleep duration, reduced SE, teeth grinding, nightmares, difficulty waking up, daytime dysfunction and excessive daytime sleepiness(773). Anxiolytic benzodiazepine medication has been found to alleviate symptoms of sleep disturbance in individuals with GAD(772); however, these medications themselves can impact on REM sleep and SWS as discussed earlier in this chapter.

2.12.6(c) Mood Disorders

Mood disorders comprise unipolar and bipolar disorders. Unipolar disorders include MDD, dysthymic disorder and other forms of depression, whereas bipolar mood disorders constitute bipolar I (manic depressive disorder with episodes of mania and depression), bipolar II (other forms of bipolar disorders which include hypomania), and cyclothymia(774). Diagnostic to the majority of mood disorders is an altered state of sleep wake; their consideration as comorbidities is therefore important. I consider major depression in this section, as it is of particular relevance to my study population.

2.12.6(c)(i) Major Depressive Disorder

MDD is defined as low mood, anhedonia and inhibition of normal social, occupational or educational functioning of duration longer than two weeks. Additional criteria include insomnia (and reduced TST) or hypersomnia, fatigue, weight change, psychomotor agitation or retardation, and thoughts of guilt, worthlessness, death and suicide(775). External factors such as social isolation, repeated stress, bullying and witnessing traumatic events can precipitate depression in some individuals, although there appears to be a genetic and biological predisposition in many cases(776). Insomnia can persist after the resolution of a depressive episode, and can present a higher risk of suicidal ideation(777, 778), highlighting the necessity for strategies to improve sleep quality in this condition. In the US in 2005, the lifetime prevalence of MDD was found to be 13.2%, with a 12-month prevalence of 5.2%, although epidemiology varies widely with time and location(779, 780). Disordered neuronal growth and plasticity and altered synaptic connections are thought to play a role in MDD, as are alterations in neurotrophins, including a reduction in brain-derived neurotrophic factor (BDNF), p11, MicroRNAs, and stress hormones (including cortisol). Higher concentrations of inflammatory cytokines (for example, interleukin and TNF-α) are also likely to contribute, and the BBB may become more porous, allowing infiltration of monocytes and activation of microglia and astrocytes within the CNS, with increased expression of VEGF by macrophages(776). Gut microbiota are also suspected to play a role in MDD(776, 781). Abnormal regulation of the HPA-axis, resulting in increased corticotrophin releasing factor(CRF) and subsequent increases in ACTH and cortisol have also been found, in addition to impairment of neural reward pathways mediated by the nucleus accumbens, hypothalamus, amygdala and hippocampus, which affect energy and motivation, sleep and circadian rhythms, appetite and fear and pleasure reactions(782). Deficiencies in serotonin metabolism and receptor binding have been observed in the thalamus and midbrain in MDD, as has a reduction of dendrites within the anterior cingulate cortex(783). Aberrant sleep architecture reported in MDD includes increased SL and early morning waking, increased time awake at night and REM during the first half of the night, with increased REM density, and reduced SWS and REML, although these vary with age and gender, with sleep differences being more marked at a younger age, and the effects of reduced SWS being more evident in males(784, 785). RLS and PLM are more prevalent in patients with depression than in other psychiatric conditions(786). Antidepressant medications may

improve sleep quality in MDD(671, 784); however, relative to normal subjects who are not taking antidepressants, they do not restore produce a “normal” sleep architecture, as illustrated earlier in this chapter.

2.12.6(d) Seasonal Affective Disorder

The relevance of describing seasonal affective disorder (SAD) is to illustrate the impact that seasonality can have on sleep wake and mood. As the seasons vary, so the balance between the length of exposure to natural light and natural dim light and darkness change in a predictable manner, which can have internal circadian sequelae in mammals and humans. SAD is a subtype of MDD and is characterised by recurrent low mood in the autumn and winter months, with associated hypersomnolence, reduced activity, increase in appetite and hyperphagia, particularly of carbohydrates, weight gain, and reduced libido(787-789). In the northern hemisphere, increasingly northern latitudes have a higher prevalence of SAD in winter months(790) compared to a prevalence of below 0.4%-1% in the United States(791). It has been hypothesised that the extended hours of darkness and diminished hours of natural light produce a delay in circadian phase and increased photoperiod of melatonin secretion in SAD(792, 793), with early morning, and to a lesser extent evening light therapy reported to produce a reduction in depressive affect(787, 794). The principal light response pathway from the retina is via dopaminergic transmission, and it is postulated that in SAD the dopaminergic system is underactive, and that reduced retinal sensitivity may also play a role(787, 792, 795). Other neurotransmitter systems implicated in SAD include the serotonergic system, which also has a role in governance of appetite and feeding behaviours, with low levels of serotonin found to correspond to winter months. Similarly, catecholamine depletion, notably noradrenaline, has been reported, and it is theorised that this results in diminished sympathetic activation and arousal(792, 796). Polymorphisms in the 5-HTTLPR and 5-HT_{2A}-1438G/A serotonin promotor genes, the dopamine receptor gene *DRD4*, the human melanopsin gene *OPN4*, and the clock gene *NPAS2* have been found to be associated with SAD(797-800). No difference in sleep architecture has been found in SAD compared to healthy subjects(793).

2.12.7 Neurological Disorders

Neurological disorders are a vast array of pathologies and aetiologies that impact on the CNS and/or peripheral nervous system (PNS). I will briefly outline disorders relevant to this study in this section. Some neurological disorders have concurrent optic nerve pathology, viz MS, NMOSD, ADEM, CP and PA. Neurodegeneration due to AD will also be considered in this section as it is relevant to CNS circuitry, particularly with regard to monoaminergic systems and loss of pRGCs.

2.12.7(a) Multiple Sclerosis

Sleep problems are higher in MS than in the general population, and are more common in women with MS than in men(801). Fatigue in MS has been found to be associated with delayed circadian phase, sleep disruption and OSA(802, 803), with disability, anxiety, depression, poor sleep and fatigue correlating with low QOL scores(804, 805). Bladder dysfunction and waking up at night to pass urine can contribute to poor sleep in MS, as can pain(806), and PLM is more prevalent in individuals MS compared to healthy individuals(807, 808). Changes in sleep architecture include increased stage 1 sleep, a reduction in TST, increased sleep fragmentation and reduced SE with a higher number of shifts between sleep stages and increased night time awakenings(808). RBD, in which REM sleep is accompanied by abnormal muscle tone and motor activity, is more frequently found in MS and other neurological conditions(809).

2.12.7(b) Neuromyelitis Optica Spectrum Disorder

Subjective and objective poor sleep have been documented in NMOSD, with 70% of patients classified as poor sleepers. Reduced sleep quality has been found to be associated with increased anxiety and depression and poorer QOL and disability(810). Pain, fatigue and sphincter dysfunction are prevalent in NMOSD, and contribute to sleep fragmentation(811, 812). Insomnia has been reported in 35% of patients with NMOSD, which may be aggravated by medication use such as agents for neuropathic pain, anticonvulsants, antidepressants and glucocorticoids, while disrupted circadian timing has also been described(810, 813). Narcolepsy is a well-documented presentation of NMOSD, and

hypersomnolence with low hypocretin levels has been reported, as has sudden onset of daytime sleepiness due to bilateral hypothalamic lesions(814-818). Thalamic atrophy has been found to be accompanied by a reduction in SWS(819). RLS and OSA have been found in 45% and 8% of patients with NMOSD respectively(735, 820).

2.12.7(c) Acute Disseminated Encephalomyelitis

Narcolepsy and hypersomnia with low hypocretin levels and basal ganglia and hypothalamic lesions has been reported in cases of ADEM(821-824). In rare cases, psychiatric symptoms, including insomnia, can be the primary features of ADEM, and at long-term follow-up, increased sleep problems have been reported in children(825-827). There is a paucity of published literature regarding subjective sleep and sleep architecture in ADEM at present. This may be because the incidence of ADEM is highest in children under 10y, and intensive treatment with steroids, immunoglobulins and plasmapheresis is often required(826, 827). In acute settings, evaluation of sleep is unlikely to be possible, and sleep parameters are likely to be affected by a hospital environment and routine.

2.12.7(d) Neurosarcoidosis

There is little published evidence regarding sleep architecture in neurosarcoidosis. Cognitive failure in neurosarcoidosis has been found to be associated with sleep disturbances(828), and lesions of the CNS have been found to impact on sleep wake in case reports. Narcolepsy has been found to be a feature of sarcoid hypothalamic lesions, in addition to sleep fragmentation, hypoventilation and low or non-existent hypocretin levels(829, 830). Hypersomnia has been reported in relation to sarcoid lesions of the basal ganglia, hypothalamus, brainstem and periventricular white matter (surrounding the lateral ventricle) with spontaneous remission observed(831). A case of neurosarcoidosis presenting as depression and insomnia, and a further case presenting with delusions and hypersomnolence have been reported(832, 833). Patients with concurrent pulmonary sarcoidosis are at greater risk of OSA, PLM and RLS(834, 835).

2.12.7(e) Sellar Tumours

Endocrine dysfunction in PA and CP can have notable effects on sleep timing and, and can alter psychological wellbeing, which in turn can disrupt sleep. Insomnia and reduced subjective sleep quality have been found in untreated PA, with alterations in circadian rhythmicity(836). OSA has also been reported to be prevalent in PA, particularly in cases of acromegaly, which has been found to be only partially reversible with intervention(837, 838). Immediately post-resection of PA, fatigue is common, but this has been observed to improve over time(839, 840), although this was not found to be the case in a postoperative study of acromegalic patients who had reduced sleep quality and duration compared to pre-operative assessment, which was associated with depression, anxiety and disease stigma(841).

Secondary narcolepsy as a result of hypothalamic failure in CP has been reported, in addition to sleep-onset REM on PSG, and cases of sleep-disordered breathing(842). CP-related obesity, also known as hypothalamic obesity, which is caused by central endocrine dysregulation, is more likely to result in sleep-disordered breathing compared to BMI-matched subjects without CP(843). Normal sleep wake rhythms with increased sleep fragmentation and excessive daytime sleepiness has been observed in PSG and SL studies of children(844). Subjectively disturbed sleep and daytime sleepiness has been reported following surgical resection of CP(845).

2.12.7(f) The Neurofibromatoses

All forms of neurofibromatosis are associated with anxiety, depression and stress that affect sleep duration and quality(846). Studies of sleep quality in NF1 have yielded mixed results. Increased risk of sleep disturbances has been reported in 50% of children with NF1, including increased SL, difficulties in maintaining sleep and in transitions between sleep and wake, in addition to excessive sweating, night terrors and somnambulation(847). This may be due to central processes of sleep being affected by the presence of neurofibromas and intracranial gliomas damaging important structures in the sleep pathway, in addition to secondary problems caused by the increased risk of impaired cognition and attention. Increased incidence of OSA has also been described in children with NF1 due to upper airway, cranial nerve and medullary involvement(848). In contrast, Perez et al (2015)(849)

found no difference in sleep disorders in NF1 compared to paediatric normative values. Leschziner et al (2013)(850) found elevated PSQI global and component scores in adults with NF1, but no change in circadian timing, and postulated that cognitive and psychological factors such as anxiety, depression and stress were likely to contribute to overall sleep quality, and that unemployment was associated with worse sleep.

Published reports of sleep quality in NF2 are sparse, although hearing loss caused by vestibular schwannoma has been reported to cause tinnitus and psychiatric disorders with associated sleep impairment(851, 852). Both NF1 and NF2 can present with laryngeal pathology, including neurofibromas and schwannomas, which can result in sleep-disordered breathing(853-855). Schwannomatosis is associated with chronic, severe pain due to tumours of the neural sheath, which can lead to poor sleep quality(856).

2.12.7(g) Idiopathic Intracranial Hypertension

An association of subjective sleep disturbance and depression has been found with IIH(857). This may be due to the high prevalence of OSA in IIH, which has been reported to be 47%, with bariatric surgery found to reduce AHI(858, 859). IIH symptomatology has been found to be alleviated with septoplasty surgery for OSA(860), and OSA has been found to be more severe in males than in females with IIH(861). IIH shares common characteristics with fibromyalgia and chronic fatigue syndrome including headaches, fatigue and impaired cognition in addition to sphincter dysfunction, all of which may impair sleep quality(862), particularly as ICP can be increased during sleep, and IIH and migraine share pathological similarities(863).

2.12.7(h) Traumatic Brain Injury and Mild Traumatic Brain Injury

TON may be associated with TBI(463). TBI is the result of rapid acceleration and deceleration shearing forces following traumatic contact producing physiological processes that result in diffuse axonal injury, which impairs stability and function of cell membranes within the CNS, with rupture precipitating glutamate release and spread of toxic metabolites leading to further cellular damage and swelling(864). There is frequently a breach in the BBB which causes release of proinflammatory cytokines, activation of microglia, aggregation of

waste proteins, and reduced efficiency of glymphatic clearance with impaired sleep(865). Sleep-regulatory structures within the hypothalamus, brainstem and reticular activating system can be affected by this metabolic cascade, with a reduction in CSF hypocretin (orexin) levels and orexin-secreting-neurones in the lateral hypothalamus, which are involved in the maintenance of arousal. Histaminergic areas, which are also wake-promoting, can be affected, including the tuberomammillary nucleus, as can noradrenergic, dopaminergic and serotonergic circuits which induce and maintain arousal. Injury to sleep-promoting areas such as the VLPO and median preoptic areas, and the melatonin-producing pineal gland, can lead to a reduction in CSF and serum melatonin post TBI, and direct injury to the retinohypothalamic tract can result in circadian disruption, with animal studies demonstrating disruption in the expression of the clock genes BMAL1 and CRY1 post TBI, and human PER3 gene carriers found to have reduced TST(864, 866).

Insomnia has been reported in 29% of patients post TBI, with 25% suffering from sleep-disordered breathing, 28% hypersomnolence and 4% narcolepsy, all of which are above population norms(864, 867). Subjectively poor sleep quality and increased daytime sleep propensity have also been reported in TBI, with objective findings including increased SL, reduction in TST and increased WASO, and structural changes including elevated SWS and diminished NREM stage 2 sleep. mTBI is defined as a Glasgow Coma Scale of between 13 and 15 following the insult, and sleep disturbance has been reported in 50% of cases, with PSQI global and component scores and levels of insomnia higher than in the general population at 6 months post insult(867, 868).

Due to the array of psychological, emotional and cognitive sequelae of mTBI and TBI, factors such as anxiety, MDD, bipolar disorder, PTSD and use of psychoactive or sleep-altering medications can also impact on sleep quality with increased risk of morbidity in younger patients. Higher prevalence of sleep-disordered breathing may be due to elevated BMI, injury to muscles of respiration, prescribed medications and reduced mobility with supine posturing at night(864, 866). Repeated mTBI and TBI carry a risk of development of AD, and there is an overlap of disease processes, with the chronic pro-inflammatory environment surrounding CNS neurones and infiltration of soluble β-amyloid and Tau protein following brain injury condensing to form plaques and neurofibrillary tangles creating AD-promoting

conditions. AD itself is associated with reduced sleep quality and duration and myriad neuropathological mechanisms of sleep disturbance(865).

2.13 Demographic Influences on Sleep Wake

2.13.1 Sex

Overall, females have reported poorer subjective sleep quality of shorter duration, longer SL and a higher prevalence of insomnia than males(869-871). Poorer quality sleep, and shorter endogenous circadian cycles in females has been confirmed objectively with actigraphy(872-874). Women have been found to be more sensitive to artificial desynchronisation of circadian rhythms, for example shift work, with higher levels of sleep disturbance than in males, and later chronotypes have been found to be associated with depression in young adult females, which may lead to further sleep disturbance(875, 876).

During stages of life, sleep quality in males and females varies, and biological and hormonal changes may contribute to differences in sleep patterns(877). In adolescents, subjective sleep quality has been found to be worse in girls than in boys, which was associated with higher used of screen time in the evenings and increased consumption of caffeinated drinks after dinner(878, 879). Among college students, young adult females have been found to have increased SL, WASO and daytime naps than male students(880). Oestrogen has been found to reduce SL and WASO and increase TST, while progesterone has been found to reduce anxiety and support respiration(881). Subjective sleep quality has been found to be reduced premenstrually and during menstruation, although objectively sleep parameters were comparable across menstrual phases(882-884).

Sleep quality has been found to be reduced in the third trimester of pregnancy, with a higher prevalence of insomnia. In general, pregnancy is associated with poor subjective sleep quality, and risk of RLS is higher which can also lead to sleep disturbance(885). During menopause, hormonal changes and altered body temperature may contribute to the documented increase in SL, sleep disorders and insomnia(886). Reduced levels of progesterone, and an increase in BMI and neck girth may affect night time respiration in women post-menopause, resulting in increased risk of OSA, with a generalised reduction in

melatonin levels also reported(881). Additionally, elevated BMI and low testosterone has been found to contribute to increased prevalence of OSA in middle-aged and older men(887).

In women, sleep quality has been found to deteriorate steadily with age, although this pattern is less predictable for men. In healthy older adults without sleep disorders, subjective sleep quality was poorer in women compared to men, although this did not correspond to objective PSG measurements, which have found to demonstrate worse sleep parameters in men. This indicates that perception of adequate, settled sleep may differ between the sexes(888-890).

2.13.2 Age

Sleep quality, duration and chronotype are affected by advancing age. In children, increased age is associated with a shift to a later chronotype and a reduction in sleep duration(891, 892), with puberty and adolescence producing a marked sleep phase delay, peaking at approximately age 19y(893), which, combined with early school start times cause several years of sustained sleep deprivation and SJL, can impact on mood and academic achievement(894, 895). With transition into adulthood, the circadian clock gradually shifts to a more advanced phase, and tends to stabilise around age 60y(896). For adults of all ages, a positive association of objectively good quality sleep, SWS and memory has been found, with this being stronger in younger adults(897). Objective measurement of sleep parameters in older adults have been found to demonstrate reduced TST, increased WASO, including the number and duration of night-time awakenings, and reduced SE, with only small changes in SL(898), although subjective self-report can produce divergent results, and healthy older adults have been found to be less likely to report poor subjective sleep quality(899). Daytime napping has been found to be of increased frequency, with a shift to early evening in older adults, although lifestyle factors such as retirement, and social and physical aspects may contribute, in addition to cultural and environmental elements such as daytime siestas(900). Improved mental, physical and cognitive wellbeing has been found to positively correlate with subjective sleep quality, with better memory, learning and planning

abilities, and reduction in the prevalence of mood disorders and diabetes in older adults(901). Conversely, short sleep duration has been found to be associated with cerebral atrophic changes and impaired cognitive function and memory(897, 902).

Changes in sleep architecture with age have been reported, including reduced duration of SWS, with smaller and less numerous waveforms, and relatively longer durations of NREM stages 1 and 2, with reduction in sleep spindle generation(903). Reduction in homeostatic sleep and wake pressure may contribute increased sleep fragmentation and reduced sleep timing, which is also reflected by a reduction in amplitude of nocturnal melatonin secretion, with body temperature, cortisol and TSH rhythms also fluctuating within a narrower range. Additionally, a steep reduction in testosterone secretion in males and depleted oestradiol and elevated FSH in females post-menopause may diminish hormonal sleep drive and promote wakefulness(900).

2.14 Relational Aspects of Sleep

Bed partners of individuals with sleeping disorders may experience disturbed sleep, which may affect their physical, social and emotional functioning(904). In studies of OSA, partners of patients reported poor sleep, which was largely found to improve when continuous positive airways pressure (CPAP) was used by OSA sufferers for breathing support(905-907). Similarly, parents of children with sleep disorders have increased daytime sleepiness and reduced parental functioning(908, 909). Resident carers of dependent individuals also experienced marked daytime tiredness, and sleep disturbances related to nocturnal patient needs, which impact on mental wellbeing and QOL(910, 911).

2.15 Measurement of Sleep Wake

Sleep can be measured in terms of its timing, duration and quality using a variety of subjective and objective measures. There is overlap between the two, for example, keeping of a sleep log, which relies on an individual's recall to objectively map their rest and activity(912, 913). Sleep quality can be assessed using objective measures of sleep structure, such as PSG, in combination with subjective questionnaire data. Similarly, actigraphy (a

measure of rest and activity) in combination with sleep logs can provide information regarding sleep timing and duration. Biochemical objective markers include the rise in melatonin secretion in response to dark conditions, often referred to as dim light melatonin onset (DLMO), 24-hour monitoring of melatonin levels, and melatonin suppression on exposure to bright light, known as the melatonin suppression test (MNST)(914-916). Stress-related factors, which may influence sleep are also relevant to gain holistic picture (see Table 1).

Table 1: Evaluation of Sleep Wake

Sleep Timing and Duration	Overall Sleep Quality	Sleep Stress-Related Factors	Sleep Disorders
Pittsburgh Sleep Quality Index (PSQI)(43)	Polysomnography (PSG) in conjunction with questionnaires(917)	Hospital Anxiety and Depression Scale (HADS)(50)	Jupiter Medical Center Questionnaire (JMCQ)(918)
Epworth Sleepiness Scale (ESS)(919)	Pittsburgh Sleep Quality Index (PSQI)(43)	Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)(47, 920)	Sleep Disorders Questionnaire (SDQ)(921)
Morningness-Eveningness Questionnaire (MEQ) (Horne-Ostberg)(48)	Actigraphy (SE)(922)	Functional Outcomes of Sleep Questionnaire (FOSQ)(923)	Berlin Questionnaire(924)
Munich ChronoType Sleep Questionnaire(MCTQ)(174)	Sleep Log(925, 926)	Multiple Sclerosis Quality of Life-54 (MSQOL-54)(927)	Athens Insomnia Scale (AIS)(928)
Actigraphy with Sleep Log(929, 930)	Jenkins Sleep Scale(931)	25-Item National Eye Institute Visual Function Questionnaire 10-Item Neuro-Ophthalmic Supplement (NEI-VFQ-25-NOS)(932)	
Multiple Sleep Latency Test (MSLT)(933)	St. Mary's Hospital Sleep Questionnaire(934)	State-Trait Anxiety Inventory (STAI)(935)	
Maintenance of Wakefulness Test (MWT)(936)	Leeds Sleep Evaluation Questionnaire(937)	Beck Depression Inventory (BDI) and BDI-II(938, 939)	
Melatonin Suppression Test (MNST)(916)		Brief Impact of Vision Impairment Questionnaire (Brief IVI)(940)	
Clock genes(941-944)		Quality of Life in Neurological Disorders (Neuro-QOL) Short Forms(945)	
Stanford Sleepiness Scale(946)		Glasgow Sleep Impact Index (GSII)(947)	

2.15.1 Subjective Markers of Sleep Wake

The subjective is egocentric and pertains to individual perceptions(948). The definitive marker of the timing of the internal circadian clock is assessment of melatonin secretion, either via the saliva, serum or urine. However, this does not measure an individual's experience of their sleep and how this affects their mood, lifestyle and health, and vice versa. By its nature, the sleep period is not always easy to recollect, although generally individuals have some awareness of their bedtime, wake time, whether their sleep was disturbed, and whether they feel rested on awaking from sleep. Subjects with insomnia have been found to underestimate their TST and overestimate their SL compared to objective measurements(949), and sex and age differences in perception of sleep have also been reported(872). A large observational study of subjects 40 years and over found overestimation of both TST and SL when compared to PSG(950).

2.15.1(a) Pittsburgh Sleep Quality Index and Pediatric Sleep Questionnaire

The PSQI is the most commonly used measure of subjective sleep in clinical and research settings(951), and is used in the SOMNUS study (see Appendix D). It was first described by Buysse et al(43) as an accessible and reliable measure of sleep quality, which is measured on an overall score of 0-21 with a score greater than five indicating poor sleep quality. Specific analysis of SL (the time taken from being alert in bed to falling asleep), duration (the total amount of time spent sleeping), efficiency (the amount of time spent asleep compared to the total time in bed), disturbances, sleeping medications and daytime dysfunction (whether function during the day is affected by sleep disturbances) is also measured in its subsections. The PSQI has been found to compare favourably with PSG measurements, although some studies have identified issues in internal consistency, test-retest reliability and a lack of correspondence in PSQI and PSG findings in elderly subjects over 80 years(951, 952).

2.15.1(b) Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is used in the SOMNUS study (see Appendix D) and is a simple, pictorial measure of situational sleep propensity, and has been found to be suitable

for between-group comparisons. The scale runs from 0-24, with normal range between 2-10, and a higher score indicating a higher propensity for daytime sleepiness(919). The ESS has weak correlation with the PSQI(953), Maintenance of Wakefulness Test (MWT) and the MSLT(49), although it has not been found to relate to actigraphy and PSG (953). Its test-retest reliability may be of questionable consistency(49) although it has been found to successfully distinguish subjects with OSA and narcolepsy from normal subjects (919).

2.15.1(c) Morningness-Eveningness Questionnaire

The Morningness-Eveningness Questionnaire (MEQ), also referred to as the Horne-Ostberg sleep questionnaire, classifies subjects into Morning, Evening and Intermediate chronotypes(48, 954), and is used in the SOMNUS study (see Appendix D). Morning types have been found to have an earlier peak oral temperature than those displaying Eveningness, with differences in rising, bedtimes and peak activity times demonstrated between chronotypes. The MEQ is reliable, with age being a factor determining chronotype. Eveningness has been found to be associated with more disordered sleep, with variation in sleep schedules resulting in daytime sleepiness(955, 956). Correspondence of genetic variations with diurnal preference as determined by the MEQ has been found(942, 957). It is worth noting that the MEQ is increasingly being replaced by the MCTQ, which also explores social and work aspects of diurnal behaviour as previously described(174).

2.15.1(d) Munich ChronoType Questionnaire (MCTQ)

The MCTQ evaluates natural sleep propensities on days off compared to sleep on days with an imposed schedule, such as on workdays, and has been found to be useful tool in assessment of chronotype in shiftworkers. It has been reported to strongly correlate with the MEQ and actigraphic readings, and to concur with dim light melatonin onset(958-962).

2.15.1(e) Other Subjective Markers of Sleep Wake

Other measures of subjective sleep quality and timing comprise the Jenkins Sleep Scale, which is a brief 4-item assessment of sleep disturbance over a 4-week period(931, 963). The St. Mary's Hospital Sleep Questionnaire, was developed in hospital patients and assesses an individual's perception of the previous night's sleep(934). The Stanford Sleepiness Scale

examines daytime alertness following sleep deprivation(946, 964), and the Leeds Sleep Evaluation Questionnaire uses a series of 10 self-report visual analogue scales to gauge responses to hypnotic medications(937, 965).

2.15.2 Subjective Measurement of Sleep Disorders

2.15.2(a) Jupiter Medical Center Sleep Questionnaire

The Jupiter Medical Center Sleep Questionnaire (JMCQ) is used in the SOMNUS study (see Appendix D) and assesses sleep quality and timing, with particular regard to sleep disturbance due to symptoms of RLS and OSA (45, 966). This questionnaire is a useful tool in screening for the presence of OSA and RLS, and has been used in studies of adults with mild cognitive impairment and neoplastic disease of the CNS(918, 966).

2.15.2(b) Other Subjective Measurements of Sleep Disorders

Other subjective measures of sleep disorders include the Athens Insomnia Scale (AIS), which has been found to be a valid, consistent and applicable measure of subjective sleep difficulty(928). The Sleep Disorders Questionnaire (SDQ) determines causes of sleep disorder, including OSA, narcolepsy, PLM and psychological sleep disturbance, and has been found to be sensitive in discriminating OSA from narcolepsy(921). The Berlin Questionnaire is used as a screening tool for OSA(924, 967), although has been reported to be of less clinical diagnostic value than the SDQ(968, 969).

2.15.3 Markers of Stress-Related Sleep Factors and Quality of Life

2.15.3(a) Hospital Anxiety and Depression Scale

Many sleep problems can be related to psychological distress rather than circadian dysfunction, which can influence sleep independently of other pathologies(6). The Hospital Anxiety and Depression Scale (HADS) was designed to measure anxiety and depression traits in the general population under 65 years(50), but has since been found to be more effective as a general measurement of distress than clearly distinguishing between depression and anxiety(970, 971), and may be useful in identifying psychiatric disturbance of sleep as

opposed to SCRD. The HADS is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D), each of which has a score out of 21, with a score of 8-10 indicating mild, or possible impairment, 11-15 indicating moderate, or probable impairment, and 16-21 indicating severe impairment(972).

2.15.3(b) Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)(47) is used in the SOMNUS study (see Appendix D), and is a multidimensional measure of health-related QOL (HRQOL) which aims to ascertain the perceived impact of an individual's QOL on their physical, emotional, mental and social wellbeing and daily roles. It has demonstrated high consistency and construct validity in subjects with VI(973), and has been used to ascertain functional status(974). Normative data for the SF-36 has been found to vary across populations in different regions, so results from studies undertaken in new locations may not be comparable to those published in existing literature(975).

2.15.3(c) 25-Item National Eye Institute Visual Function Questionnaire 10-Item Neuro-Ophthalmic Supplement

The NEI-VFQ-25 was developed to evaluate VRQOL in a multicentre study of subjects with a range of visual pathologies, and includes subscales that relate to general health, and aspects of visual function including near, distance and peripheral vision, colour vision and driving in addition to the social and mental health impact of visual pathology on QOL. It was found to be reliable and valid(976). Assessment specific to neuro-ophthalmological conditions using the neuro-ophthalmic supplement (NOS) found to reliably elicit more subtle changes in visual function in subjects with MS, in addition to evaluating diplopia, ptosis and lid droop, focus, motion perception, glare, anisometropia and blurred vision in subjects with neuro-ophthalmological conditions including cranial nerve palsies, myasthenia gravis, ischaemic optic neuropathies and cortical visual loss(932). The NEI-VFQ-25 and the NOS have been used to evaluate QOL at diagnosis and post-intervention in a cohort of 165 patients with newly-diagnosed IIH, and the NOS was found to correlate with improved headache scores and frequency, resolution of transient visual obscurations and VF improvement(977, 978).

2.15.3(d) Other Markers of Stress-Related Sleep Factors and Quality of Life

Other assessments of mood include the State-Trait Anxiety Inventory (STAI)(935, 979), which has been established use as a marker of anxiety in chronic disease(980), and the Beck Depression Inventory (BDI) and BDI-II, which were designed to evaluate the severity of depressive symptomatology rather than diagnose depression, with updated constructs reflecting newer DSM criteria with good reliability and discriminatory values reported(938, 939).

Measurement of HRQOL in neurological conditions includes the Multiple Sclerosis Quality of Life-54 (MSQOL-54) instrument, which is a 54-item assessment tool used to evaluate HRQOL in individuals with MS. It is a composite of the SF-36 and 18 additional items related to MS and has been found to have good structural validity and internal consistency(927, 981, 982). Additionally, the Quality of Life in Neurological Disorders (Neuro-QOL) short form measures HRQOL in neurological disorders, including MS, with domains of social, emotional, cognitive health and physical function(945). It has been found to be have reasonable reliability and validity, and to be responsive to changes in HRQOL status(983).

With regard to the impact of reduced visual function on QOL, the Brief Impact of Vision Impairment Questionnaire (Brief IVI) measures VRQOL in individuals with VI and evaluates visual and emotional functioning. It has been found to be valid and sensitive to changes in VRQOL in a retrospective analysis of multiple cohorts(940). Additionally, the Low Vision Quality of Life questionnaire measures psychometric, functional and social properties of the effects of low vision, and has been found to have good reliability and internal consistency(984), and an array of other questionnaire tools measure VRQOL specific to cataract, glaucoma, AMD and other classes of ocular pathology(985, 986). Specific to neuro-ophthalmology, the Self-Perception supplement of the Adult Strabismus Questionnaire has been found to be valid, and the Amblyopia and Strabismus Questionnaire is recommended to be used in conjunction with other markers of VRQOL to evaluate outcomes in strabismus and amblyopia in adults(986-988). Sleep-related QOL (SRQOL) measures include the Glasgow Sleep Impact Index (GSII), which has been developed to assess SRQOL in individuals with poor sleep, particularly in insomnia, and has been found to have good construct validity and sensitivity to change(947), and the Functional Outcomes of Sleep Questionnaire (FOSQ), which was designed to assess the impact of excessive sleep, for example in OSA, on

activities of daily living, and has been reported to have good reliability and validity(923, 989).

2.15.4 Objective Makers of Sleep Wake

Objective is defined as

"Not being influenced by personal feelings, interpretations or prejudice; based on facts; unbiased(990)"

Objective outcome measures of sleep are measures that are conducted according to a set protocol, are reproducible and quantifiable, and can consistently be interpreted in the same manner. They aim to minimise bias due to individual perceptions or variations(991). In the following sections, I will outline physical and physiological objective measurements of sleep wake followed by biochemical objective measurements. These are relevant as they are frequently used alongside subjective measures of sleep quality and timing. PSG is considered to be a gold standard of sleep metrics and is frequently used for comparison in studies of other sleep measurement tools.

2.15.4(a) Physical and Physiological Measures

Physical relates to the body, whereas physiological refers to bodily functioning(992, 993). Physical measures include rest-activity cycles and reported sleep and wake, whereas physiological measures include peripheral oxygen saturation, respiratory function, body temperature, and electrical brain, ocular, cardiac and muscle activity(994). Actigraphy is an example of the first, whereas PSG comprises a combination of physical and physiological measures, which I will discuss below.

2.15.4(a)(i) Actigraphy

Actigraphy allows ambulatory recording of rest and activity over a set period of hours, days or weeks. The measurement device usually takes the form of an accelerometer, which is worn on the non-dominant wrist, from which stored data can then be analysed(995, 996). It

is considered a valid measure of sleep wake and can be used to diagnose circadian rhythm abnormalities, including delayed, advanced and non-24-hour sleep wake disorders(997).

2.15.4(a)(ii) Polysomnography

PSG is considered the gold standard objective measure of sleep(998). It comprises the simultaneous assessment of EEG from electrodes positioned in a standard pattern across the head, ocular movements via EOG, and muscle tone via EMG and is usually conducted overnight(999). A hypnogram is the pattern of different sleep stages (wake, S1-S4, REM) that is determined from the EOG and EMG readings obtained(1000). PSG determines sleep stage and is often combined with pulse oximetry and measures of respiration, heart rate and rhythm and blood pressure to assist in the diagnosis of OSA and PLM disorder(1001, 1002), however is unlikely to generate new information in the diagnosis of APSD or DPSD(181).

2.15.4(a)(iii) Multiple Sleep Latency Test

The MSLT, a valid objective measure of sleep propensity, quantifies how quickly an individual falls asleep. It is a standard investigation for narcolepsy but not for circadian dysregulation(1003). The MSLT is often performed the day following overnight PSG and involves multiple sequential physical and physiological outcomes, including EEG, EOG, EMG, ECG and respiratory flow(933).

2.15.4(a)(iv) Maintenance of Wakefulness Test

The MWT(936) is an objective assessment of an individual's capacity to stay awake over a set duration, and can be used to identify excessive daytime sleepiness and unintentional sleep events, and is relevant in industrial safety(1004).

2.15.4(a)(v) Sleep Logs or Diaries

Sleep logs or diaries are generally self-recorded by study participants but aim to provide semi-objective data regarding SL, duration, depth, night-time awakenings and daytime naps. In normal subjects, these have demonstrated good concordance with PSG, but this may not

be true of chronic insomnia(1005, 1006). Sleep diaries are indicated in the assessment of advanced, FR and irregular sleep-wake disorders(181).

2.15.4(b) Biochemical Measures

2.15.4(b)(i) Serum, Salivary and Urinary Melatonin and Melatonin Suppression Test

Serum melatonin (N-acetyl-5-methoxytryptamine) is a direct marker of melatonin release by the pineal gland, ocular and other body tissues in accordance with the circadian cycle. It can be measured at sequential intervals during the day and night, and is analysed by radioimmunoassay(RIA)(1007), enzyme-linked immunosorbent assay (ELISA), or electrochemiluminescence immunoassay (ECLIA)(1008-1010). It is recommended that melatonin sampling takes place under constant conditions(1011), with relatively constant positioning, as serum and salivary melatonin concentrations are increased in standing compared to supine(1012). Salivary melatonin analysis has been found to accurately reflect serum melatonin(1011), although collection of salivary samples may be practically more challenging than serum collection as a subject needs to be awake, whereas serum can be sampled via a peripheral cannula in a subject who is asleep(1013). Measurement of urinary melatonin is via 6-sulphatoxymelatonin (aMT6s), melatonin's primary urinary metabolite, which reliably corresponds to serum melatonin, and can also be measured by RIA and ELISA(1008). The MNST aims to determine function of the RHT and its relations to the pineal gland, using melatonin as a marker. It involves exposure of subjects to bright light over a set period (90-100 minutes) at the expected peak plasma melatonin onset. A positive test result is achieved if there is a 33% drop in plasma melatonin compared to the reading taken 60 minutes prior(916).

2.15.5 Genetic Markers

An array of mammalian circadian clock genes have been identified in the determination of chronotype known as clock and clock-related genes (*Bmal1; CLOCK; PER1, PER2, PER3; CRY1, CRY2; REV-ERBα; RORα, RORβ, RORγ; NPAS2; CK1ε, CK1δ*), which in their mutated states may lead to loss of rhythmicity and altered circadian period(1014-1016). A single nucleotide

variation in *CLOCK* (*CK*) has been observed to lead to a preference for eveningness(1017), although other studies have not found this association(797, 1018, 1019). Genetic polymorphisms of *PER2* and a missense mutation of *CK1δ* have been noted to correlate with familial advanced sleep phase syndrome(941, 1020-1022), and a silent polymorphism of *PER1* has been found to be associated with extreme diurnal preference, as has a length polymorphism of *PER3*, which has also been ascertained to relate to DPSD(942, 957, 1023). No published studies have yet performed analysis of clock genes in relation to OND and sleep wake.

2.16 Summary

Sleep is important for health and wellbeing, and sleep cycles are under circadian control, which relies on functional RGCs within the optic nerves to deliver light information to the SCN. Optic nerve function can be measured in the clinical setting with simple tests such as VA, colour vision, contrast sensitivity and pupillary responses. Formal VF testing is frequently a requirement, as it shows correspondence to RGC function. ERG is involved and time-consuming but is of great value in isolating RGC responses and detecting optic nerve pathology in its early stages. OND have a wide range of aetiologies, but all involve RGC dysfunction and associated loss of visual function.

Circadian misalignment can be debilitating, and can be seen in individuals with poor vision, while shift work and jet lag often require an individual to adjust to a sleep wake cycle that is in conflict with their natural circadian phase. Other non-circadian sleep disorders are also prevalent, including OSA, RLS, PLM and narcolepsy.

Other influences on sleep quality, duration and timing include exogenous factors, including substances such as caffeine, smoking, alcohol and prescribed medications, some of which may also affect RGC function and cause alterations to circadian physiology and influence other aspects of sleep. Endogenous processes including pain, sphincter dysfunction and fatigue can interfere with sustained sleep and cause nighttime waking, sleep fragmentation and excessive daytime sleepiness, and while physical exercise can be beneficial to healthy sleep its timing can affect sleep quality, while low levels of physical activity can negatively

impact on sleep. Physical activity and other lifestyle influences such as social activities and mealtimes can have a weak effect on circadian timing and are known as zeitgebers.

Psychiatric morbidity, including anxiety and depression, can lead to altered sleep quality, duration and timing, which may contribute to the diagnosis of these conditions, while chronic neurological diseases associated with OND have systemic manifestations that can effect alterations in sleep physiology and architecture and can lead to reduced sleep quality.

Sleep quality, duration and timing can be evaluated subjectively and objectively, and biochemical measures such as melatonin can assess circadian rhythmicity. Genetic studies of clock genes are a developing field.

It is evident that sleep and the conditions which shape its dimensions are multifactorial and complex. Quantifying the impact of each contributor to sleep quality is challenging, but consideration of sleep quality is clearly important in the clinical setting because of the health benefits of good quality sleep and the detrimental effects of sleep impairment. It is therefore pertinent to evaluate sleep quality, duration and timing in healthcare and to attempt to parse the contribution of discrete components that influence sleep. The scope of this study is to evaluate sleep quality and timing in a population with OND, as their experience of sleep may face the additional challenges of circadian dysregulation mediated by RGC damage, the psychological burden of their pathology, and the impact of chronic systemic conditions which often coexist with OND.

Chapter 3: Systematic Literature Review

3.1 Introduction

This chapter comprises a systematic review of published studies relating to the impact of OND and glaucomatous optic neuropathy on sleep quality and timing.

From current evidence described in my background chapter it is clear that sleep quality is affected in individuals with VI. Individuals with visual loss due to OND are likely to have damage to RGCs which may affect the integrity of the RHT and circadian functioning. This may affect sleep quality and timing along with other endogenous and exogenous influences on sleep, and forms the rationale for my systematic review.

The objective of my review was to evaluate current published literature regarding subjective sleep quality and timing in OND. I have included glaucomatous optic neuropathy in my literature as it is frequently considered alongside OND as it also demonstrates loss of pRGCs, as opposed to other common ocular conditions such as cataract and age-related macular degeneration where VI is a result of an opaque obstruction of the visual axis and degeneration of photoreceptors, respectively(1024, 1025). However, due to its specific characteristics and prevalence, glaucoma has been investigated in a separate arm of SOMNUS and is not evaluated in my observational study of OND and sleep wake.

I commence this chapter by describing my systematic search strategy. This included four databases (Medline, EMBASE, PsychINFO and PubMed), and reference lists of retrieved studies. I then describe and compare the results from the 43 original studies yielded, identifying notable themes found in the papers, using the broad pathological classifications of OND, hereditary diseases, neurological diseases and glaucoma, with the specifics of OND and glaucomatous pathologies detailed in Chapter 2. I then describe conspicuous themes, including the assessment of visual function, the use of control groups and sample size, and illustrate the quality assessment that I conducted. My background chapter describes outcome measures of sleep wake frequently used in the literature.

I have summarised my data descriptively. Meta-analysis was not applicable due to heterogeneity in study designs and outcome measures used. Out of 43 studies, 34

demonstrated a measurable effect on subjective sleep quality and timing in subjects with OND or glaucomatous conditions. A further two studies showed differences in objective but not subjective markers of sleep wake(114, 115), three were inconclusive(812, 1026, 1027) and four found no effect(280, 1028-1030).

The overall findings indicate that OND and glaucomatous conditions have an impact on sleep quality, duration and timing. This may be related to damage or loss of pRGCs and light input to the RHT from the optic nerves, with consequent reduction in light entrainment of the circadian system. However, due to the complex systemic nature of some pathologies which affect the optic nerves, lifestyle and other factors, there are many possible contributors, as discussed in Chapter 2.

3.2 Methods

I used the 2020 PRISMA checklist(1031) to search systematically for relevant publications (for full details see Appendix A), and the PICOS (Population, Intervention, Comparison, Outcome, Study type) search tool(1032) to construct my search strategy, as per Table 2.

I registered my review in the PROSPERO international register of systematic reviews with the title “The Impact of Optic Nerve Disorders and Glaucomatous Conditions on Sleep Wake (Circadian) Rhythms” (reference CRD42017083345)(1033).

Table 2: PICOS Search Strategy (Adapted from Methley et al, 2014(1032))

	Search Tool	Search Terms (See Appendix B)
P	Population	All search terms relating to OND or glaucoma
I	Intervention	All terms relating to subjective sleep quality and timing
C	Comparison	N/A
O	Outcome	Subjective sleep quality and timing
S	Study Type	Original Research – interventional and observational Studies Qualitative and quantitative research

My eligibility criteria included: Original Research, English Language, Human subjects, and publication in a peer-reviewed journal. I did not apply limits to the date of publication, study design, or outcome measures used, as I expected that the number of studies meeting the criteria would be small. I excluded conference abstracts and review papers. My requirements were that studies assessed subjective sleep quality or timing in subjects with an OND or a glaucomatous condition. I excluded publications addressing other forms of sleep disorder (for example OSA and, PLM, RLS and narcolepsy), unless sleep quality and/or timing were also considered, as these do not primarily relate to endogenous circadian rhythms. I also excluded acute postoperative studies, which could be highly impacted by environmental factors (such as hospital wards) and pain.

3.2.1 Information Sources

I conducted my literature search from 19th November 2021 to 20th November 2021. I used the Healthcare Databases Advanced Search (HDAS) via NHS OpenAthens to search the Medline, EMBASE, PsychINFO and PubMed databases, and did not apply limitations to the year of search.

A full electronic search strategy can be found in Appendix B. The key words I used included “optic atroph*”, “glaucoma*”, “sleep qualit*” “sleep tim*”. Where appropriate, I used expanded search terms (ADJ3) and the Medical Subject Headings (MeSH) thesaurus for key

words and terms to capture as many relevant pathologies or outcome measures as possible. I limited my search to include human studies, primary research and English language. I then searched the reference lists of relevant articles. This yielded 119 relevant results, which was reduced to 45 studies once duplicates were removed. Figure 4 indicates my selection process.

Additionally, I searched the reference lists of original papers and reviews describing blind or visually impaired subjects in relation to sleep wake and found five further relevant studies. On reading the full text of the 50 studies yielded, seven were excluded as they did not specifically address sleep quality or timing in OND or glaucoma, leaving a total of 43 studies.

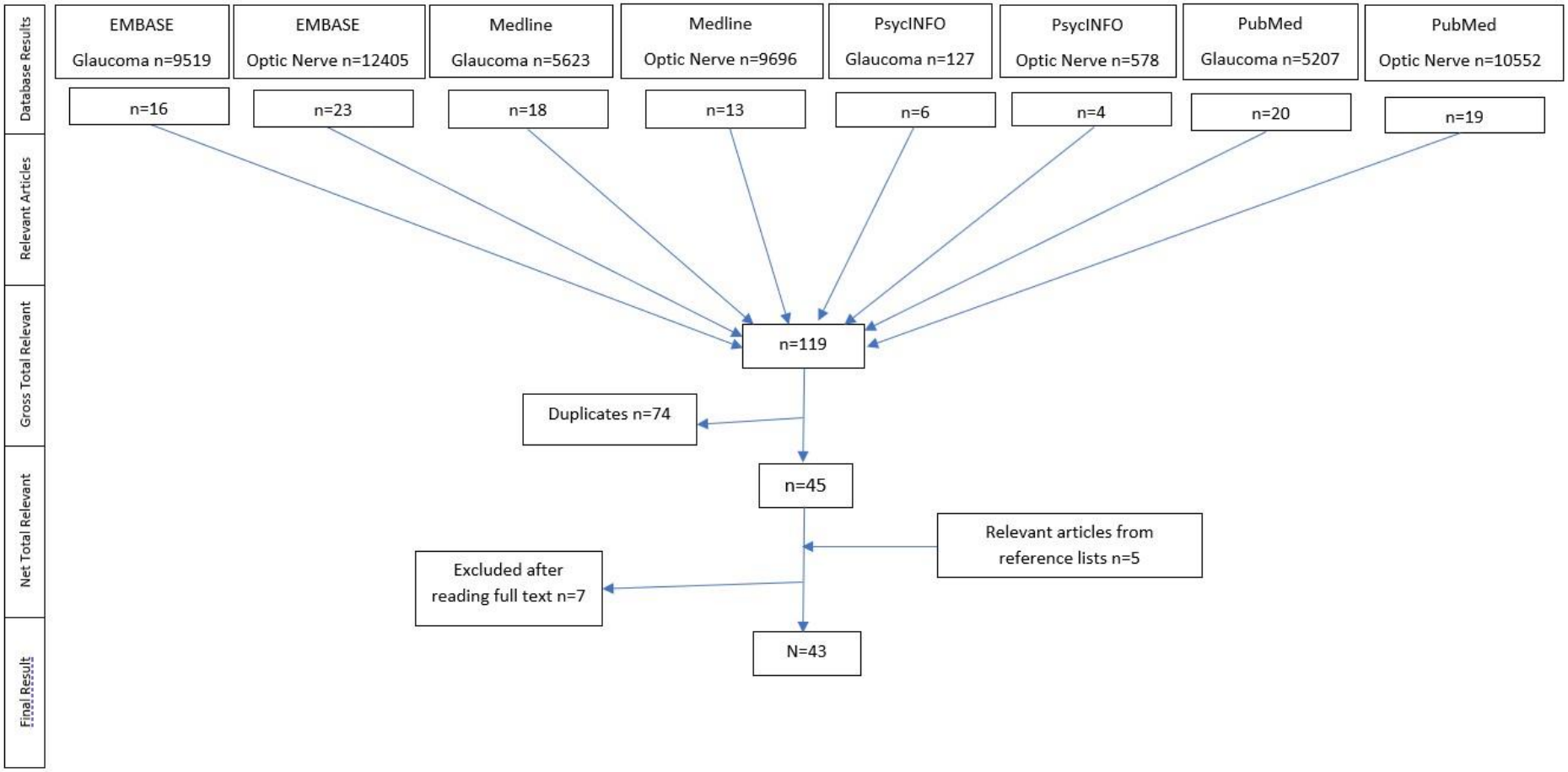


Figure 4: Systematic Literature Search November 2021-January 2022

3.3 Results of Literature Search

In total, I identified 43 studies relevant to OND, glaucoma and subjective sleep quality, which are summarised in Table 3. In general, OND appeared to be associated with poor sleep quality and timing. I have arranged the studies in general pathological groupings of OND and glaucoma and have included a more in-depth results table in Appendix C. I will examine the content of each of these studies in this chapter, with particular attention to the themes of optic nerve and glaucomatous pathologies, visual assessment, comparison of control subjects, exclusion criteria used and sample size. I will then discuss the rigour of the studies yielded, including the quality of the study designs used. I will then give a comprehensive overview of my results categorised according to outcome measures used.

Table 3: Systematic Literature Search Results

Author(s)	Pathology Type	Subjects	Study Design	Findings	Comments
1. Prihodova et al (2021)(1028)	LHON, DOA	LHON/DOA: 13 symptomatic, 23 asymptomatic	Cross-sectional	PSQI, ESS: No difference in scores (p>0.05). PSG: No correlation with subjective sleep data (p>0.05)	No true control group
2. La Morgia et al (2010)(1034)	LHON, DOA	9 HON, 9 NS controls	Cross-sectional	PSQI: Positive correlation with melatonin suppression in HON & controls (p=0.019) ESS, MEQ: No difference (p>0.05); SF-36: Worse in HON (P<0.05)	Detailed ophthalmological data Small sample size
3.Munch et al (2015)(280)	HON, OAG	11 HON, 11 OAG, 22 NS controls	Cross-sectional	OAG subjects sleepier during LE (p=0.016). PSQI worse in HON and OAG (p<0.041)	Detailed ophthalmological data VA worse HON>OAG (p=0.005) OAG group older>HON (p<0.009) Small numbers
4.Flynn-Evans et al (2014)(1035)	OA, glaucoma	6 OA, 8 glaucoma	Cross-sectional	Sleep diaries/urinary aMT6s: 57% OA & glaucoma subjects normally entrained NPL vision, 50% normally entrained, 50% abnormally /non-entrained	No NS control group Small numbers
5.Lockley et al (1997)(1036)	Buphthalmos, TON, congenital OA	1 buphthalmos, NPL; 1 TON, NPL; 1 congenital OA, VA≥3/60	Cross-sectional	PSQI:5 in buphthalmos; 14 in TON; 7 in congenital OA	No control group Small numbers
6.Adeoti (2010)(1037)	Glaucoma, OA	56 glaucoma, 10 OA	Cross-sectional	PSQI: Mean score 8.6±3.1 glaucoma, 9.9±3.4 OA Daytime napping 62.5% glaucoma, 50% OA. Short sleep 50% glaucoma, 60% OA. Interrupted sleep 30.35% glaucoma, 20% OA. Increased SL 21.43% glaucoma, 0% OA	No control group Non-validated questionnaire

7.Tabandeh et al (1998)(15)	OND, glaucoma	45 OND, glaucoma, 44 NS controls	Cross-sectional	PSQI: Mean 6.6±4.3 OND/glaucoma, 2.9±0.5 controls. Correlation of sleep quality with visual loss (NPL vision vs PL or better vision vs controls (p<0.001))	No group demographics No statistical analysis
8.Wee & Van Gelder (2004)(114)	OND	11 OND/glaucoma, 14 other VI, 12 NS controls	Cross-sectional	Sleep quality questionnaire: Comparable Actigraphy: Higher nap time, wake time instability, SL in OND compared to other VI and NS (p<0.01, p=0.02, p=0.02)	Sleep quality questionnaire not validated Differences in morning alarms
9.Bischoff et al (2015)(305)	WS	n=19 WS, n=25 T1DM, n=25 HC	Cross-sectional	PSQ: More symptoms WS (p=0.001). Increased sleepiness in WS (p=0.01). WS more at risk of sleep problems (p<0.01) n=6 with WS hypersomnolence disorder	No ophthalmological examination PSQI performed in WS over 18, but not reported Small sample
10.Webb et al (2010)(1038)	SOD	6 SOD, 10 HC	Cross-sectional	Sleep diary, actigraphy: Reduced SE SOD (p<0.001)	Small numbers VA, no VF
11.Rech et al (2020)(1039)	BBSOAS	54 BBSOAS	Observational	Sleep difficulties 61%	No control No validated questionnaires
12.Pickering et al (2014)(974)	CP	15 treated CP, 15 HC	Cross-sectional	PSQI: Increased SL, daytime dysfunction in CP (p=0.04, p=0.05) SF-36: Lower general health in CP (p=0.01) Actigraphy: Earlier morning wake times CP (p=0.01)	NPL vision excluded No visual assessment
13.Joustra et al (2014)(1040)	NFMA and CP	17 NFMA, 17 HC, 8 CP	Cross-sectional	VFD 82% NFMA, 88% CP Berlin Questionnaire: Impaired sleep quality in NFMA, CP (p<0.05; p=0.004) CSS: Impaired sleep quality in NFMA, CP (p<0.05; p=0.01); ESS: Increased in CP (p=0.02)	No detailed visual assessment

				SF-36: Poorer function in NFMA. CP (p<0.05; p=0.001)	
14.Sagan et al (2021)(1041)	PA	29 PA, including 15 OCC	Pre- and post resection	PSQI: Improved sleep quality, duration & SE (p<0.05) ESS: Comparable pre & post in OCC (p>0.05) SF-36: Correlation of ESS in OCC and no OCC (P<0.05)	No visual assessment recorded Small sample No HC
15.Romeijn et al (2012)(1042)	Suprasellar tumour ± OCC	33 OCC, 17 no OCC	Cross-sectional	PSQI: Later bedtimes in OCC (p=0.03); ESS comparable (p=0.71) 24-hour skin temperature: Daytime gradient lower in OCC (p=0.03)	No ophthalmological assessment No HC
16.Borgers et al (2011)(1043)	Sellar tumour ±OCC	38 OCC, 18 no OCC	Cross-sectional	PSQI: Comparable (p=0.238). Later habitual bedtime in OCC (p=0.044); ESS: Comparable (p=0.879); AIS comparable (p=0.279) Actigraphy: Shorter TST, later sleep onset in OCC (p=0.034, p=0.020)	No ophthalmological assessment No HC
17.DelRosso et al (2014)(468)	TON	38yF, B/L optic nerve & chiasm damage	Case report	Modified ESS: 10/18 PSG: TST 325 min, SL 48 min, WASO 143 min, SE 52% Hypnogram: Multiple awakenings	Single-subject No confirmation of VA
18.Tian et al (2014)(1044)	TON: IOFB touching optic nerve	5 IOFB, lateral orbitotomy for removal	Case series	Sleep difficulties in n=2, improved post removal Anxiety in n=3 subjects, resolved post removal VA improved in n=3	Small numbers No HC
19.Tsika et al (2015)(1045)	AION	8 B/L AION, 10 U/L AION, 29 NS controls	Cross-sectional	PSQI: Comparable (p=0.27) MEQ: U/L AION & HC - morning types. B/L AION intermediate types	Detailed ophthalmological data Small numbers

20.Hishikawa et al (2019)(1046)	SMON	106 with SMON, 110 HC	Cross-sectional	PSQI: Poor sleep in 75.6% SMON vs 39.6% HC. All subscales worse in SMON (p<0.05) AIS: Insomnia in 89.6% SMON vs 54.4% HC. All subscale components worse in SMON (all p<0.01)) ESS: All subscale components worse in SMON (p<0.01)	No assessment of vision
21.Turkoglu et al (2020)(1047)	MS ± ON	10 MON; 16 SMS, including 8 SON	Cross-sectional	PSQI: Comparable (p=0.326) ESS: Higher in MON (p=0.07). Higher in MON/SON vs other SMS (p=0.027) PSG: MON: Reduced SL, REML, TWT (p=0.026, p=0.038, p<0.001). Increased SE, NREM (p=0.023, p=0.022); Serum melatonin lower in MON (p=0.042)	Small sample No visual function data No HC
22.Barzegar et al (2018)(812)	NMOSD, MS	41 NMOSD, 136 MS	Cross-sectional	PSQI: Comparable (p>0.05) Worse depression scores in NMOSD (p<0.01)	No visual assessment No HC
23.Shi et al (2016)(1048)	NMOSD	n=73 with NMOSD	Cross-sectional	PSQI: Mean 7.74±4.4. 68% poor sleepers (score >5) MSQOL-54: Correlation of PSQI with physical component (p<0.01)	No visual assessment No HC
24.Miao et al (2017)(1049)	NMOSD	42 stable NMOSD	Cross-sectional	PSQI: 64% poor sleep. Mean 7.5±4.9. Correlation of PSQI & depression (p=0.001), pain (p=0.006), EDSS (p=0.024)	No visual assessment No HC
25.Pan et al (2015)(1050)	NMOSD	33 NMOSD, 20 HC	Cross-sectional	Fatigue higher in NMOSD (p=0.002) PSQI: Higher in NMOSD with fatigue than NMOSD without fatigue (p=0.046) ESS: Higher in NMOSD with fatigue (7.3±1.3) vs NMOSD without fatigue (3.8±0.7)	No visual assessment

26.Seok et al (2017)(1026)	NMOSD ± fatigue	25 NMOSD + fatigue, 10 NMOSD without fatigue	Cross-sectional	PSQI: NMOSD + fatigue: Poorer sleep quality (p=0.009), higher prevalence of poor sleepers (p=0.004) BDI-II: Depression worse in NMOSD + fatigue (p=0.001); SF-36: Physical, mental components worse in NMOSD + fatigue (p=0.033, p=0.04)	No visual assessment No HC
27.La Morgia et al (2016)(115)	AD	16 AD, 10 HC	Cross-sectional	ESS/PSQI: Comparable (p>0.05) OCT: RNFL thickness reduced in AD (p=0.04) Actigraphy: Reduced SE in AD (p=0.001)	No assessment of VA or VF Small numbers
28.Leger et al (2002)(1051)	Glaucoma	8 glaucoma, registered blind, 24 NS controls	Cross-sectional	PSQI: All glaucoma (n=8) had PSQI>5	Small numbers
29.Gubin et al (2021)(1052)	POAG	65 S-POAG, 50 A-POAG	Interventional pre & post- 90d melatonin	Sleep diaries at baseline: Sleep duration shorter, sleep phase longer in A-POAG (p<0.01, p=0.02) PSQI improved post intervention in S-POAG & A-POAG (p<0.01)	Detailed visual assessment No HC
30.Gubin et al (2019)(1053)	POAG	Same sample as Gubin et al (2021)	Cross-sectional	MEQ: A-POAG more morningness (p<0.05) RCG loss associated with delayed phase body temperature rhythm (P<0.00001)	No HC
31.Gracitelli et al (2016)(1054)	POAG	30 POAG, 10 NS controls	Cross-sectional	ESS: Higher in glaucoma (p=0.029) Correlation of ESS with glaucoma severity (p<0.001) PSG: ESS associated with more/longer night-time arousals (p=0.039, p<0.001). Inverse correlation of ESS with SE (p=0.002)	Detailed ophthalmological examination
32.Lanzani et al (2012)(1055)	POAG	n=9 B/L A-POAG, 9 HC	Cross-sectional	Sleep log/questionnaire: Poor subjective sleep quality more prevalent in A-POAG	Detailed ophthalmological examination Small numbers

				Actigraphy: Longer wake times, less TST, lower SE in glaucoma (p<0.05, p<0.05, p<0.01)	
33.Ma et al (2018)(1056)	PACG, POAG	80 PACG,120 POAG, 120 HC	Cross-sectional	PSQI: Sleep disorder more prevalent PACG (p=0.000) Morning serum melatonin: Higher in PACG and POAG (p<0.001)	Only IOP recorded. No VA/VF/disc assessment Large sample
34.Wang et al (2013)(641)	POAG, PACG	92 POAG, 48 PACG, 210 HC	Cross-sectional	PSQI: Higher prevalence of sleep disorder in POAG (p<0.05) Higher prevalence of sleep disturbance in PACG 41-80y & 61-80y (p<0.001, p<0.05)	Large numbers
35.Chin et al (2020)(1057)	POAG/PACG	79 POAG, 27 PACG, 89 HC	Cross-sectional	PSQI: PACG: Median score higher (p=0.004), higher proportion with PSQI>5 (p=0.013, p=0.511); poorer sleep when VA≤6/15 (p=0.092, p=0.074) ESS: Comparable (p=0.959)	Assessment of VA and VF Underpowered study
36.Bierings et al (2019)(1029)	OAG (POAG, PXF, pigment dispersion)	159 OAG	Cross-sectional	MCTQ: No differences in sleep times (p>0.05)	Bias due to 19% unreturned questionnaires
37.Lee et al (2016)(1058)	OAG	368 OAG, 9042 NS controls	Epidemiological	Sleep <5h/night highest prevalence of glaucoma, followed by sleep ≥9h/night (p=0.072 for trend)	Detailed ophthalmological exam Sleep questionnaire not validated
38.Ahmadi et al (2020)(1030)	NTG	15 NTG, 17 HC	Cross-sectional	PSQI: Comparable (p=0.63)	Detailed ophthalmological assessment Small sample size
39.Ayaki et al (2016)(1059)	Glaucoma	69 glaucoma, 71 NS controls	Cross-sectional	PSQI: Global, SL worse in advanced glaucoma (p=0.02, p=0.01) Earlier bedtime in advanced glaucoma (p=0.007)	Detailed ophthalmological examination
40.Agorastos et al (2013)(1060)	Glaucoma	49 glaucoma + VFD; 37 glaucoma without VFD	Cross-sectional	PSQI: VFD: Higher global score, sleep disturbance, SL (p=0.046, p=0.022, p=0.011), higher proportion of poor sleepers (p=0.005)	Detailed ophthalmological examination No HC

41.Ayaki et al (2015)(1027)	Glaucoma	109 glaucoma	Cross-sectional	PSQI: >5 in 34.9% glaucoma subjects	No NS controls
42.Qiu et al (2019)(1061)	Glaucoma	6784 glaucoma, 3742 HC	Epidemiological	Odds of DDG higher with sleep≥10h/night & SL≤9min or ≥30min (p=0.01, p<0.01) Odds of VFD higher with sleep ≤3h/night or ≥10h/night (p=0.03, p<0.01)	Sleep questionnaire not validated Large numbers excluded
43.Jung & Park (2016)(1062)	Glaucoma	570 glaucoma, 11,509 NS controls	Epidemiological	Glaucoma related to short (≤5h) or long (≥9h) sleep (p=0.041)	Detailed ophthalmological examination Sleep questionnaire not validated

Key: AION=Anterior ischaemic optic neuropathy; AIS=Athens Insomnia Scale; A-POAG=Advanced POAG; BDI-II: Beck Depression Inventory Score-II; BBSOAS=Bosch-Boonstra-Schaaf optic atrophy syndrome; B/L=Bilateral; CI=Confidence interval; CP=Craniopharyngioma; CSS=Clinical Symptom Score for Sleep; DOA=Dominant optic atrophy; ERG=Electroretinography; ESS=Epworth Sleepiness Scale; FR=Free running; GCC=Ganglion cell complex; HADS=Hospital Anxiety and Depression Scale; HADS-A=HADS anxiety subscore; HADS-D=HADS depression subscore; HC=Healthy controls; HD-OCT=High definition optical coherence tomography; HON=Hereditary optic neuropathy; HVF=Humphrey visual field; IOFB=Intraorbital foreign body; LE=Light exposure; LHON=Leber hereditary optic neuropathy; MCTQ=Munich ChronoType Questionnaire; MD=Mean deviation; MFI=Multiple Fatigue Index; MNST=Melatonin suppression test; MON=Optic neuritis as first demyelinating event; MPS=Minimum pupil size; MS event; NAION=Nonarteritic anterior ischaemic optic neuropathy; NFMA=Nonfunctioning pituitary macroadenoma; NMOSD=Neuromyelitis optica spectrum disorder; NS=Normally sighted; NTG=Normal tension glaucoma; OA=Optic atrophy; OAG=Open angle glaucoma; OCC=Optic chiasm compression; ON=Optic neuritis; OND=Optic nerve disorder; PA=Pituitary adenoma; POAG=Primary open angle glaucoma; PSG=Polysomnography; PSQI=Pittsburgh Sleep Quality Index; PXF=Pseudoexfoliation; RNFL=Retinal nerve fibre layer; RNFLT=RNFL thickness; SE=Sleep efficiency; SF-36: Medical Outcomes Study Short-Form 36 Item Questionnaire; SL=Sleep latency; SMON=Subacute myelo-optic neuropathy; SMS=MS where first event was not optic neuritis; SON=Optic neuritis during course of MS rather than initial event; S-POAG=Stable POAG; SOD=Septo-optic dysplasia; TON=Traumatic optic neuropathy; U/L=Unilateral; VA=Visual acuity; VF=Visual fields; VFD=Visual field defects; VI=Visual impairment; WASO=Wake after sleep onset

3.3.1 Optic Nerve Disorders

Eight studies analysed subjective sleep wake in OND(15, 114, 468, 1035-1037, 1044, 1045), with subjective sleep disturbance found in seven studies(15, 114, 468, 1035-1037, 1044). Confirmation with objective evaluation of sleep wake was also reported in four studies(114, 468, 1035, 1036), with one study showing comparable sleep quality with controls in AION but altered chronotype(1045).

Tsika et al (2015)(1045) conducted a study of eight individuals with bilateral AION in comparison to 10 with unilateral AION and 29 normally sighted controls, and did not find any difference in subjective sleep quality between groups, although there appeared to be an impact on chronotype as subjects with bilateral OND were more likely to be intermediate types compared to those with unilateral AION and controls, who were more likely to be morning types. DelRosso et al (2014)(468) reported a case of bilateral TON in a patient with NPL vision with increased subjective daytime sleepiness, and reduced SE and TST on PSG. Tian et al (2014)(1044) reported a case series of five subjects with intraorbital foreign bodies with optic nerve damage, two of whom had sleep disturbance which improved following removal.

Wee and Van Gelder (2004)(114) observed sleep quality and locomotor activity 11 subjects with VI due to OND or glaucoma, including two with ONH, one with TON and four with ROP leading to OA and glaucoma, in comparison to 11 subjects with VI due to other pathologies and 12 normally sighted controls, and found that subjective sleep quality (using a non-validated questionnaire) was comparable between groups, but that total nap time, SL and wake time instability were higher in those with OND and glaucoma compared to those with other forms of VI and controls. Adeoti (2010)(1037) investigated sleep quality and duration in 10 subjects with OA as part of a study of 170 blind subjects, and found that mean PSQI>5 indicated sleep disturbance in OA, and that the majority of subjects with OA reported short sleep duration. Tabandeh et al (1998)(15) compared 45 subjects with OND and glaucoma to 44 controls as part of a wider study of 403 blind subjects. Mean PSQI was found to be raised in OND and glaucoma compared to controls, and extent of visual loss was found to correlate with worse sleep quality. Flynn-Evans et al (2014)(1035) reviewed sleep diaries and urinary aMT6s production in six subjects with OA and eight subjects with glaucoma in their report of

127 blind female subjects and found that 57% of subjects with OA and glaucoma had normally entrained circadian rhythms, which decreased to 50% in OA and glaucoma subjects with NPL vision. Lockley et al (1997)(16) studied sleep quality and melatonin rhythms in 49 blind subjects, of whom one had congenital OA, one had TON, and one had buphthalmos with glaucoma, and found poor sleep quality with abnormal entrainment in the subjects with congenital OA and TON, and a FR circadian rhythm in the subject with buphthalmos.

3.3.2 Hereditary Diseases

Three studies examined hereditary optic nerve diseases(280, 1028, 1034), and two studies evaluated hereditary systemic diseases in which optic nerve involvement was present(305, 1039). Overall, studies of HON showed few outcomes which demonstrated sleep disturbance compared to those with normal sight, in contrast to studies of inherited systemic disorders with associated optic nerve dysfunction in which there was a notable impact on sleep propensity and quality.

La Morgia et al (2010)(1034) studied nine subjects with HON (five with LHON and four with DOA) in comparison to nine normally sighted controls and found no difference in daytime sleepiness or melatonin suppression between groups, although physical function and pain were worse in HON compared to controls. Prihodova et al (2021)(1028) found no difference in subjective sleep quality or daytime sleep propensity in 13 subjects with symptomatic HON (10 with LHON and three with DOA) compared to 23 subjects with genetically confirmed asymptomatic LHON. This was confirmed by objective PSG data being similar to population norms, with no difference in OSA prevalence or PLM. Munch et al (2015)(280) found comparable subjective sleepiness in 11 HON patients compared to 11 matched normally sighted controls, although subjective sleep quality was worse in HON. Subjects with HON demonstrated melatonin suppression similar to controls on MNST, and PLR was similar in HON and controls, except for larger minimum pupil size in HON.

Bischoff et al (2015)(305) and Rech et al (2020)(1039) both assessed young subjects with hereditary systemic disorders with optic nerve involvement. Bischoff et al (2015)(305) assessed sleep outcomes in 19 individuals with WS in comparison to 25 controls with type 1 diabetes and 25 healthy controls, and found increased sleepiness and risk of sleep problems

in individuals with WS, with six found to have hypersomnolence disorder. Rech et al (2020)(1039) reported presentations in 54 subjects with BBSOAS, 82% of whom had OA, and 49% of whom had ONH, and found that parent-reported sleep disturbance was present in 61% of subjects.

3.3.3 Neurological Diseases

Fourteen studies yielded by my systematic literature search observed sleep wake in neurological diseases with optic nerve involvement. In general, group differences were noted between those with pathology and control subjects, particularly in subjects with sellar tumours, with evidence being less convincing in studies of demyelinating and autoimmune diseases. In systemic diseases, there are many potential contributors to differences in sleep wake, including fatigue, pain and endocrine dysfunction, which are highlighted by several of the authors.

3.3.3(a) Demyelinating and Autoimmune Diseases

In the six studies of demyelinating and autoimmune neurological diseases yielded in my systematic review(812, 1026, 1047-1050), there was no clear consensus of the impact of OND on sleep quality, and none of the studies gave details of any assessments of visual function. In one case, the presence of ON in MS appeared to correspond to more favourable sleep quality than in other presentations of MS(1047), although poorer sleep quality in NMOSD was found in four studies(1026, 1048-1050). In general, these study populations were compared within or to similar pathologies(812, 1026, 1047) or were uncontrolled(1048, 1049), with subjects in only one study being compared to a healthy control group(1050).

Turkoglu et al (2020)(1047) found comparable sleep quality but increased daytime sleepiness in 10 subjects with ON (MON) as an initial demyelinating event in MS compared to other MS patients (SMS). Objective readings showed better SE and reduced WASO in MON, and lower serum melatonin. Barzegar et al (2018)(812) found that subjective sleep quality was comparable between 41 patients with NMOSD compared to 136 matched MS

patients, with poorer sleep in males compared to females with MS, although worse depression scores were found in NMOSD. Shi et al (2016)(1048) assessed sleep and QOL in 73 patients with NMOSD and found 68% were poor sleepers, with high mean PSQI score, and correlation of PSQI with mental, physical and global components of the MSQOL-54. Miao et al (2017)(1049) identified a correlation of poor sleep quality with depression, pain and disability in 42 subjects with NMOSD, of whom 64% were found to have subjective sleep impairment. Pan et al (2015)(1050) found that mean PSQI was higher in 33 subjects with NMOSD compared to 20 healthy controls, with higher fatigue scores in NMOSD. Seok et al (2017)(1026) investigated fatigue in NMOSD and found that those with fatigue were more likely to have poor sleep quality, depressed mood and worse QOL than those without.

3.3.3(b) Sellar Tumours

Five studies evaluated sleep in patients with sellar tumours(974, 1040-1043), three of which specifically studied OCC(1041-1043), and all found a measurable difference in subjective sleep parameters, with three studies also finding measurable objective differences in sleep parameters and circadian timing(974, 1042, 1043), although details of ophthalmological evaluations were lacking in all five studies.

Joustra et al (2014)(1040) studied 17 subjects with non-functioning pituitary macroadenoma (NFMA) (82% had VFD), 8 with a history of CP (88% of whom had VFD) and 17 healthy controls, with findings of reduced sleep quality and poorer physical function in NFMA and CP, and increased daytime sleepiness and fatigue, and poorer social function and health perception in CP compared to controls.

Sagan et al (2021)(1041) reported improved subjective sleep quality, sleep duration and SE post resection in 15 patients with a history of OCC due to PA, and correlation of daytime sleepiness with bodily pain and mental health scores in OCC. Romeijn et al (2012)(1042) studied 50 patients with a history of sellar tumours, 33 of whom had a history of OCC and found later bedtimes and lower proximal to distal skin temperature gradient in OCC, with comparable ESS scores between patient groups. Borgers et al (2011)(1043) also found later bedtimes in 38 patients with sellar tumours and OCC in comparison to 18 patients without

OCC, with other PSQI and ESS scores comparable, although actigraphy showed a shorter TST and confirmed later sleep onset in OCC patients.

Pickering et al (2014)(974) examined 15 patients with a history of CP compared to 15 matched healthy controls and found increased subjective SL and daytime dysfunction and earlier morning wake times on actigraphic measurements in CP.

3.3.3(c) Other Neurological Diseases

One study evaluated an iatrogenic neurological disease. Hishikawa et al (2019)(1046) found a higher prevalence of poor sleep quality, insomnia, daytime sleepiness and use of sleep medications in 106 individuals with SMON compared to 110 matched healthy controls, with all PSQI subscales worse in SMON.

One publication detailed sleep in congenital neurological pathology. Webb et al (2010)(1038) identified reduced SE on sleep diary and actigraphy in six children with SOD compared to 10 matched healthy controls, with impaired circadian timing in two children with SOD.

One study evaluated a neurodegenerative disease. La Morgia et al (2016)(115) found lower RNFL thickness, SE and variability in locomotor activity in sleep and wake periods between participants with AD compared to age-matched controls, although evaluations of subjective sleepiness and daytime sleep propensity were comparable. They also analysed postmortem ocular tissue and found that pRGCs were of reduced density, abnormal morphology, and dendrites were of smaller diameter in AD compared to controls.

3.3.4 Glaucoma

Twenty-two studies examined the relationship of glaucomatous pathologies with subjective sleep wake, of which 11 did not specify glaucoma type, 10 evaluated OAG, three evaluated angle closure glaucoma, and one evaluated congenital glaucoma. In general, associations were found between the presence and severity of glaucoma with poor sleep quality, sleep duration and altered chronotype, with indeterminate or no group effect found in a minority of cases. Notable features of these studies included a thorough ophthalmological

assessment, which was not the case in studies of autoimmune and inflammatory pathologies or sellar tumours. This may be explained by glaucomatous pathology being more specific to the organ of vision, whereas studies of neurological diseases had a greater emphasis on overall functioning, mood and quality of life, and were conducted primarily by neurologists, endocrinologists and neurosurgeons. Several studies employed actigraphy, PSG and melatonin analysis alongside subjective measures of sleep. Six studies focused on subjects with low vision, and included a subset of subjects with glaucoma(15, 114, 1035-1037, 1051), some of which contained low numbers. For example, Lockley et al's (1997)(1036) study of patients with blind registration included one subject with congenital glaucoma and NPL vision who was found to have a PSQI score of 5 and FR urinary melatonin rhythm.

3.3.4(a) Undefined Glaucoma

Eleven papers in this review analysed subjective and objective sleep in glaucoma of unspecified type(15, 114, 1027, 1035, 1037, 1051, 1058-1062), of which nine showed worse subjective sleep quality, SL, TST and differences in bedtimes and daytime napping(15, 1035, 1037, 1051, 1058-1062). One study found objective differences in sleep parameters, but comparable subjective sleep quality(114), and one study was inconclusive as it compared subjects with glaucoma to those with other ocular pathologies but not to a normally sighted control group(1027). Three studies were epidemiological evaluations of sleep in subjects with glaucoma, and five studies were of patients with glaucoma with low vision. Three studies had low numbers of glaucoma subjects(114, 1035, 1051), and five studies did not have a normally sighted control group(1027, 1035, 1037, 1059, 1060), with one study employing within-pathology comparisons(1060), and four studies comparing sleep across a range of ocular pathologies(1027, 1035, 1037, 1059).

Agorastos et al (2013)(1060) observed that VFD were associated with worse subjective sleep quality, anxiety and depression in glaucoma. Ayaki et al (2015)(1027) found that 34.9% of their sample of 109 patients with glaucoma had poor sleep quality, although no comparison was made with a healthy control group. Ayaki et al (2016)(1059) found that advanced glaucoma with VFD<-12dB was associated with earlier bedtimes, poor sleep quality, increased SL and depression.

3.3.4(a)(i) Epidemiological studies

Jung and Park (2016)(1062), Lee et al (2016)(1058) and Qiu et al (2019)(1061) conducted nationwide epidemiological surveys and found the presence of glaucoma to be associated with excessively short or long SL and sleep duration, depressive mood and anxiety.

3.3.4(a)(ii) Low Vision

Six publications observed subjects with low vision, including subsets of participants with glaucoma(15, 114, 1035-1037, 1051). Leger et al (2002)(1051) studied eight subjects with glaucoma in their evaluation of sleep wake in 26 blind subjects with NPL vision, negative ERG and FR circadian rhythms and found that all glaucoma subjects had poor subjective sleep quality. Tabandeh et al (1998)(15) studied a combined group of 45 subjects with either OND or glaucoma and found their mean PSQI score to be 6.6±4.3 compared to 2.9±0.5 in control subjects. Wee and Van Gelder (2004)(114) studied four young people with VI due to glaucoma amongst a group of eleven subjects with OND and found no difference in subjective sleep quality compared to controls, although actigraphy identified increased nap times, SL and wake time instability in OND. Flynn-Evans et al (2014)(1035) studied sleep diaries and aMT6s in eight women with glaucoma as part of a group of 14 blind subjects with OND and found that overall 57% had normally entrained circadian cycles, which reduced to 50% when only those with NPL vision were evaluated, with the remaining 50% being either abnormally entrained or non-entrained. Adeoti (2010)(1037) also studied blind subjects, 56 of whom had glaucoma, with mean PSQI score 8.6±3.1, daytime napping in 62.5%, short sleep duration in 50%, and interrupted sleep in 30.35% of subjects with glaucoma. As mentioned, Lockley et al (1997)(1036) observed one subject with congenital glaucoma and NPL vision, who had a normal PSQI and FR urinary melatonin rhythm.

3.3.4(b) Open Angle Glaucomatous Pathology

Ten studies in this review involved participants with either OAG, POAG or NTG(280, 641, 1029, 1030, 1052-1057). Six studies confirmed poorer subjective sleep quality, timing, duration or difference in chronotype in OAG(280, 641, 1052-1055), and two studies showed objective, but not subjective differences in OAG compared to controls(1030, 1056). A

further two studies found no group effect(1029, 1057). Of note, two studies had control groups that contained partners and relatives(1029, 1055), which may have compromised study findings, three studies contained less than 20 subjects with OAG(280, 1030, 1055), and one study was underpowered(1057).

3.3.4(b)(i) Open Angle Glaucoma

Bierings et al (2019)(1029) used the MCTQ to examine sleep timing in subjects with OAG compared to a control group comprising relatives, friends and neighbours, and did not find any differences in sleep timing or variability in sleep parameters between groups, although notable disparities in age, gender and working patterns were found between groups in addition to the possibility that sleep patterns between the two groups may not have been fully independent of each other. Munch et al (2015)(280) compared 11 subjects with OAG to 11 matched normally sighted controls and found worse baseline PSQI score, and increased subjective sleepiness in OAG with light exposure during the MNST, but similar melatonin responses in OAG and controls.

3.3.4(b)(ii) Primary Open Angle Glaucoma

Chin et al (2020)(1057) studied 79 patients with POAG in comparison to 89 normally sighted controls and did not observe a difference in subjective sleep quality or daytime sleepiness between groups, with no association found between worsening VA and poorer sleep quality, although higher depression scores correlated with poorer sleep quality in all subjects. Wang et al (2013)(641) reported a higher prevalence of sleep disorder in POAG compared to healthy controls, and poorer sleep quality correlated with advancing age in both groups. Ma et al (2018)(1056) studied 120 participants with POAG and 120 normally sighted controls and found no difference in the prevalence of poor subjective sleep quality between groups, although morning serum melatonin was higher in POAG, and raised melatonin was found to correlate with depression, anxiety and subjective sleep disturbance in POAG. Of note, a PSQI score of >7 was used to indicate poor subjective sleep quality, rather than the consensus score of >5. Lanzani et al (2012)(1055) compared nine individuals with bilateral advanced POAG to nine normally sighted controls (who included spouses and relatives) and found a higher prevalence of poor subjective sleep quality POAG. This was confirmed with

actigraphic recordings of reduced nighttime sleep and SE in POAG, although there may have been interdependence in subjective and objective sleep assessments between groups. Gracitelli et al (2016)(1054) evaluated subjective daytime sleepiness in 30 patients with POAG compared to 10 normal controls and found that mean ESS scores were higher in POAG, with higher scores correlating with glaucoma severity. This was confirmed with PSG where higher ESS scores were associated with increased number and duration of nighttime arousals after sleep onset, and inversely correlated with SE. Poor ESS scores were also associated with abnormal PLR responses. Gubin et al (2019)(1053) compared participants with advanced POAG (A-POAG) to those with stable POAG (S-POAG) and found that participants with A-POAG had chronotypes which tended towards morningness on MEQ, and that RGC loss was associated with delayed circadian phasing of body temperature. Gubin et al (2021)(1052) used the same cohort of A-POAG and S-POAG participants in a 90-day interventional study of slow-release melatonin before bedtime and found that baseline sleep diaries showed shortened mean sleep duration and longer mean sleep phase in A-POAG, with improvement in global PSQI and all component scores in both groups post intervention.

3.3.4(b)(iii) Normal Tension Glaucoma

Ahmadi et al (2020)(1030) studied 15 patients with NTG and 17 healthy controls and found similar global and component PSQI scores between groups, although PLR was abnormal in NTG. A negative association with severity of VFD and RNFL thickness was identified, but not with PLR.

3.3.4(c) Angle Closure Glaucoma

Three publications included participants with PACG, with all three studies finding an association of PACG with poor sleep quality(641, 1056, 1057). All three studies included subjects with POAG with two studies finding worse subjective sleep in PACG(1056, 1057). One study was under-powered(1057), but numbers were large in two studies(641, 1056).

Chin et al (2020)(1057) observed 27 patients with PACG in comparison to 79 patients with POAG and 89 normally sighted controls and found that mean PSQI scores were higher in

PACG, with no difference between POAG and controls. They also found a higher prevalence of poor sleep in PACG compared to controls, which was not the case for POAG, with ESS similar between all groups. Wang et al (2013)(641) found a higher prevalence of subjective sleep disturbance in patients with PACG aged 41-80 compared to healthy controls, and Ma et al (2018)(1056) evaluated sleep in 80 subjects with PACG, 120 with POAG and 120 normal controls, and found a higher prevalence of poor subjective sleep quality in PACG compared to POAG and controls, with sleep disturbance associated with sex and worse eye IOP, and elevated morning serum melatonin in all glaucoma subjects.

3.3.5 Assessment of Visual and Optic Nerve Function

A key finding of my literature review was that reported assessment of visual function varied widely between studies. The majority of smaller studies and studies specifically of mitochondrial, congenital, hereditary, vascular and glaucomatous optic neuropathies generally recorded a more detailed visual assessment with at least the specifics of VA and VF recorded, and additional recordings of IOP, pupil function including PLR and RAPD, high-definition OCT (HD-OCT) and ERG.

3.3.5(a) Detailed Ophthalmological Assessment

26 studies recorded specific details of ophthalmological evaluations, with at least VA or VF recorded (15, 114, 280, 641, 1027-1030, 1034-1038, 1044, 1045, 1051-1055, 1057-1062). These tended to be studies conducted by ophthalmologists or vision scientists, and included detailed mensuration of visual parameters, particularly in cases of hereditary, vascular and glaucomatous optic neuropathies, and in studies of subjective sleep wake in patients with low vision. Irregularities in this general picture include Ma et al (2018)(1056), who recorded IOP but not VA or VF in their evaluation of patients with primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG), meaning that measures related to optic nerve function were omitted. Additionally, La Morgia et al (2016)(115) in their study of patients with AD used OCT RNFL to extrapolate optic nerve function, presumably as assessment of VA and VF require a degree of subjective input, which may not have been reliable in AD.

3.3.5(b) Nonspecific Ophthalmological Assessment

Assessment of optic nerve function was mentioned, but not described specifically in seven studies(305, 468, 1039-1043). These tended to be studies of patients with OCC, which were led by endocrinology and neurosurgery teams, and in which the presence of OCC had been confirmed by reduction in an individual's VA or VF. This was also the case in groups of patients where the presence of OA had been confirmed or excluded in the absence of any further ophthalmological data, as in Bischoff et al's (2015)(305) study of young people with WS, Rech et al's (2020)(1039) study of Bosch-Boonstra-Schaaf syndrome, in which OA was confirmed in 82% of subjects, but no further details were given, and in DelRosso et al's (2014)(468) study of a patient with TON in which it was confirmed that pupils were fixed and dilated, but no other assessment of visual function was published.

3.3.5(c) No Ophthalmological Assessment

Eight studies did not document any visual assessment(812, 974, 1026, 1046-1050). These were largely studies of demyelinating, autoimmune and iatrogenic conditions including MS, NMOSD and SMON, in which sleep disorders were assessed in association with the global disease entity, rather than specifically in relation to their associated OND, and tended not to be conducted by ophthalmology teams. Of note, Turkoglu at al (2020)(1047) evaluated ON as a first demyelinating event in MS (MON) in comparison to its occurrence at a later stage in the disease process (SON) and to MS with other clinical features, but no further visual assessment was recorded. Pickering et al (2014)(974) studied sleep in patients with CP, with exclusion of subjects with NPL vision, and no further details of ophthalmic assessment.

3.3.5(d) Duration and Rapidity of Visual Loss

Duration of visual loss was recorded in eight studies(15, 305, 1034-1037, 1047, 1051), and rapidity of visual loss was recorded in three studies(15, 1036, 1037), with no association found between either the time since onset or speed of visual loss on sleep evaluation in all publications. Adeoti et al (2010)(1037) found that neither rapidity nor duration of visual loss were associated with severity of sleep disorder in their study of 138 blind patients (66 of whom had either glaucoma or OA). Similarly, Lockley et al (1997)(1036) did not find an

association between the duration or rapidity of onset of visual loss and circadian rhythm in subjects with NPL vision. Tabandeh et al (1998)(15) noted no effect of the rapidity, time since loss of vision or pattern of VFD on PSQI score, with no difference in sleep quality between congenital and acquired causes of VI, as was the case in Leger et al's (2002)(1051) study. Turkoglu et al (2020)(1047) recorded age of disease onset in patients with MS, comparing those with MON to those with other presenting features and found lower EDSS scores and progression indices in MON despite time since presentation being longer. Flynn-Evans et al (2014)(1035) recorded the age at which subjects became legally blind but did not discuss correlation with circadian type. No comment was made by Bischoff et al (2015)(305) who presented demographic data on time since onset of OA but did not comment on its association with sleep quality in subjects with WS, as was the case in La Morgia et al's (2010)(1034) study of LHON and DOA in which age of onset of visual loss was recorded but without any assessment of correlation.

Disease duration, in the absence of the specifics of timing of visual loss was recorded by Barzegar et al (2018)(812) as a demographic comparison to evaluate similarity between groups of participants with MS and NMOSD, however its impact on fatigue or sleep quality was not discussed further. Furthermore, Seok et al (2017)(1026) recorded median disease duration in patients with NMOSD with and without fatigue and did not find a correlation between degree of fatigue and time since NMOSD onset, although Shi et al (2016)(1048) found that disease duration was associated with worse health-related QOL in NMOSD.

3.3.6 Control groups

3.3.6(a) Controls without Ocular Pathology

21 studies compared subjects with OND and glaucoma to normally sighted, healthy controls(114, 115, 280, 305, 641, 974, 1030, 1034, 1038, 1040, 1045, 1046, 1050, 1051, 1054, 1056-1059, 1061, 1062). These comprised epidemiological studies(1058, 1061, 1062), which had a natural pool of control subjects, and studies of glaucoma and HON also featured, most of which had a clear objective of comparing visual function and sleep parameters within the pathological group studied to normally sighted populations. In contrast, the aims of studies of patients with systemic disease tended to be comparisons

between pathological groups (for example between NMOSD with and without fatigue(1026)) or within subjects pre- and post-resection of sellar tumours(1041), which may explain these contrasts.

Matching of controls to minimise confounding(1063) was undertaken in 10 studies, the majority of which had smaller sample sizes, with age matching reported in all cases(115, 280, 974, 1034, 1038, 1040, 1045, 1046, 1050, 1051). Other parameters matched including sex(1034, 1038), BMI, waist and hip circumference(974, 1040) and occupation(1051). Of note, Munch et al (2015)(280) in their study of HON and glaucoma recruited 22 age-matched controls, but inclusion criteria for controls specified a PSQI score of ≤5, and chronotype score on MEQ between 30 and 70 (to exclude any extremes), meaning that any differences in sleep quality and timing with subjects with HON and glaucoma may have been artificially amplified as this control group may have been less representative of the range of sleep parameters within the general population.

Matching of controls also included postmortem subjects. La Morgia et al in their study in 2010(1034) compared subjective sleep and mood and melatonin suppression in nine participants with mitochondrial HON with nine control subjects who were not age- or sex matched, and also investigated pRGC population and density in postmortem eyes of three subjects with mitochondrial HON and three age-matched control eyes without ocular pathology. In their 2016 study, La Morgia et al(115) compared RNFL thickness and subjective sleepiness in 21 patients with AD to 74 age-matched controls, with actigraphy analysis in a subgroup of the study population, and also immunostained retinae of 14 postmortem AD subjects and 13 age-matched controls for pRGC enumeration.

Wee and Van Gelder (2004)(114) and Bischoff et al (2015)(305) did not specifically report matching controls in their studies of optic neuropathy in young people, but recruited control groups within a comparable age range, so age demographics were similar between groups. Of note, a limitation of Wee and Van Gelder's(114) study of young people with optic neuropathies living in a boarding school is the presence or absence of a morning alarm between study and control institutions, which may have interfered with natural sleep and wake times.

Non-matched healthy controls were compared to subjects with OND and glaucoma in nine studies(641, 1030, 1054, 1056-1059, 1061, 1062). In these studies, patient and control groups tended to be larger in size. This included one epidemiological survey in the United States(1061) and two in Korea(1058, 1062) in which sleep duration and quality were evaluated, and respondents with glaucomatous pathology were compared to respondents without ocular pathology.

3.3.6(b) Comparison within Pathological Groups

13 publications compared groups with similar pathologies or used within-group controls(812, 1026, 1027, 1035-1037, 1041-1043, 1047, 1052, 1053, 1060), with this design most frequently seen in studies of OCC(1041-1043), demyelinating and autoimmune conditions(812, 1026, 1047), glaucoma(1027, 1052, 1053, 1060), and studies of low vision with multiple ocular pathologies(1035-1037).

Sagan et al (2021)(1041) evaluated sleep quality, subjective daytime sleepiness and QOL in 29 patients post transsphenoidal resection of PA, 15 of whom had previous OCC, but with no healthy control comparison. This was also the case in Romeijn et al's (2012)(1042) study, in which sleep quality and distal and proximal body temperature were compared in 50 patients with a history of sellar tumours and pituitary insufficiency, 33 of whom had a history of OCC, and 17 of whom did not. Borgers et al (2011)(1043) compared PSQI, ESS, AIS and actigraphy in 56 patients with a history of treated sellar tumours and pituitary insufficiency, 38 of whom had previous OCC.

Turkoglu et al (2020)(1047) compared subjective sleep quality, daytime sleepiness and PSG in 10 patients with MON to 16 patients with other primary clinical presentations of MS (SMS), which included eight patients with ON presenting later in the disease process (SON). Barzegar et al (2018)(812) compared PSQI, fatigue scores, depression, anxiety and QOL in 41 subjects with NMOSD compared to 136 subjects with MS, and Seok et al (2017)(1026) compared sleep quality, pain scores, depression and QOL in participants with NMOSD, 25 of whom had diagnosed fatigue, and 10 of whom had not.

Agorastos et al (2013)(1060) compared sleep quality and mood in 49 subjects with a diagnosis of glaucoma and presence of VFD with 37 subjects with a diagnosis of glaucoma

without VFD. Gubin et al (2019)(1053) evaluated chronotype and body temperature circadian rhythm in 50 individuals with advanced POAG in comparison to 65 individuals with stable POAG, and used the same participant groups in their interventional study of slow-release melatonin(1052) to evaluate its effect on sleep quality, mood, IOP, ERG, body temperature circadian rhythm, and salivary melatonin levels. Ayaki et al (2015)(1027) appraised PSQI and HADS scores in 730 patients with a range of ocular pathologies, including 109 patients with glaucoma, but their sample was not compared to a normally sighted control group.

In their study of 49 subjects with blind registration, Lockley et al (1997)(1036) stratified participants into groups of those with vision of light perception (LP) versus those with no perception of light. They compared subjective sleep quality and urinary melatonin levels between groups. Adeoti (2010)(1037) evaluated sleep quality in 138 blind patients in subject groups stratified by degree and causes of blindness, and Flynn-Evans et al (2014)(1035) investigated sleep timing and urinary melatonin production in 127 legally blind women divided into those with vision of LP or better vs NPL.

3.3.6(c) Comparison with Relatives and Carers ("Contaminated Controls")

Confounders can arise in a study where the control group is not independent of the study population, which may have been the case in four studies yielded by this systematic review(15, 1028, 1029, 1055), as they recruited spouses, relatives and carers as control subjects, who may have been bed partners or lived in the same house as study subjects and consequently had similar patterns of sleep and wake. Prihodova et al (2021)(1028) compared participants with genetically confirmed and phenotypic presentation of LHON and DOA to subjects with genetically confirmed but non-phenotypic (asymptomatic) LHON, with 13 out of 23 control participants being relatives of those with symptomatic LHON, which may have led to "contamination". Similarly, Bierings et al (2019)(1029) recruited partners, relatives, friends and neighbours as controls in their study of chronotype in open angle glaucoma (OAG), and Tabandeh et al (1998)(15) studied sleep quality in 388 blind subjects stratified into those with PL or better and those with NPL vision and compared a control group of 44 individuals which included relatives of blind subjects. Lanzani et al (2012)(1055) recruited nine age-matched control subjects in their study of subjective and actigraphic

sleep evaluation in advanced POAG. Controls were randomly recruited from a pool of partners, relatives and friends of patients and staff, meaning that sleep disturbance due to poor sleep of a partner was a possibility.

3.3.6(d) No Control Group

Five studies did not have a control group(468, 1039, 1044, 1048, 1049). These were either case series and case reports or looked at within-group clinical features and correlations.

Shi et al (2016)(1048) observed 73 individuals with NMOSD and analysed relationships between fatigue, mood, sleep quality and QOL, while Miao et al (2017)(1049) analysed relationships between PSQI, mood, disability and fatigue in 42 patients with NMOSD. Rech et al (2020)(1039) discussed phenotypic expression and underlying genotypes in 51 individuals with BBSOAS and found that 82% had OA, 49% had ONH and 61% had sleep difficulties, and Tian et al (2014)(1044) reported five cases of unilateral intraorbital foreign bodies with resulting unilateral low vision, with subjective sleep impairment in two cases, both of which improved following foreign body removal via lateral orbitotomy. DelRosso et al (2014)(468) published a case report of an individual with bilateral TON with resulting blindness, increased daytime sleepiness and irregular sleep pattern on PSG.

3.3.7 Exclusion Criteria

Exclusion criteria in many studies were aimed at eliminating any confounders for sleep quality and timing or of isolating the pathological process under investigation, and included a recent history of transmeridian travel, either within the past three months(641, 1056), shortly before(974) or during the study period(1054). A history of shift work(974, 1029, 1051), or shift work during the past three months(641, 1056) or during the study period(1029, 1042, 1043, 1054) was also a criterion in some papers.

Systemic criteria for exclusion included a history of psychiatric or neurological disorders(15, 280, 305, 812, 974, 1037, 1040, 1046, 1050, 1051, 1053, 1060), and chronic illnesses including cancer, diabetes, endocrine disorders and cardiovascular disease(280, 641, 974, 1026, 1030, 1040, 1045, 1048, 1049, 1051, 1053). Exclusions based on medication and social

history included a history of psychoactive medication use(305, 812, 974, 1030, 1036, 1037, 1040, 1047, 1049, 1050, 1054, 1060) or substances or medications that affect sleep(1035-1037, 1040, 1056) including NSAIDs and beta-blockers(974), smoking(280), alcohol abuse(641, 1047, 1049, 1056) and recreational drug use(641, 1049). Confounding ophthalmological comorbidities were excluded in some papers(1053, 1057, 1060), including cataract(1053, 1059, 1062), dry eye(1059) or non-OND or non-glaucomatous posterior pole pathologies(115, 641, 1045, 1053, 1057, 1059, 1062).

3.3.8 Sample Size

Eighteen studies in this review comprised fewer than 20 subjects(114, 280, 305, 468, 974, 1028, 1030, 1034, 1036-1038, 1040, 1041, 1044, 1045, 1047, 1051, 1055). In general, smaller studies contained more thorough ophthalmological assessments and more detailed subjective and objective evaluations of sleep, pupillary and biochemical parameters, many of which require careful planning and are time-consuming, meaning that recruitment to the study is likely to be lower. Additionally, Chin et al's (2020)(1057) study was identified as being under-powered at 75%, in which subjective sleep quality and timing was measured in 79 subjects with POAG, 27 with PACG and 89 healthy controls, reducing the validity of their statistical analysis.

Of the studies with less than 20 subjects with OND or glaucoma, Bischoff et al (2015)(305) compared sleep quality, duration, mood, cognition and psychiatric state in 19 young subjects with WS (18 of whom had a diagnosis of OA) to 25 subjects with type 1 diabetes and 25 healthy controls. Tsika et al (2015) conducted extensive ophthalmological examination of eight subjects with bilateral, and 10 with unilateral AION in their study of subjective sleep quality, chronotype and PLR. Prihodova et al (2021)(1028) studied subjective sleep quality, daytime sleepiness and PSG in 13 symptomatic and 23 asymptomatic patients with mitochondrial HON, with stratification of visual loss in symptomatic patients. Joustra et al (2014)(1040) studied daytime sleepiness, mood and salivary melatonin in 17 patients (88% of whom had a history of VFD) with NFMA and eight with CP (VFD history in all CP patients) in comparison to 17 control subjects. Pickering et al (2014)(974) investigated subjective sleep quality, and used sleep diaries and actigraphy to

evaluate sleep in 15 participants with CP compared to 15 healthy controls. Sagan et al (2021)(1041) conducted subjective sleep evaluations in 29 patients with PA, 15 of whom had OCC, with no other visual assessment documented.

Both Ahmadi et al (2020)(1030) in their study of subjective sleep quality and PLR in 15 subjects with NTG and 17 healthy controls, and Munch et al (2015)(280), who evaluated subjective sleepiness, PLR and salivary melatonin concentrations in 11 subjects with HON, 11 with OAG and 11 healthy controls, conducted in-depth ophthalmological assessments. Wee and Van Gelder (2004)(114) carried out an investigation of subjective sleep quality and actigraphy in 11 young people with OND and glaucoma compared to 14 young subjects with VI and 12 normally sighted controls. Adeoti's (2010)(1037) study included 10 subjects with OA and 56 with glaucoma as part of a study of 170 blind subjects with subjective sleep quality assessed with regard to degree, rapidity, duration and cause of visual loss. Turkoglu et al (2020)(1047) reported a history of ON as the only evidence of ophthalmological assessment in their study of 10 subjects with MON, eight with SON and eight with other MS presentations. Their assessment of sleep was detailed however, with PSG carried out in all subjects, in addition to subjective sleep quality and daytime sleepiness questionnaires.

Detailed ophthalmological assessments were conducted by La Morgia et al (2010)(1034) in 9 subjects with HON and 9 healthy controls with outcomes including PSQI and serum melatonin suppression, and by Lanzani et al (2012)(1055), who studied 9 subjects with advanced POAG and 9 healthy controls using sleep questionnaires, sleep diaries and actigraphic sleep evaluation.

Leger et al's (2002)(1051) study contained 8 patients with glaucoma as part of a wider study of sleep in 26 blind individuals with FR circadian rhythms, all of whom had NPL vision, absent pupillary reflexes and negative ERG, with measurement of subjective sleep quality, actigraphy, PSG and urinary melatonin secretion. Webb et al (2010)(1038) evaluated parental sleep diaries, actigraphy and serum melatonin in 6 children with SOD and severe-to-profound VI in comparison to 10 children without ocular pathology. Lockley et al (1997)(1036) studied one subject with buphthalmos, one with TON and one with congenital OA in their study of sleep quality and melatonin rhythms in 49 blind individuals, indicating employment of in-depth sleep analysis in several smaller studies.

With regard to case series and case reports, Tian et al (2014)(1044) described a case series of 5 patients with TON, detailing VA and sleep quality pre- and post-intraorbital foreign body removal. DelRosso et al (2014)(468) reported a case of bilateral TON in an individual with bilateral NPL vision and irregular sleep wake rhythm, which was assessed using the ESS, PSG and actigraphy, showing a more in-depth appraisal of outcomes compared to some of the larger study populations.

3.4 Rigour of Studies

When reviewing these studies, it is important to note the following observations: Ophthalmological data, including VA, VF, analysis of RNFL and electrophysiology to determine RGC function was often scarce, which was particularly evident in studies of systemic neurological disorders which included OND. From the authors' associations and correspondence noted in these publications, it was clear that these papers were written from a neurology (in populations of participants with MS or NMOSD), endocrinology or neurosurgery (in populations of participants with sellar tumours) point of view, which may explain the lack of precise ophthalmological information. Measurement of sleep quality and timing was not consistent across studies, and factors unrelated to pRGC integrity, such as pre-existing sleep disorders or sleep-modifying medications were not accounted for, and frequently sample sizes were small. Some studies were controlled, but control participants were not recruited to all studies, and several were case series or single case reports. A wide range of subjective, objective and biochemical outcome measures were used to evaluate sleep quality and phasing. Collectively, a broad spectrum of OND and glaucomatous pathologies were studied.

3.5 Quality of Evidence

My literature search did not yield any controlled interventional studies. Out of the 43 papers yielded, two reports were self-controlled interventional studies, 39 were observational cross-sectional studies and two were case series or case reports. I used adapted versions of the National Heart, Lung and Blood Institute Study Quality Assessment Tools(1064) to

evaluate the quality of each study, and denoted studies as “good quality” if they met 75% or more of the criteria, of which there were a total of six papers. Key findings included a paucity of information regarding rate of recruitment, lack of power calculations of statistical adjustment for confounders, in addition to a deficiency of reported ophthalmological data in a notable subsection of studies.

Gubin et al (2021)(1052) conducted a pre- and post-interventional study of melatonin in 115 subjects with advanced (n=50) versus stable (n=65) POAG and observed subjective sleep quality and body temperature circadian rhythm. Although the study objectives were clear and the study populations were well defined, evaluation of sources of bias such as rate of recruitment, blinding of assessors and a power calculation were absent, meaning that it only met 63.6% of the modified quality assessment criteria (see Table 4). Sagan et al (2021) conducted an assessment of subjective sleep quality and QOL pre- and post-transsphenoidal resection of PA in 29 patients, 15 of whom had OCC. 54.5% of the modified criteria were met including a well-defined objective, study population and outcome measures with statistical analysis, however, no comment was made on blinding of assessors, and there was no explanation of why all of the 55 eligible patients were not recruited. There was also no evidence of a power calculation or an interrupted series design (see Table 4).

Of the 39 observational studies in this review, six studies met 75% of the adapted criteria (see Table 5), with scores of individual studies detailed in Table 6. Common positive themes were clear objectives and definition of populations and adequate timescales, but detractors included little information regarding the rate of recruitment, sample power calculations or adjustment for confounders to reduce sample bias. None of the studies conducted predominantly by neurology, endocrinology or neurosurgery teams conducted thorough visual assessments(812, 974, 1026, 1039, 1041-1043, 1046-1050), so comparison of visual function to sleep outcomes was not possible in these cases. In epidemiological studies it was not clear whether sleep outcomes were measured prior to or contemporaneously with assessments of glaucoma characteristics(1058, 1061, 1062).

I used an adapted quality assessment tool for case series to evaluate Tian et al’s (2014)(1044) study and DelRosso et al’s (2014)(468) case report (see Table 7). Neither study could be defined as “good quality”. Tian et al (2014)(1044) recruited similar cases, but did not employ validated outcome measures, instead using descriptors of subjective sleep

quality which are less generalisable, and DelRosso et al (2014)(468) used outcome measures with well documented protocols but did not clarify their initial objectives.

Table 4: Criteria for Pre-Post Studies with No Control Group Adapted from: National Heart, Lung and Blood Institute Study Quality Assessment Tools Public Domain, Study Quality Assessment Tools | NHLBI, NIH	Gubin et al (2021)	Sagan et al (2021)
1. Was the study question or objective clearly stated?	✓	✓
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	✓	✓
3. Were the participants in the study representative of the general or OND/glaucoma population?	CD	CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?	CD	×
5. Was the sample size sufficiently large to provide confidence in the findings?	NR	NR
6. Was the intervention clearly described and delivered consistently across the study population?	✓	✓
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	✓	✓
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	NR	NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	✓	✓
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	✓	✓
11. Were outcome measures taken multiple times before the intervention and multiple times after the intervention (i.e. interrupted time-series design)?	✓	×
Total	7	6

Key: ✓=present; ×=absent; CD=Cannot determine; NA=Not applicable; NR=Not reported

Table 5: Modified Quality Assessment Tool for Observational Studies

Criteria Adapted from: National Heart, Lung and Blood Institute Study Quality Assessment Tools Public Domain, Study Quality Assessment Tools | NHLBI, NIH	
1. Was the research question or objective in this paper clearly stated?	
2. Was the study population clearly specified and defined?	
3. Was the participation rate of eligible persons at least 50%?	
4. Were subjects recruited from similar populations during a similar time period? Were inclusion and exclusion criteria prespecified and applied uniformly?	
5. Were sample size justification, power description, or variance and effect estimates provided?	
6. Was the ocular pathology of interest measured prior to the sleep outcome(s) being measured?	
7. Was the timeframe sufficient to reasonably expect to see an association between OND or glaucoma and sleep if it existed?	
8. Did the study examine different severities of loss of visual function in relation to the outcome (e.g., VFD, VA, RNFL loss either in categories or as a continuous variable)?	
9. Was the assessment of visual function clearly defined, valid, reliable, and implemented consistently across all study participants?	
10. Were the sleep outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	
11. Was loss to follow-up after baseline 20% or less?	
12. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	

Key: ✓=present; ✕=absent; CD=Cannot determine; NA=Not applicable; NR=Not reported

Table 6: Quality Assessment of Observational Studies in this Systematic Review

Adapted from: National Heart, Lung and Blood Institute Study Quality Assessment Tools Public Domain, Study Quality Assessment Tools | NHLBI, NIH

Criteria	Prihodova et al (2014)	La Morgia et al (2010)	Munch et al (2015)	Flynn-Evans et al (2014)	Lockley et al (1997)	Adeoti (2010)	Tabandeh et al (1998)	Wee & Van Gelder (2004)	Bischoff et al (2015)	Webb et al (2010)	Rech et al (2020)	Pickering et al (2014)	Joustra et al (2014)
1. Objective	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Population	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Participation rate	NR	NR	✓	✓	NR	✓	✓	NR	NR	NR	NR	✓	×
4. Similar populations	✓	✓	×	NA	NA	NA	✓	×	×	NR	×	NR	✓
5. Sample	×	×	×	×	×	×	×	×	×	×	×	×	×
6. Pathology measured first	✓	✓	✓	✓	✓	✓	✓	✓	CD	✓	✓	✓	✓
7. Timeframe	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. Severity of visual function	✓	✓	×	✓	✓	✓	✓	✓	×	×	×	×	×
9. Assessment of visual function	✓	✓	✓	✓	✓	✓	NR	NR	×	✓	×	×	×
10. Outcomes	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓
11. Loss to follow-up	NA	NA	NA	✓	✓	NA	NA	NA	NA	NA	NA	NA	NA
12. Confounders	×	×	✓	✓	×	×	✓	×	×	NA	×	×	×
Total	8	8	8	10	8	8	9	6	3	6	4	6	6

Criteria	Romeijn et al (2012)	Borgers et al (2012)	Tsika et al (2015)	Hishikawa et al (2019)	Turkoglu et al (2020)	Barzegar et al (2018)	Shi et al (2016)	Miao et al (2017)	Pan et al (2015)	Seok et al (2017)	La Morgia et al (2016)	Leger et al (2002)	Gubin et al (2019)
1. Objective	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Population	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Participation rate	NR	NR	NR	✓	✓	NR	NR	NR	×	NR	NR	NR	NR
4. Similar populations	NA	NA	✓	✓	✓	✓	NA	NA	✓	NA	NR	✓	NA
5. Sample	✓	×	×	×	×	✓	×	×	×	×	✓	×	×
6. Pathology measured first	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. Timeframe	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. Severity of visual function	×	×	✓	×	×	×	×	×	×	×	×	✓	✓
9. Assessment of visual function	×	×	✓	×	×	×	×	×	×	×	✓	✓	✓
10. Outcomes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
11. Loss to follow-up	✓	✓	NA	NA	NA	NA	NA	✓	NA	NA	✓	✓	✓
12. Confounders	✓	✓	×	×	×	✓	×	×	×	×	×	×	×
Total	8	7	8	7	7	8	5	6	6	5	8	9	8

Criteria	Gracitelli et al (2016)	Lanzani et al (2012)	Ma et al (2018)	Wang et al (2013)	Chin et al (2020)	Bierings et al (2019)	Ayaki et al (2015)	Ayaki et al (2016)	Ahmadi et al (2020)	Agorastos et al (2013)	Qiu et al (2019)	Lee et al (2016)	Jung & Park (2016)
1. Objective	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Population	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Participation rate	NR	NR	NR	NR	NR	✓	NR	✓	✓	NR	✓	✓	✓
4. Similar populations	✓	✓	✓	CD	CD	✓	NA	CD	NR	NA	✓	✓	✓
5. Sample	×	×	×	×	✓	×	×	×	×	×	×	×	×
6. Pathology measured first	✓	✓	✓	✓	✓	✓	CD	✓	✓	✓	×	×	×
7. Timeframe	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. Severity of visual function	✓	×	×	✓	✓	✓	×	✓	×	✓	×	×	×
9. Assessment of visual function	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10. Outcomes	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	×	×	×
11. Loss to follow-up	✓	✓	×	NA	NA	NA	NA	NA	✓	NA	NA	NR	NA
12. Confounders	✓	×	×	×	✓	✓	✓	×	×	✓	✓	✓	✓
Total	10	8	6	6	9	10	6	8	8	8	7	7	7

Key: ✓=present; ×=absent; CD=Cannot determine; NA=Not applicable; NR=Not reported

Table 7: Criteria for Case Series Adapted from: National Heart, Lung and Blood Institute Study Quality Assessment Tools Public Domain, Study Quality Assessment Tools | NHLBI, NIH	Tian et al (2014)	DelRosso et al (2014)
1. Was the study question or objective clearly stated?	✓	×
2. Was the study population clearly and fully described, including a case definition?	✓	✓
3. Were the cases consecutive?	NR	NA
4. Were the subjects comparable?	✓	NA
5. Was the intervention clearly described?	✓	NA
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	×	✓
7. Was the length of follow-up adequate?	CD	✓
8. Were the statistical methods well-described?	NA	NA
9. Were the results well-described?	✓	✓
Total	5	4

Key: ✓=present; ×=absent; CD=Cannot determine; NA=Not applicable; NR=Not reported

3.6 Measurement of Sleep Wake

The following paragraphs detail the measures of sleep that were found in the 43 review articles. I will illustrate subjective measures of sleep wake, mood and QOL, then give an overview of objective and genetic markers of sleep wake that were used.

3.6.1 Subjective Sleep Quality and Timing

3.6.1(a)Pittsburgh Sleep Quality Index and Pediatric Sleep Questionnaire

The PSQI was used in 28 of the 43 studies evaluated(15, 16, 115, 280, 305, 641, 812, 974, 1026-1028, 1030, 1034, 1037, 1041-1043, 1045-1052, 1056, 1057, 1060), 21 of which showed subjective sleep disturbance in participants with OND and glaucoma (15, 16, 280, 641, 974, 1026, 1027, 1034, 1037, 1041, 1042, 1046-1052, 1056, 1057, 1060). In their study of patients with Wolfram Syndrome (WS), Bischoff et al, (2015)(305) used the PSQI in adult subjects, in parallel with the Pediatric Sleep Questionnaire (PSQ) in subjects under 18 years(1065). They found a group effect in PSQ score, with poorer sleep and higher levels of sleepiness in WS compared to controls. However, the PSQ has primarily been used to identify OSA, PLM and RLS in children as opposed to circadian functioning(1066), and PSQI findings were not reported.

Lockley et al (1997)(16) found a PSQI of five in a blind subject with congenital glaucoma and buphthalmos, in conjunction with circadian dysrhythmia and delayed melatonin phase as part of an uncontrolled study of eight blind children. Prihodova et al (2021)(1028) studied 18 individuals with symptomatic mitochondrial optic neuropathies in comparison to 18 individuals with genetically confirmed LHON and DOA without VI, and found mean PSQI>5, but with comparable scores between groups, although a control group without VI or genetically confirmed mitochondrial optic neuropathies was not recruited. La Morgia et al (2010)(1034) used the PSQI to collect baseline data in their study of subjects with mitochondrial optic neuropathies in comparison to controls, and found a correlation with percentage difference in PSQI score and melatonin suppression in both controls and subjects with mitochondrial optic neuropathy. Munch et al (2015)(280) used the PSQI to assess subjective sleepiness in participants with HON and glaucoma and found poorer sleep quality in both conditions compared to control participants.

Pan et al (2015)(1050) studied 33 patients with NMOSD and found that those who were fatigued had higher PSQI scores than those without fatigue symptoms, although no ophthalmological assessment was recorded. Shi et al (2016)(1048) found a mean PSQI of 7.7 in patients with NMOSD, indicating poor sleep quality within the study population. Miao et al (2017)(1049) studied 42 participants with stable NMOSD and found a 64% prevalence of poor sleep and mean PSQI of 7.5±4.9, and correlation of PSQI with depression and pain-affective descriptions on the Expanded Disability Status Scale (EDSS), although a visual assessment was not conducted and there was no control group. Seok et al (2017)(1026) analysed 25 subjects with NMOSD with measurable fatigue and 10 subjects with NMOSD without fatigue. Mean PSQI in subjects with fatigue was 7.7±3.5 in comparison to 4.2±2.2 in those without fatigue, and the proportion of poor sleepers (PSQI>5) was higher in subjects with fatigue. Once again, a healthy control group was not enrolled in the study, and there was no documentation of visual function. Barzegar et al (2018)(812) compared 41 subjects with NMOSD with 136 age-and sex-matched controls with MS and found similar PSQI scores between groups, although males with MS had poorer sleep quality than females with MS. No visual assessment was reported, and a parallel set of healthy controls was not recruited. Turkoglu et al (2020)(1047) evaluated sleep quality in 10 patients with ON as a primary demyelinating event of MS (MON) in comparison to 16 patients who presented with non-ophthalmic demyelinating events (SMS), of whom eight (SON) later presented with ON. Mean PSQI scores were >5 in both groups (7.0 ± 3.1 in MON and 7.5 ± 2.9 in SMS), although scores were comparable between MON and SMS patients, and between those with a history of ON (MON+SON) in comparison to the remaining eight SMS patients with no ON history. No ophthalmological assessment was conducted to evaluate association of visual parameters with sleep, and no healthy controls were recruited. Hishikawa et al (2019)(1046) reported poor sleep quality in 75.6% of 106 participants with SMON compared to 39.6% of 110 age- and gender-matched healthy controls, with statistically poorer sleep quality, SL, SE, daytime dysfunction and increased use of sleep medications in SMON, although no assessments of optic nerve function were reported.

Romeijn et al (2012)(1042) used the PSQI to evaluate sleep in 33 patients with OCC and pituitary insufficiency compared to 17 patients with pituitary insufficiency alone and found that those with OCC had later bedtimes, although there was a higher proportion of males in

the OCC group, and no healthy control subjects were included in this analysis. Borgers et al (2011)(1043) found later habitual bedtimes on PSQI assessment in patients with OCC and pituitary insufficiency in comparison to those with pituitary insufficiency alone, with other PSQI parameters being comparable, although assessment of visual function and a control group with no history of pituitary lesions may have compromised their findings. Sagan et al (2021)(1041) studied 29 subjects with PA, 15 of whom had a history of OCC and in whom PSQI scores showed improved sleep quality, duration and SE post resection, although details of visual assessments to verify OCC were not included. Pickering et al (2014)(974) found worse subjective sleep quality and daytime dysfunction in participants with CP compared to healthy controls, which was confirmed with objective measures, although patients who were visually blind were excluded.

Tsika et al (2015)(1045) assessed subjective sleep quality in participants with AION and age-matched controls and found no difference in global score. La Morgia et al (2016)(115) studied 21 patients with AD and 74 age-matched controls, who were also found to have comparable PSQI scores.

Ayaki et al (2016)(1059) evaluated sleep wake in 69 participants with glaucoma in comparison to 71 healthy controls. They found that participants with advanced glaucoma had worse sleep quality and longer SL compared to controls, and corresponding loss of RGCs on RNFL evaluation in participants with glaucoma, although no objective measures of sleep wake were used to confirm subjective findings. Agorastos et al (2013)(1060) assessed 49 patients with moderate to severe glaucoma in comparison to 37 patients with mild glaucoma and found that subjective sleep quality as measured by the PSQI was worse in severe glaucoma, although a control group without ocular pathology was not recruited. Gubin et al (2021)(1052) conducted an interventional study of 2mg slow-release melatonin at 10.30pm for 90 days in 65 subjects with stable POAG (S-POAG) and 50 subjects with advanced POAG (A-POAG). A detailed visual assessment was conducted, including VA, VF, IOP, high-definition OCT RNFL to assess RGC loss, and PERG, with repeat IOP and PERG post-intervention. Baseline PSQI scores for sleep quality, sleep duration, SL and SE were worse in A-POAG, and post-intervention all recorded PSQI parameters improved in both groups, although a placebo control group was not compared. Ahmadi et al (2020)(1030) reported similar PSQI scores between 15 subjects with normal tension glaucoma (NTG) and 17 healthy

controls, with mean global scores of 3.93 and 3.38 respectively. Visual function in the NTG group was relatively high, with mean ETDRS VA of 83.5 with 95% confidence interval (CI) 77-90.1. VF MD was also mild to moderate in most NTG participants, with mean 9.05dB and 95% CI 5.75-12.55dB, suggestive of some RGC function, although RNFL thickness and PLR were reduced in NTG. Ma et al (2008)(1056) found that subjective sleep quality was poorer in primary angle closure glaucoma (PACG) and primary open angle glaucoma (POAG) in comparison to controls, which corresponded to elevated morning melatonin levels. Wang et al (2013)(641) found increased subjective sleep disturbance in 92 patients with POAG and 48 patients with PACG compared to 199 controls, with reduction of sleep quality with age in both POAG and controls subjects, and a non-significant trend for worsening VFD to correspond to poorer sleep quality in POAG. Chin et al (2020)(1057) studied sleep quality in 79 subjects with POAG, 27 with PACG and 89 healthy controls, with higher median PSQI and poorer sleep quality found in PACG. Combined POAG and PACG subjects with severe VFD of ≤-12dB were found to have worse sleep quality, as was the case in PACG subjects with VA of 6/15 or less. Mean MD was 5.89±7.0 in POAG and 6.33±7.9 in PACG indicating mild glaucoma severity in a proportion of subjects.

Ayaki et al (2015)(1027), as part of a wider study of sleep wake and mood in patients with ocular pathology, found that mean PSQI in 109 patients with glaucoma was 9.8, indicating poor sleep, although comparisons were not made to a healthy control group. Tabandeh et al (1998)(15) used PSQI evaluation in a controlled study of sleep quality in 388 subjects with low vision, including 45 with glaucoma or OND, in whom mean PSQI indicated poor sleep quality, with correlation of poor vision with sleep disturbance found, although this was not confirmed with objective measures. Adeoti (2010)(1037) conducted a study of subjective sleep wake in 170 patients with low vision including 56 patients with glaucoma and 10 with OA with mean PSQI scores of 8.6±3.1 and 9.9±3.4 respectively, and an association confirmed between degree of loss of vision and sleep disturbance in the group as a whole, although no comparison was made to a control group.

3.6.1(b) Epworth Sleepiness Scale

The ESS was employed in 12 studies I evaluated(115, 974, 1028, 1034, 1040-1043, 1046, 1047, 1050, 1054), and showed a mixture of non-significant findings and increased daytime sleepiness in OND and glaucoma.

La Morgia et al (2010)(1034) used ESS to collect baseline data in their study of melatonin suppression in subjects with mitochondrial optic neuropathies in comparison to controls, with comparable findings. Prihodova et al (2021)(1028) found no difference in 18 subjects with genetically confirmed LHON and DOA with VI compared to 18 without VI using ESS. However, 13 of the asymptomatic LHON subjects were relatives of those with VI, which may have compromised the control data if they lived together, as their sleep and wake times may have been interdependent. Pan et al (2015)(1050) found that ESS scores were higher in patients with NMOSD who reported fatigue than those without fatigue symptoms, but degree of VI was not clarified in their study. Romeijn et al (2012) used the ESS to compare subjective daytime sleep propensity in 33 patients with OCC and pituitary insufficiency in comparison to 17 patients with pituitary insufficiency alone and found no difference, although no comparison was made to a healthy control group and a detailed visual assessment was not documented. Sagan et al (2021)(1041) studied 15 patients with OCC due to PA, in whom ESS was comparable pre- and post-resection, with notable absence of ophthalmological evaluation in their study. Borgers et al (2011)(1043) found ESS scores to be comparable in patients with OCC and pituitary insufficiency and those with pituitary insufficiency alone, in the absence of a healthy control group. Joustra et al (2014)(1040) reported increased daytime sleep propensity in eight patients with CP compared to 17 healthy controls but did not detail visual findings. Pickering et al (2014)(974) found that ESS scores showed increased daytime sleepiness in CP patients compared to healthy controls, and were associated with low midnight melatonin concentrations, although this did not reach significance. Turkoglu et al (2020)(1047) reported higher ESS scores in ON as a first event in MS, and in ON that developed at any time during the course of MS compared with MS patients with no history of ON, although no assessment of ON severity or laterality was considered. Hishikawa et al (2019)(1046) found excessive daytime sleepiness with universally worse component scores on ESS in SMON compared to controls, although assessment of optic nerve function was absent in their publication. La Morgia et al (2016)(115) studied patients with AD in comparison to healthy controls and did not find any

notable difference in ESS scores between groups. Gracitelli et al (2016)(1054) found that daytime sleepiness was higher in 30 patients with POAG compared to 10 control subjects, which also corresponded to reduced SE on PSG and increased night time arousals, although subjective sleep quality was not assessed.

3.6.1(c) Morningness-Eveningness Questionnaire

The MEQ was used in four studies that I evaluated(280, 1034, 1045, 1053), with mixed findings. Two studies showed notable differences in chronotype in OND and glaucoma(1045, 1053), one study found no difference between OND and controls(1034), and one study used the MEQ as a tool in the selection process for control participants(280). La Morgia et al (2010)(1034) used the MEQ for baseline screening of participants with mitochondrial optic neuropathies and control participants prior to conducting studies of melatonin suppression, with no difference in MEQ scores reported. Munch et al (2015)(280) also used the MEQ for baseline screening of control subjects to eliminate extremes of chronotype in comparison to subjects with HON and glaucoma. Tsika et al (2015)(1045) found a tendency toward intermediate chronotype in participants with bilateral AION in comparison to those with unilateral pathology and controls, who were more likely to be morning chronotypes, and Gubin et al (2019)(1053) found that subjects with advanced POAG were more likely to be morning types that those with stable POAG.

3.6.1(d) Munich ChronoType Questionnaire

One study used the MCTQ, with equivocal findings between subjects with glaucoma and controls. Bierings et al (2019)(1029) used the MCTQ to evaluate chronotype in 221 patients with glaucoma in comparison to 163 controls, who were largely spouses, relatives and friends of glaucoma patients. No difference was found between patients and controls; however, the control group was younger ($p<0.001$), had a higher percentage of female participants ($p=0.005$), and was more likely to be in employment ($p=0.004$) than the glaucoma group, and the sleep of the control group (if relatives or partners of glaucoma patients) may have influenced by that of the glaucoma group. Of note, the median VF MD was -4.5 in the glaucoma group, indicating relatively mild pathology, and increased glaucoma severity was found to be associated with fluctuation of chronotype ($p=0.023$).

3.6.2 Sleep Disorders

3.6.2(a) Athens Insomnia Scale

Two studies in this review (1043, 1046) used the AIS as an assessment tool for sleep disorders, with no consensus in findings: One study found comparable levels of sleep disorders in OND and controls(1043), and one found a markedly higher incidence in OND(1046). Borgers et al (2011)(1043), used the AIS to assess subjective sleep disorders in 56 patients with pituitary insufficiency, 38 with OCC in and 18 without OCC and found no differences between groups. Hishikawa et al (2019)(1046) in their investigation of 106 individuals with SMON found that all AIS components were worse in SMON compared to controls, and that 89.6% of subjects with SMON compared to 54.4% of control subjects experienced insomnia.

3.6.2(b) Sleep Disorders Questionnaire

Two studies in this review used the SDQ(1042, 1043), with opposing results. Borgers et al (2011)(1043) did not find any difference in SDQ scores in subjects with pituitary insufficiency and OCC in comparison to those with pituitary insufficiency alone. Romeijn et al (2012)(1042) in their study of subjective sleep quality, daytime sleepiness and 24-hour skin temperature in 50 patients with pituitary insufficiency, found correlation of excessive daytime sleepiness (p=0.02) and OSA (p-0.009) with proximal skin temperature during the day.

3.6.2(c) Berlin Questionnaire

The Berlin Questionnaire was used in three studies in this review(115, 1034, 1040), with two studies finding indistinguishable results between OND and controls(115, 1034), and one study finding increased sleep disturbance in OND(1040). La Morgia et al (2010)(1034) screened participants using the Berlin Questionnaire in their study of melatonin suppression in mitochondrial optic neuropathies in comparison to a control group, although no significant results were reported. La Morgia et al (2016)(115) also used the Berlin questionnaire in their study of patients with AD in comparison to control subjects, and found

a comparable risk of OSA between groups, while Joustra et al (2014)(1040) found a high risk of sleep disturbance in subjects with NFMA and CP compared to controls.

3.6.3 Stress-Related Sleep Factors and Quality of Life

3.6.3(a) Hospital Anxiety and Depression Scale

The HADS was used in parallel with sleep measures in two studies evaluated in this review (1027, 1059), which produced conflicting data regarding the association of glaucoma and depression. Ayaki et al (2016)(1059) observed 69 subjects with glaucoma and 71 normally sighted controls and found no difference in anxiety or depression scores between groups using the HADS, although there was a difference in sleep quality. Ayaki et al (2015)(1027) found higher HADS depression (HADS-D) scores in patients with glaucoma compared to those with other ocular pathologies, although no comparison with healthy subjects was included in their analysis.

3.6.3(b) State-Trait Anxiety Index

The STAI was used in one study in this review and a positive association was found with glaucoma severity. Agorastos et al (2013)(1060) found that patients with severe glaucoma and marked VFD had higher trait anxiety than those with mild glaucoma and minimal or no VFD.

3.6.3(c) Beck Depression Inventory (BDI) and BDI-II

The BDI was used in three publications(280, 1050, 1052), with two out of three studies showing correlations between BDI and disease severity(1050, 1052). Munch et al (2015)(280) used the BDI to screen normally sighted controls subjects for depression and excluded those with scores greater than 10. They then found comparable scores between subjects with HON, glaucoma and the control group, although depression scores in the control group may have been artificially lowered and less representative of the general population in view of this selection process. Pan et al (2015)(1050) found that mean BDI scores were higher in NMOSD patients with fatigue than those without, and Gubin et al (2021)(1052) found that BDI scores correlated with shorter sleep duration, later sleep and

body temperature phase, loss of RGC volume and pattern ERG recordings in subjects with glaucoma.

Three studies used the BDI-II to evaluate depression (812, 1026, 1060), with associations found with pathological presentations and disease progression in all three. Agorastos et al (2013)(1060) found that worse depression scores were associated with disease severity in glaucoma, while Barzegar et al (2018)(812) found increased depression in MS compared to NMOSD, with higher scores in males than in females in both pathological groups. Seok et al (2017)(1026) found that depression was higher in subjects with NMOSD with fatigue than those without.

3.6.3(d) Medical Outcomes Study 36-Item Short Form Health Survey

The SF-36 was used in six studies in this review(812, 974, 1026, 1034, 1040, 1041). All six studies found notable associations of pathology with pain, physical or mental component scores. La Morgia et al (2010)(1034) used the SF-36 to collect baseline data in their study of melatonin suppression in participants with mitochondrial optic neuropathies and control participants, and recorded poorer physical functioning and pain scores in subjects with OND. Pickering et al (2014)(974) found that participants with CP had worse general health in comparison to controls, although mental and physical component scores were comparable. Joustra et al (2014)(1040) found poorer physical function in NFMA and CP, and poorer social function and health perception compared to controls, and Sagan et al (2021)(1041) found that ESS correlated with physical pain and mental health scores in subjects with a history of OCC, and that PSQI correlated with general health and physical and social function in subjects with PA in the absence of OCC history. Seok et al (2017)(1026) reported poorer physical and mental component scores in subjects with NMOSD presenting with fatigue compared to those without fatigue, and Barzegar et al (2018)(812) found worse physical and mental component scores in patients with NMOSD compared to those with MS, and poorer mental component scores in males with MS compared to females.

3.6.3(e) Multiple Sclerosis Quality of Life (MSQOL)-54

One study, Shi et al (2016)(1048) used the MSQOL-54 to evaluate quality of life in 73 patients with NMOSD, with an association found between physical component score and subjective sleep quality, although no comparison was made to a control group.

3.6.3(f) Quality of Life Measures Specific to Visual Function

No vision-specific QOL measures were used in the studies in this literature review; neither the NEI-VFQ-25 neuro-ophthalmology supplement nor any glaucoma-related evaluations were documented in any of the publications.

3.6.2 Objective Markers of Sleep Wake

Several publications included objective analyses of sleep wake and circadian rhythm in addition to evaluations of subjective sleep quality and duration, and in general a group effect in OND and glaucoma was found. Assessments included actigraphy in seven studies, all of which demonstrated differences in locomotor activity in OND and glaucoma compared to controls, and PSG, which was used in six studies, the majority of which showed altered sleep measurements and waveform in OND and glaucoma. Six out of nine studies using sleep logs or diaries indicated group or case differences in OND and glaucoma, while analysis of melatonin levels and responses, which was used in eight papers, appeared to vary with the underlying optic nerve pathology.

3.6.2(a) Physical and Physiological Measures

3.6.2(a)(i) Actigraphy

Actigraphy was used in seven studies evaluated (114, 115, 974, 1038, 1043, 1051, 1055), and universally showed altered sleep parameters in study populations with OND and glaucoma. Pickering et al (2014)(974) used actigraphy to study patients with CP and healthy controls and found that low midnight melatonin was associated with reduced physical activity counts, reduced TST and SE in patients, although the only notable group effect was a shorter time of sleep offset in CP. La Morgia et al (2016)(115) conducted an actigraphic study of 16

patients with AD and 10 healthy controls, and found that SE was worse and daytime activity was reduced in AD, but there were no differences in circadian patterns of rest and activity between groups. Lanzani et al (2012)(1055) observed rest-activity patterns in nine patients with bilateral advanced POAG and nine normal controls, and found reduced SE and TST, increased activity at night but no impact on daytime napping in the group with POAG. No differences in circadian phase were found between groups. Wee and Van Gelder (2004)(114) conducted an actigraphic study of 11 young people with OND with low vision in comparison to 14 with low vision due to other causes and 12 control subjects and found increased SL in subjects with OND in comparison to those without OND and controls. Webb et al (2010)(1038) evaluated objective sleep wake in six children with SOD and in 10 age- and sex-matched controls and found reduced SE in all children with SOD, and an arrhythmic rest-activity pattern in one child. Borgers et al (2011)(1043) assessed sleep wake using actigraphy in 38 patients with OCC and pituitary insufficiency in comparison to 18 with pituitary insufficiency alone and found later bedtimes, sleep onset and TST in those with OCC. Leger et al (2002)(1051) found worse SE and reduced TST in their study of 26 blind subjects, eight of whom had glaucoma, compared to normally sighted controls.

3.6.2(a)(ii) Polysomnography

PSG was used in six studies evaluated (468, 1028, 1047, 1050, 1051, 1054) with four studies finding worse sleep parameters and sleep architecture in OND and glaucoma(468, 1050, 1051, 1054), one study finding improved sleep recordings in OND with MS compared to MS alone(1047), and one study finding no effect in OND(1028).

Pan et al (2015)(1050) used PSG to compare fatigued and non-fatigued patients with NMOSD and found reduced stage 3 sleep in fatigued patients. Gracitelli et al (2016)(1054) performed PSG in 30 patients with POAG and 10 normal control subjects and found that increased daytime sleep propensity correlated with increased night time arousals, increased arousal duration after sleep onset and reduced SE. Leger et al (2002)(1051) conducted a PSG study of 26 blind subjects, including eight with glaucoma, who were found to have lower TST and SE than healthy controls. DelRosso et al (2014)(468) in their case study of a patient with bilateral TON and NPL vision found shortened TST, reduced SE and increased WASO, with multiple nocturnal awakenings recorded on hypnographic readings. Turkoglu et al

(2020)(1047) in their study of ON as a first- or ever- event in MS noted better SE and longer NREM duration in MON compared to other MS patients. Individuals with ON as an ever-event were found to have improved SE, longer NREM duration and reduced total wake time compared to those with MS with no history of ON. Prihodova et al (2021)(1028) found no correlation of PSG with subjective sleep outcomes, and sleep structure, respiratory findings and PLM recordings were comparable to normative data in their study of mitochondrial HON.

3.6.2(a)(iii) Sleep Logs or Diaries

Sleep logs were used in nine studies evaluated(280, 974, 1034, 1035, 1038, 1043, 1051, 1052, 1055), often in parallel with actigraphy, PSG or melatonin analysis. The majority of studies demonstrated altered rest-activity patterns in sleep diary recordings in populations with OND and glaucoma, although one study showed equivocal results using a sleep diary, but altered actigraphy in glaucoma(1055). Sleep diaries were used in two studies for baseline group assessments(280, 1034).

Flynn-Evans et al (2014)(1035) used sleep diaries to assess circadian timing in 127 women with low vision, including eight women with glaucoma, and found that five subjects with glaucoma were normally entrained, two were abnormally entrained and one showed no entrainment to day and night, although this subjects group was small, and no control group was recruited. Borgers et al (2012)(1043) used sleep diaries alongside actigraphy in 38 patients with OCC and pituitary insufficiency in comparison to 18 with pituitary insufficiency alone and found reduced TST in the group with OCC. Leger et al (2002)(1051) used sleep diaries concurrently with actigraphy and PSG, which showed reduced TST and SE in blind subjects compared to healthy controls. Gubin et al (2021)(1052) used sleep diaries at baseline and found a shorter mean sleep duration in advanced POAG compared to stable POAG, and Webb et al (2010)(1038) studied six children with SOD in comparison to 10 age- and sex-matched controls using actigraphy alongside sleep diaries, and found reduced SE and increased frequency and duration of night time awakenings in SOD, with one child with SOD displaying no discernible rest-activity pattern. Subjects in Pickering et al's (2014)(974) study of 15 patients with CP and 15 healthy controls kept sleep diaries in conjunction with actigraphic measurements. Analysis of sleep diaries showed a non-significant trend towards

an earlier time of sleep offset in CP patients, which reached significance on analysis of actigraphic recordings. Lanzani et al (2012)(1055) found that sleep logs were comparable between nine patients with bilateral advanced POAG and nine healthy controls, although actigraphy showed increased night-time activity in patients with POAG. La Morgia (2010)(1034) in their study of nine individuals with mitochondrial optic neuropathies in comparison to nine normally sighted controls used sleep diaries for one week prior to conducting the MNST to gather baseline sleep-wake data, with all subjects displaying a melatonin suppression response, although findings from the baseline sleep diaries were not discussed. Munch et al (2015)(280) also used sleep diaries to establish baseline compliance with a designated 8-hour night time sleep schedule in individuals with HON and control subjects.

3.6.2(b) Biochemical Measures

3.6.2(b)(i) Melatonin

Melatonin analysis was employed in nine studies(280, 974, 1034-1036, 1038, 1047, 1052, 1056) (three using RIA(1034-1036), three using ELISA(1047, 1052, 1056), one using competitive electrochemiliminescence immunoassay(974), and two unstated(280, 1038)). Serum melatonin was analysed in four out of eight studies(1034, 1038, 1047, 1056), salivary melatonin in two(280, 974), and urinary melatonin in two(16, 1035). Two studies used a melatonin suppression test to assess circadian pathways(280, 1034). The results of melatonin analyses in these reports appear to be influenced by the type of OND studied. For example, mitochondrial optic neuropathies appear to demonstrate preservation of pRGCs and melatonin responses(280, 1034), whereas some studies of glaucomatous disorders do not support intact retinohypothalamic pathways(1036, 1052, 1056) as described below.

3.6.2(b)(i)(i) Serum Melatonin

Of the four studies using serum melatonin(1034, 1038, 1047, 1056), a measurable difference between individuals with OND or glaucoma and controls was found in three(1038, 1047, 1056), with one study of mitochondrial optic neuropathies demonstrating comparable results with controls subjects(1034). La Morgia et al (2010)(1034) used serum melatonin to

observe response to bright light in nine subjects with mitochondrial optic neuropathies and nine control subjects, and found melatonin suppression in both groups. Ma et al (2008)(1056) measured morning serum melatonin and found that levels were elevated in 80 patients with PACG and in 120 patients with POAG compared to 120 normally sighted controls, suggesting a delay in circadian phasing, although no evaluation of RCG function on ophthalmological testing was published. Webb et al (2010)(1038) analysed serum melatonin to investigate circadian phasing in six children with SOD in comparison to 10 age- and sex-matched controls. Of the children with SOD, two produced virtually no melatonin and had irregular sleep patterns, one had higher than usually daytime melatonin, so that DLMO was difficult to ascertain, two had normal melatonin profiles with sleep fragmentation, and one had a normal melatonin profile and lack of rest-activity rhythmicity. Turkoglu et al (2020)(1047) found that serum melatonin was lower in patients with MON compared to those with other initial presentations of MS, although it was comparable in patients with MS and any history of ON versus those without ON.

3.6.2(b)(i)(ii) Salivary Melatonin

Salivary melatonin was utilised in three publications evaluated (280, 974, 1052) with a measurable difference observed between subjects in two studies(974, 1052), and no effect of HON on melatonin suppression found in one paper(280).

Munch et al (2015)(280) used salivary melatonin to asses circadian rhythmicity in 11 subjects with HON (including three with LHON and one with an OPA1 mutation) and 11 subjects with glaucoma in comparison to 22 matched controls and found that melatonin suppression was comparable between groups, despite marked visual morbidity. However, Pickering et al (2014)(974) evaluated 24-hour salivary melatonin profiles of individuals with CP in comparison to healthy controls and found that low midnight melatonin was associated with reduced SE, time of night sleep, TST and physical activity counts in CP, although individuals with NPL vision were excluded, and no ophthalmological assessments were recorded. Gubin et al (2021)(1052) assessed salivary melatonin rhythms in a subset of 15 patients with advanced POAG and found delayed circadian phasing.

3.6.2(b)(i)(iii) Urinary Melatonin

Two studies of patients with low vision used urinary aMT6s analysis to assess circadian rhythmicity(16, 1035), with examples of both normal and abnormal entrainment in one study(1035), and one study finding FR and abnormal entrainment in subjects with OND and glaucoma(1036), although numbers were small and no statistical analysis of OA or OND was conducted in either study.

Flynn-Evans et al(2014)(1035) found that a larger proportion of blind subjects with OA or glaucoma displayed normal entrainment on urinary aMT6s RIA. Among the six subjects with OA, three had LP vision, two of whom were normally entrained and one of whom was non-entrained; and three had NPL vision in which one subject was normally entrained, one was abnormally entrained and one was non-entrained. Eight participants had glaucoma, and of the seven with PL vision, four were normally entrained, two were abnormally entrained and one was non-entrained, and one subject with glaucoma had NPL vision with normal entrainment. Lockley et al (1997)(16) found abnormally entrained rhythms in two subjects with OND (one with TON and one with congenital OA), and a FR circadian rhythm and nap times in one subject with buphthalmos as part of an uncontrolled study of 49 blind subjects.

3.6.2(b)(i)(iv) Melatonin Suppression Test

Two studies employed a MNST approach in the evaluation of the integrity of circadian pathways(280, 1034), with preservation of melatonin suppression responses in both studies of subjects with mitochondrial optic neuropathies, other HON and glaucoma, which is suggestive of pRGC sparing in some pathologies.

La Morgia et al (2010)(1034) used the MNST in nine participants with mitochondrial optic neuropathies and nine controls and found that melatonin suppression occurred in both groups, with selective preservation of pRGCs found in postmortem eyes of subjects with mitochondrial optic neuropathies. Munch et al (2015)(280) observed 11 participants with HON and 11 with glaucoma in comparison to 22 normally sighted controls and found that melatonin response to light exposure was preserved despite loss of VA, VF and RNFL. However, results for participants with glaucoma may have been skewed as two subjects within the group who failed to demonstrate increased salivary melatonin prior to light exposure were excluded from the analysis.

3.6.3 Genetic Markers of Sleep Wake

One study, Gubin et al (2021)(1052) performed genotyping for clock genes on a subset of 15 patients in their interventional study of melatonin in POAG. No outcomes for clock gene testing were reported; however, carriers of the G-allele polymorphism of the MTNR1β melatonin receptor gene were found to have delayed melatonin rhythms.

3.7 Discussion

My review demonstrates that OND and glaucomatous conditions have a measurable impact on sleep wake. This takes the form of altered subjective sleep quality(280, 305, 641, 974, 1027, 1037, 1048, 1055, 1059), efficiency(115), duration(1043, 1062, 1067), timing of sleep and wake(114, 1043), and daytime napping and sleepiness(114, 305, 974, 1055). Objectively, melatonin production(974, 1034, 1038) and suppression(116), rest and activity patterns(114, 115, 974, 1038, 1043, 1055), circadian function(1036, 1051), pRGC number(115, 1034) and morphology(115) are demonstrably different in OND and glaucomatous conditions. Eight out of 43 studies (18.6%) examined duration of visual loss in relation to sleep quality and timing, with no positive associations found, although this information was only available in a small proportion of studies yielded.

Drawbacks included small sample sizes, although studies with smaller sample sizes tended to carry out extensive evaluations of visual function and objective and/or biochemical analyses, for example La Morgia et al (2010)(1034). Uncontrolled studies, such as Seok et al (2017)(1026) and studies with contaminated control groups, including the recruitment of spouses and family members were prevalent in this review, which could impact on sleep evaluation in control subjects (for example Bierings et al (2019)(1029)). Dissimilar control groups were present in some studies, as in Wee and Van Gelder's (2004)(114) study of young subjects with VI who were compared to healthy controls at a separate institution who had a markedly different morning routine. A dearth of information regarding visual function was noteworthy in studies of OND associated with neurological or endocrinological conditions, for example, Romeijn et al (2012)(1042), and unvalidated outcome measures,

including sleep assessment measures designed by the study authors, meant that generalisability of findings was limited, as in Adeoti (2010)(1037).

In systematic reviews and meta-analyses, publication bias may be suggested by a high proportion of studies reporting significant findings(1068, 1069). In this systematic review, 34 studies demonstrated measurably altered subjective sleep quality, duration or timing, with a further two studies showing altered objective sleep parameters, and three with inconclusive results, meaning that only four out of 43 studies (90.7%) did not show any effect, which is suggestive of potential publication bias.

I used a ROBIS tool to evaluate risk of bias within my systematic review methodology(1070). Strengths of my systematic review include the use of multiple databases and reference lists to obtain relevant articles. Selection of studies in my review was conducted according to eligibility criteria set using a PICOS guideline(1032), and no limits on date of publication were set. All studies yielded by my literature search that met my eligibility criteria were included in this review. I also used a modified NIH quality assessment tool to identify flaws and risk of bias within the studies(1064). Weaknesses of this review include limiting study selection to English language only, which was done for practical reasons, and the inclusion of published original papers only, as unpublished "grey" literature may have reduced publication bias. In addition, I was the sole author of this systematic review, meaning that a second author could not verify inclusion or exclusion of studies against the eligibility criteria and confirm that the overarching aims of the systematic review were met. I used Healthcare Databases Advanced Search (HDAS) to conduct my search of EMBASE, Medline, PsychINFO and PubMed. As HDAS closed in April 2022, this could lead to difficulty in replication of my search strategy, and I have included screenshots of my database searches with full search terms and expanded MeSH terms in Appendix B. Other factors that may have affected outcomes include heterogeneity of studies, and a lack of robust findings with absence of sensitivity analyses, power analyses or adjustment for confounders in the majority of papers.

3.8 Future Directions

Findings from my systematic review point to a need for a sufficiently powered large-scale controlled study of subjective sleep quality and timing in OND, which includes assessment of visual function, duration of VI, valid and reliable outcome measures of sleep quality and timing, with consideration of general health, mood and lifestyle, with adjustment for confounders.

3.9 Conclusion

Sleep quality and timing can have a profound effect on health and wellbeing. Good quality sleep is vital for optimum functioning. Clinically, patients with OND and glaucoma should be regularly asked about their sleep quality, timing, mood and QOL, and sleep disorders should be addressed alongside their medical and ophthalmological needs.

Chapter 4: Methods for Observational Study (Prospective and Retrospective Components)

4.1 Introduction

I conducted an observational cross-sectional study of sleep quality and timing in individuals with OND.

My research was based at Oxford Eye Hospital, within ERGO, and prospective data collection from participants with OND from multiple sites was undertaken between August 2016 and August 2018. A further retrospective data collection from participants recruited to SOMNUS at Oxford University Hospital was carried out in February 2022. A detailed descriptive analysis was carried out for a subgroup of participants with NMOSD and demyelinating disorders from the retrospective sample.

In this chapter I have used the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (1071, 1072) to provide a structured description of my methods. I discuss the background of the SOMNUS Study, ethical approval, aims and objectives, and methods, including subject recruitment, data collection and data analysis, of the prospective and retrospective components of my observational study.

4.2 Background and Setting

4.2.1 SOMNUS Study and Ethical Approval

I recruited participants with OND from neuro-ophthalmology and neurology clinics across multiple sites of the SOMNUS (Effect of Ocular Diseases on Body Clocks and Circadian Rhythms) National Institute for Health Research (NIHR) multicentre portfolio study (REC Reference – South Central – Oxford B 11/SC/0093; NIHR CMPS Reference 10558) (see Appendices D and E). As demonstrated by the REC reference code, this study was granted ethical approval (on 06/05/2011). In addition to the OND group, individuals meeting criteria from five other categories of ocular disorders including glaucoma, age-related macular degeneration, anophthalmia, diabetic retinopathy and inherited retinal disease were recruited to separate arms of the study across 10 sites (see Figure 5). A control group was

recruited in parallel from the study sites. Criteria for controls included being normally sighted, not having participated in shift work or transmeridian travel of greater than one time zone in the past three months and not a partner of an individual with an ocular disorder.

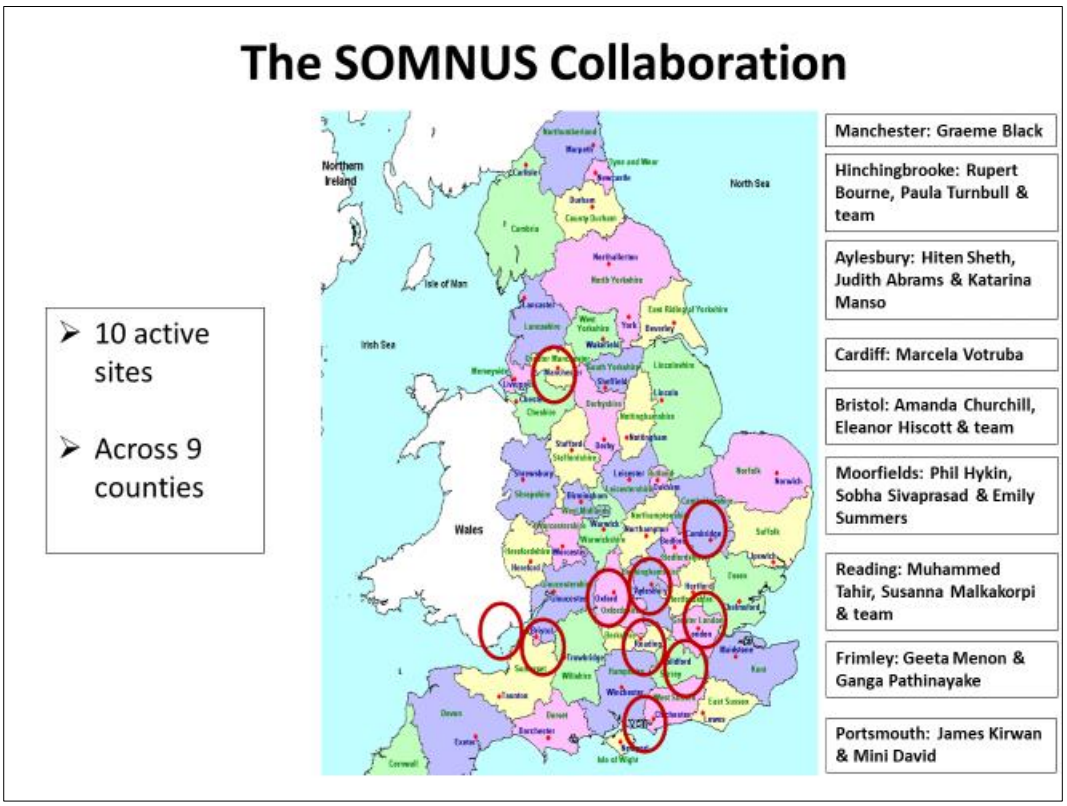


Figure 5: Principal Investigators and Specialist Nurses Recruiting to SOMNUS

From: Eye Research Group Oxford (2017). Reproduced with kind permission.

The work for my thesis was carried out a discrete arm of the SOMNUS study. To facilitate recruitment of participants with OND, a separate amendment (amendment 7.1, added 12/07/2017, reference as above) of the SOMNUS protocol was added and approved. All data were anonymised for analysis and formal written consent was obtained from participants in accordance with Good Clinical Practice (GCP)(41). The study was conducted in accordance with the tenets of the Declaration of Helsinki(42). Participants were free to withdraw their consent at any time, with subsequent removal of their data from the study.

4.3 Aims and Objectives

The aim of my observational study was to investigate the nature of the relationship between OND and sleep quality and timing.

Specific objectives for my observational study were to:

(a) Collect subjective sleep quality and timing, general health, QOL and mood data from individuals with OND (with details of ocular history, time since diagnosis and visual function) and from a normally sighted control group

(b) Statistically analyse data collected from individuals with OND and controls to determine whether OND and other health and lifestyle factors have an impact on sleep quality and timing.

4.4 Methods

4.4.1 Subjects

4.4.1(a) Prospective Component

4.4.1(a)(i) Participants with OND

I prospectively recruited participants with OND from ophthalmology and neurology clinics at five sites across the UK as part of my prospective study based on SOMNUS.

My intention was to recruit a large, representative sample of participants with OND. As OND are relatively less common than glaucoma, age-related macular degeneration and diabetic retinopathy(1073-1076) (all of which were investigated in separate arms of the SOMNUS study), recruitment of a sufficiently-powered sample was challenging. Therefore, I did not exclude any individuals with OND based on their past medical history, use of medications, travel history or working patterns. I collected information on participants' OND diagnoses, visual function, medical and medication history.

4.4.1(a)(ii) Control Participants

To form a control group, I recruited normally sighted participants with no history of ocular disease from seven UK sites in accordance with the SOMNUS study protocol. In accordance with all other arms of the SOMNUS protocol these participants were excluded if they reported current use of medications that influence sleep wake, including sleeping medications, psychiatric medications, glucocorticoids and beta-blockers. I also excluded control participants if they had a recent (within the past 3 months) history of transmeridian travel greater than one time zone or shift work. Controls were excluded if they were partners or carers of SOMNUS study participants due to the potential influence of their partners' or dependents' sleep patterns on their own sleep. Data collected from controls that I recruited were added to a data bank of controls that had been recruited from other arms of the SOMNUS study, so that as large and as representative a sample as possible could be analysed.

4.4.1(a)(ii)(i) Unmatched Controls

As per Bland and Altman (1994)(1077), subjects with OND were not matched to control subjects: as this is a large study with many variables, comparison with an unmatched control group and subsequent adjustment for variables using regression analysis was appropriate for this study.

4.4.1(b) Retrospective Component

I conducted a retrospective study of subjects with OND recruited from Oxford University Hospital in February 2022. These subjects had been recruited to the OND arm of SOMNUS during the prospective data collection period. I confirmed my findings from the raw data by cross-checking electronic patient records (EPR). To do this I used information stored in a separate database in line with anonymity and data protection guidelines. I ensured that the information that I collected in retrospect corresponded to the time of questionnaire completion.

4.4.1(b)(i) Subjects with Autoimmune and Demyelinating Optic Neuropathies

I conducted a detailed review of a subset of subjects with autoimmune and demyelinating OND from the data set of subjects with OND recruited from Oxford University Hospital. These included subjects with NMOSD, MS, CIS and ADEM. I cross-checked details of their raw data against the EPR (corresponding to the timing of questionnaire completion) using information stored in a separate database in line with anonymity and data protection guidelines.

4.4.1(c) Ethical Considerations

Ethical approval for this study was granted as described in Section 4.2.1. I obtained written informed consent from participants after I had explained the nature and possible consequences of the study. Consent was either taken on initial meeting with a participant, or a consent form and questionnaire pack was given to potential participants along with a pre-paid envelope with the address of ERGO if they felt that they would like to take more time to consider their decision. At all points it was emphasised that participation was entirely voluntary, and I ensured that participants were aware that they were free to withdraw from the study at any time, with removal of their data from the study database. The SOMNUS Patient Information Leaflet and Consent Form can be found in Appendix D.

4.4.2 Methodology

4.4.2(a) Prospective Study Methodology

4.4.2(a)(i) Clinical Information from Medical Notes

Information regarding ophthalmological diagnoses, past ocular history, past medical history and medication history were obtained from OND participants' medical notes, which was discussed with them and included in the consent process. This was used to supplement some of the information in the GHQ, for example when a participant could not remember the specifics of their ocular or medical history or what medications they were taking. Details of the most recent VA and VF recordings were also obtained.

4.4.2(a)(ii) Ophthalmological Examination

I recorded VA in OND participants, which was measured in Logarithm of the minimum angle of resolution (LogMAR) where available. Alternatively, I used a standardised tool to convert Snellen VA into LogMAR VA (See Appendix F), so that the results could be coded to a csv programme for analysis.

I used the best visual acuity of the better eye (BVA) of each participant in my statistical analysis to reflect the maximal visual and RGC function available to that patient.

Where it was available as part of their routine clinic workup, I recorded participants' HVF mean deviation (MD) to evaluate central and peripheral vision in OND participants. No electrophysiological information to evaluate RGC function was available in participants with OND.

4.4.2(a)(iii) Questionnaires

I collected subjective data from participants using a compilation of seven questionnaires to assess multiple aspects of sleep, physical, emotional and social functioning, general health, lifestyle and mood (see Appendix D) in individuals with OND and control participants. The questionnaires that I used comprised:

1. The PSQI. This assesses seven dimensions of sleep (sleep quality, SL, sleep duration, habitual SE, sleep disturbance, use of sleeping medications, and daytime dysfunction)(43). It has a high degree of sensitivity and specificity for identifying sleep disorders. Scoring is on a scale of 0-21, with a score of greater than five indicating poor sleep quality, indicative of a sleep disorder(953). A score of 10 or more has been used in previous studies to denote severe sleep impairment(1078);
2. The JMCQ. This assesses the presence of RLS and OSA(45, 966) and has been used in a small number of published studies (918, 966);
3. The GHQ. This was used to collect demographic, socioeconomic, and general health data, including past medical history, drug history and psychiatric history. It was adapted from the PHQ(46), and is not a validated tool. It provided the information on

existing medical conditions, medications and lifestyle choices that may have affected sleep in participants with OND and the control group;

4. The SF-36. This assesses physical, emotional and social functioning aspects of QOL(47), has been found to have good consistency and item validity, and has been used in studies of subjects with OND as part of a systemic disorder, which reflects a notable proportion of subjects with OND in this study(973, 974, 1079);
5. The MEQ. I used this to evaluate chronotype, i.e. diurnal preference, or an individual's natural tendency towards being a "morning lark" or a "night owl"(48). It has been found to be reliable and has been used to determine chronotype in studies of vascular and mitochondrial optic neuropathies(955, 1034, 1045);
6. The ESS, which is an assessment of daytime sleepiness. This runs on a scale from 0-24 with a normal being classified as a score between two and 10(49, 919). It consists of a pictorial representation of subjective daytime sleep propensity, and has been found to correspond to the MSLT and MWT, which measure objective aspects of daytime sleepiness(49). The ESS has been used to assess sleep wake in participants with autoimmune, demyelinating, compressive and mitochondrial optic neuropathies in published studies(1034, 1042, 1080, 1081);
7. The HADS. This provides an assessment of anxiety (HADS-A) and depression (HADS-D) in two separate subscores of 0-21, with a subscore greater than seven indicating the presence of anxiety or depression(50). It has been found to be an effective measure of general psychological distress(970, 971), and has been used to evaluate mood alongside the study of sleep wake in subjects with glaucoma and diabetes(1027, 1059, 1082).

4.4.2(b) Retrospective Study Methodology

I reviewed anonymised raw data front sheets, completed SOMNUS study questionnaires (see Appendix D) and GHQ details of medication history, shift work and transmeridian travel. I also reviewed OSA screen details from the JMCQ. I confirmed my findings from the ophthalmological, medical and medication history data by cross-checking the EPR. I ensured that the information that I collected in retrospect corresponded to the time of questionnaire completion.

4.4.2(b)(i) Goldmann Visual Fields

On searching the EPR and SOMNUS raw data packs, I found that 12 out of the 110 subjects had GVFs contemporaneous to questionnaire completion.

Goldmann kinetic perimetry is a test of full-field perimetry and measures stimuli at different light intensities (measured from 1-4 for every 5dB change, with smaller increments graded from a-e) and stimulus sizes from 0 (1/16mm^2) to V (64mm^2), which are mapped over circular isopters, according to the intensity and size of stimulus viewed over the visual field(151). Techniques for digitising and evaluating the volume of a GVF to produce a single numerical value have been described, but this does not equate to MD(1083, 1084). In contrast, HVF tests the central 30 degrees of vision and produces a numerical quantification of VF loss (MD), variability of the VFD (pattern standard deviation) and percentage of full VF present (visual field index), with progression indices also used to compare VF over time(151, 1085).

I reviewed the literature and sought expert advice from two ophthalmology professors regarding the possibility of numerical conversion of GVF data to MD for analysis. It was determined that conversion of Goldmann data to a comparable numerical MD value for analysis alongside HVF data was not feasible.

4.4.2(b)(ii) Methodology for Subset with Autoimmune and Demyelinating Optic Neuropathies

I reviewed VA, VF, ocular history including cataract, and medical and medication history from raw data front sheets. I reviewed health and lifestyle information obtained from the GHQ, the JMCQ OSA screen and HADS data and cross-checked these details against the EPR. I ensured that the information that I collected corresponded to the time of questionnaire completion. Additionally, I collected EPR data contemporaneous with the time of questionnaire completion which included:

(a) Time since diagnosis, divided into ordinal categories of <1 year, 1-<3 years, 3-<5 years and 5+ years since diagnosis as per Wingerchuk et al (2007)(328)

(b) Whether the subjects were inpatients or outpatients (inferred from coinciding stays for intravenous infusions or inpatient treatments under the neurology department)

(c) BVA data, with review of questionnaire front sheets and EPR. I then used the Royal National Institute of Blind People (RNIB) criteria (2022)(1086) for certification of VI (CVI) to define subjects as sight impaired (SI), severely sight impaired (SSI) or as not meeting the criteria

(d) Additional HVF MD measurements. For all subjects with HVF data available, I categorised VFD as mild if MD >-6dB; moderate if MD of -6 to -12dB, and severe if MD <-12dB as per Chin et al (2020)(1057)

(e) The presence of sphincter dysfunction, pain and fatigue.

4.4.3 Methods of Analysis

4.4.3(a) Data Analysis of Prospective Component

I manually entered all paper-based demographic and questionnaire data into an Excel csv and subsequently analysed this data using R-2.15 (R Development Core Team 2012, University of Auckland, Auckland, New Zealand; available at http://www.R-project.org).

I used a generalised regression model using the binomial family to fit proportional responses. I used a multiple linear regression model to assess the relationship between PSQI and HADS in OND compared to controls adjusted by age, sex, BMI, season, chronotype, daytime sleepiness, anxiety and depression. PSQI and HADS scores were square root transformed to fit assumptions of linearity. I used the most parsimonious cumulative linked mixed-model (using the ordinal library in R) to analyse the component scores of the PSQI. I used a Wilcoxon rank-sum test to carry out simple group comparisons of continuous variables and Fisher's exact test to check comparability of overall good and poor sleep, anxiety and depression, and daytime sleepiness scores between individuals with OND and control participants. Details of the R code can be found in Appendix G.

4.4.3(a)(i) Retrospective Power Calculation (For Prospective Component)

I conducted a retrospective power calculation using the R package pwr.f2 test. For a moderate effect size (Cohen's f 2) of 0.15 with 9 predictors and power of 0.8, the required

sample size is 100, meaning that the prospective OND sample of 122 subjects, and the retrospective sample of 110 participants were sufficiently powered(1087, 1088).

4.4.3(b) Data Analysis for Retrospective Component

4.4.3(b)(i) Sensitivity Analysis

I manually entered paper-based and EPR data retrospectively collected from the 110 subjects with OND recruited from Oxford University Hospital into an Excel csv and conducted a sensitivity analysis for use of systemic glucocorticoids, shift work, transmeridian travel and OSA screen using a general linear model and a linear model (see Appendix G). It was not feasible to conduct a sensitivity analysis for chronic global neurological disease as this was present in a large proportion of the study population with OND. As this sample formed the majority of the population of my prospective study, its use for a sensitivity analysis was deemed acceptable by team statisticians.

4.4.3(b)(ii) Subjects with Autoimmune and Demyelinating Optic Neuropathies

I entered paper-based and EPR data into an Excel csv for analysis of retrospective data collected from subjects with autoimmune and demyelinating OND. I used descriptive statistics to present my findings in this subset of data, as the sample size was not sufficiently powered to conduct a meaningful statistical analysis.

Chapter 5: Results of Observational Study (Prospective and Retrospective Studies of Sleep Quality and Timing in Optic Nerve Disorders)

5.1 Introduction

This section sets out the results of my observational study of subjective sleep quality and timing in OND and control participants. I will start by presenting my analysis of prospective data including demographics, general health and sleep disorders followed by sleep, wake, mood and QOL in participants with OND versus control participants. I will then describe the range of pathologies within my study population.

In Section 5.8, I report my retrospective study data, including descriptive analysis of data from the subset of participants with autoimmune and demyelinating OND.

I have used CONSORT(1089) diagrams to illustrate flow of participants through the prospective and retrospective components of my observational study (See Figure 6(a-c)).

Figure 6(a): CONSORT Diagram Demonstrating Flow of Participants with Optic Nerve Disorders through Prospective Study

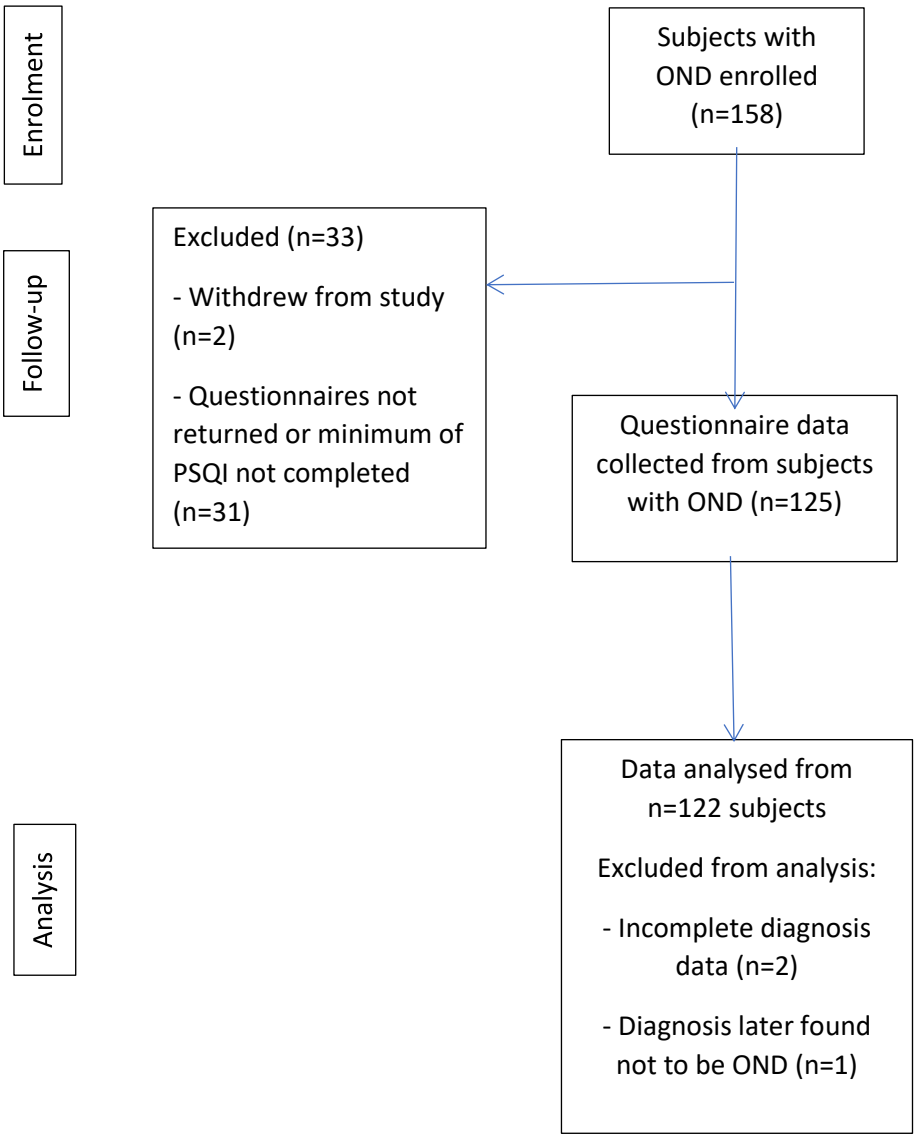


Figure 6(b): Flow of Control Participants through Prospective Study

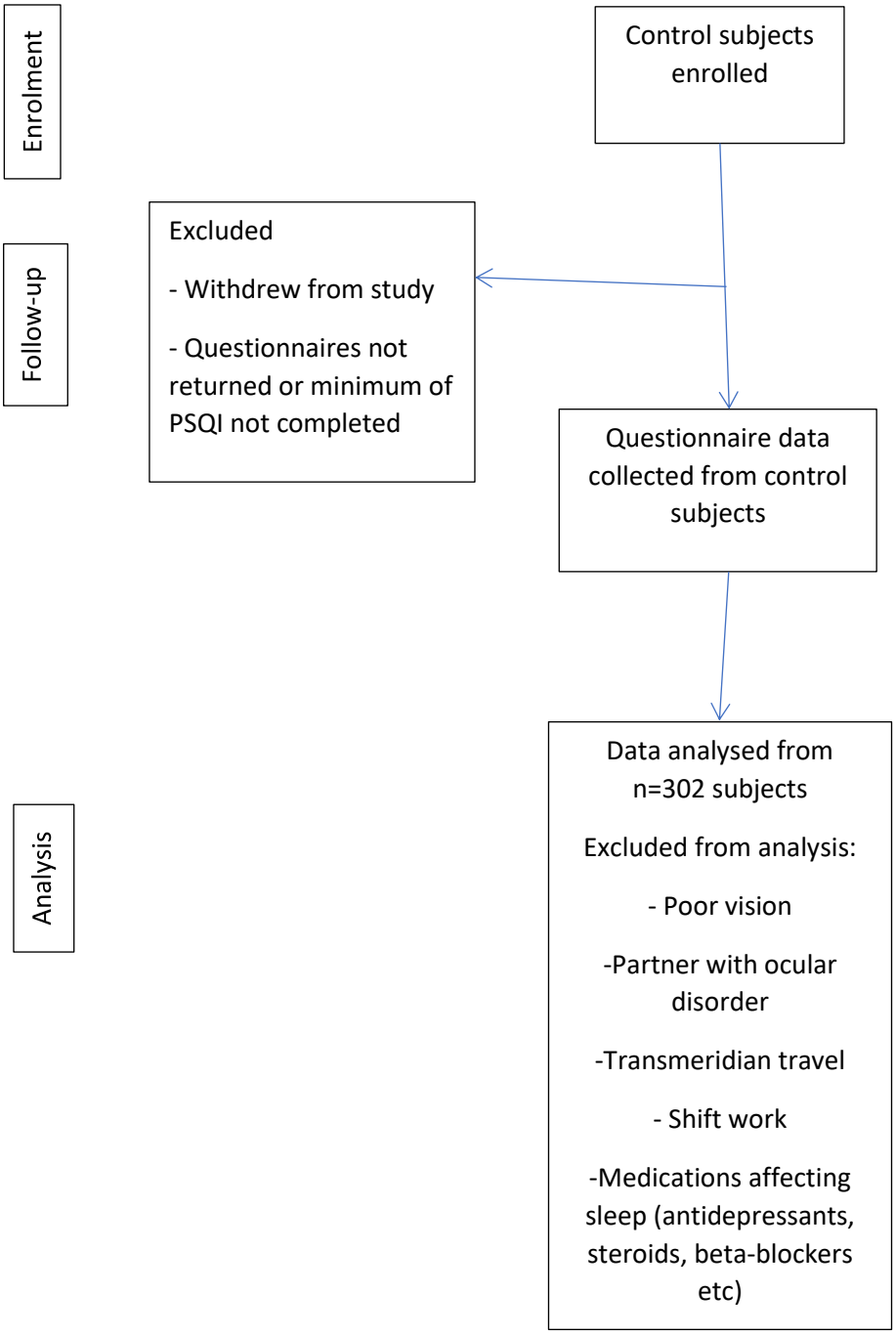
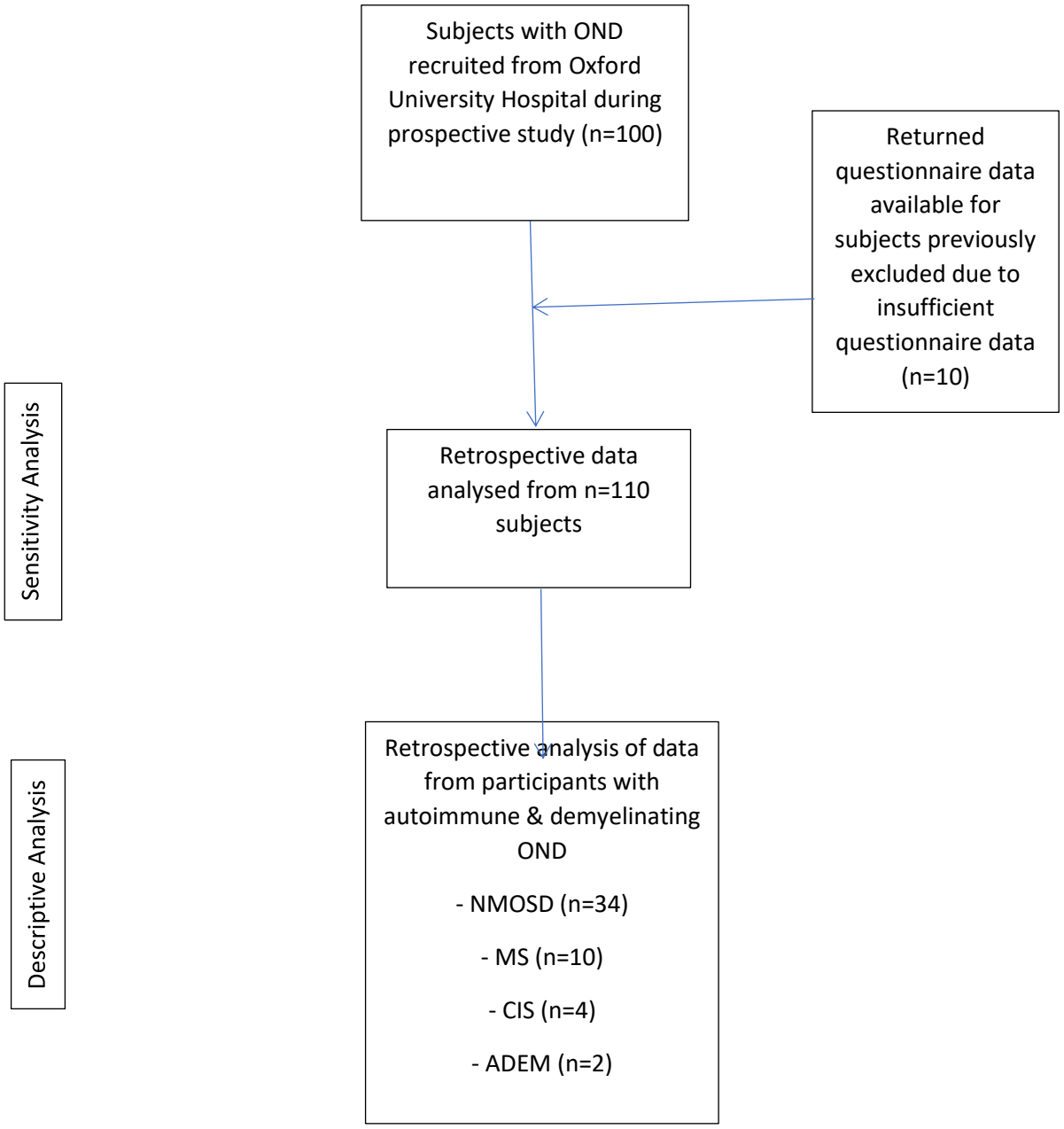


Figure 6(c): Flow of Participants with Optic Nerve Disorders through Retrospective Study



5.2 Demographics

I recruited a total of 158 individuals with OND. I included 122 individuals with OND in my analysis (36 were excluded due to incomplete age, diagnosis and PSQI data, or due to withdrawing from the study, see Figure 6a). A total of 302 control participants with excellent VA (LogMAR </= 0) participated (see Figure 6b).

My comparison of demographic data between OND and control participants is shown in Table 8. Age (W= 19640, p=0.4), chronotype (W=19724, p=0.4) and the season the questionnaires were completed in (($\chi^2(3)=2.4718$, p=0.5) were comparable between OND and control participants. Neither BMI (W=13906, p=0.005) nor sex ($\chi^2(1)=18.783$, p<0.001) were comparable between groups.

Caffeine (p=0.9) and alcohol (p=0.2) intake were comparable between OND and control groups. There was a trend for the number of cigarettes smoked per day to be comparable between groups (p=0.07).

Table 8: Demographic Comparison of OND and Control Groups

	OND (n=122)	Controls (n=302)	Statistics	p value*
Mean Age (SD)	46.4 (16.1)	44.8±16.3	W=19640	p=0.4
Sex M/F	60/62	83/219	X^2=18.783 (df=1)	p<0.01*
% Male	49.2	27.4	X^2=18.783 (df=1)	<0.01*
Mean BMI kg/m^2 (SD)	28.3 (7.0)	26.5±6.5	W=13906	0.005*
Mean LogMAR VA (SD)	0.4 (0.7)	0	-	-
Moderate VI or Better <1.00 n (%)	105 (86.1)	302	-	-
Severe VI >1.00 n (%)	17 (13.9)	0	-	-
Caffeine n daily intake (%)	93 (76.2)	247 (81.8)	W=18588	0.9
Nicotine n daily smokers (%)	15 (12.3)	19 (6.4)	W=17682	0.07
Alcohol n>14 units/week (%)	17 (13.9)	30 (9.9)	W=20360	0.2

Key: BMI= Body mass index; df=Degrees of freedom; LogMAR=Logarithm of the minimum angle of resolution; M/F=Males/Females; OND=Optic nerve disorder; SD=Standard Deviation; VA=Visual acuity; VI=Visual impairment; W=Wilcoxon value; X^2=Chi squared value; *significance at p≤0.05

5.3 General Health Questionnaire

I excluded control participants if they had a history of psychiatric conditions, were taking psychiatric medication, anxiolytics, sleeping medications, or beta-blockers.

In the OND group, 38 participants (31.1%) were taking steroid medications; 10 participants (8.2%) were taking benzodiazepines or other sleeping medications; five (4.1%) were taking oral beta-blockers and one (0.8%) was taking a topical beta-blocker (eye drops). 36 (29.5%) OND participants had a history of anxiety, depression or other mental health condition, and 19 (15.6%) were taking psychiatric medications.

Participants were asked in the GHQ whether they had performed any shift work in the last year, and whether they had travelled across more than one time zone in the past three months (GHQ questions 28 and 29, see Appendix D). Eight out of 122 participants with OND (6.6%) said that they had undertaken shift work in the last year, and 15 out of 122 participants with OND (12.3%) said that they had travelled across more than one time zone in the past three months. I conducted a sensitivity analysis on the retrospective data that I collected (detailed in Section 5.8) to assess the impact of inclusion of participants with OND who had engaged in shift work or transmeridian travel.

5.4 Jupiter Medical Center Questionnaire

116 participants with OND completed the JMCQ, which was used to screen for OSA and RLS as detailed below.

5.4.1 Obstructive Sleep Apnoea Risk

Questions 16, 17 and 18 of the JMCQ were used to screen for risk of OSA (see Appendix D), with an answer of “Yes” to all three questions taken as a positive screen. Five out of the 116 participants with OND (4.3%) who completed the JMCQ answered yes to all of these questions. Studies of OSA in the general adult population have reported a prevalence of approximately 3-7% in adult males and 2-5% in adult females(1090).

5.4.2 Restless Leg Syndrome and Parasomnia Risks

Questions 9a-9e of the JMCQ (see Appendix D) were used to screen for risk of RLS. 71 out of 116 participants with OND (61.2%) were found to be at risk of RLS. This was in comparison to 55 out of 302 control participants (18.2%).

Questions 6h and 6i of the JMCQ (see Appendix D) were used to screen for risk of parasomnias. This was found in 34 out of 116 participants with OND (29.3%), which is higher than the prevalence of parasomnias in the general adult population of approximately 4%(199).

5.5 Sleep Wake, Mood and Quality of Life in OND and Controls

Poor sleep (PSQI>5) was reported in 65.6% of individuals with OND and in 39.7% in controls ($\chi^2(1)=20.69$, $p<0.0001$) (See Table 9). Daytime sleepiness (ESS) ($p=0.3$) and anxiety ($p=0.6$), but not depression ($p<0.001$) scores were comparable between groups (see Tables 9-12 and Figures 7-9). All QOL component scores except emotional wellbeing (EMWB) ($p=0.5$) were not comparable between groups (see Table 12).

5.5.1 Sleep Scores in OND versus Controls

Individuals with OND were more likely to report poor sleep (PSQI score >5) than controls (Binomial GLM; $p<0.001$, McFadden's $R^2=0.26$) (see Table 9). Across the whole study population, sleep worsened with increasing age ($p<0.001$) and BMI ($p=0.03$), and females ($p=0.04$) were more likely to report poor sleep than males. Poor sleep was associated with increased anxiety ($p<0.0001$) and depression ($p=0.036$) (see Table 11).

Overall sleep quality scores were worse in individuals with OND than controls ($p<0.0001$, $R^2=0.33$). Overall sleep quality worsened with increasing age ($p=0.02$) and BMI ($p=0.0005$). Females had worse sleep scores than males ($p=0.02$) and as sleep scores worsened, so did anxiety ($p<0.0001$) and depression ($p=0.0009$) scores.

There was no difference in overall MEQ scores between OND and controls ($W=19724$, $p=0.4$) nor in the proportion of the MEQ categories (01,2,3,4) between ON and controls

(X2=2.4718, df=3, p=0.5) (see Table 10). This means that chronotype was comparable between groups.

5.5.2 Sleep Components underpinning Sleep Quality Scores in OND versus Controls

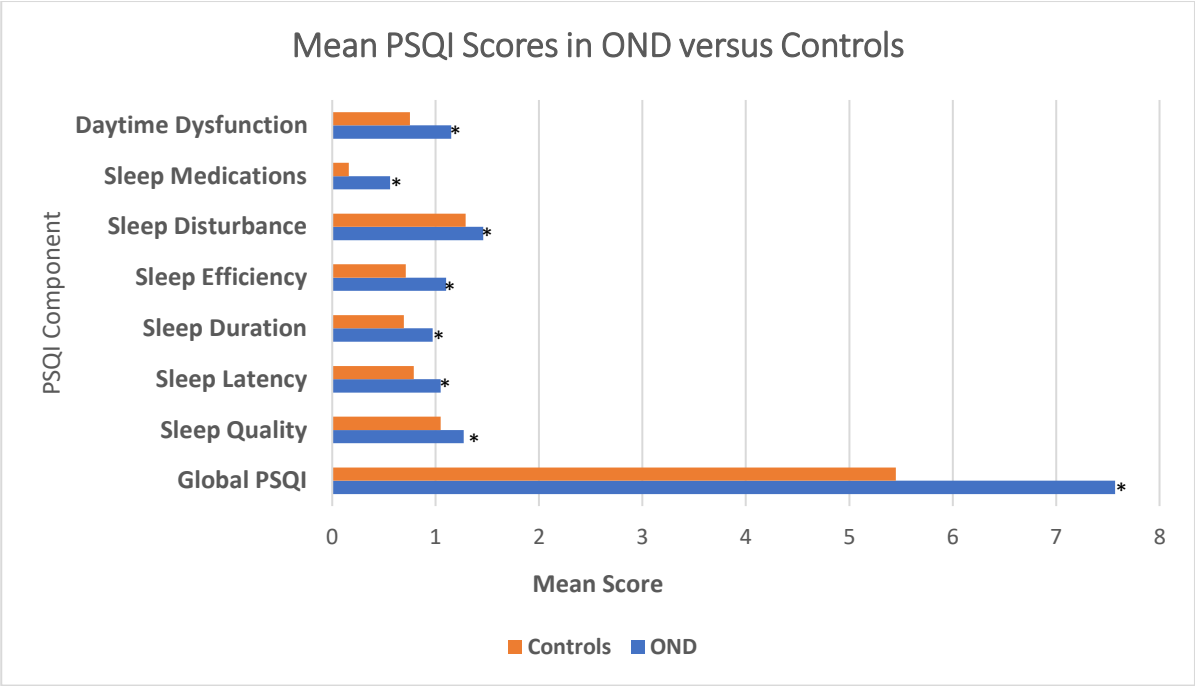
Individuals with OND had worse sleep quality (p=0.03), longer SL (p=0.003), longer sleep duration (p=0.02), worse SE (p=<0.001), increased sleep disturbance (p=0.04) and were more likely to take sleep medicines (p=0.03) and have worse daytime dysfunction (p=0.05) than controls (see Table 9).

Table 9: Global PSQI and PSQI Subscores in OND versus Controls

PSQI Score	OND	Controls	Statistics	p Value
PSQI >5 n (%)	80 (65.6)	120 (39.7)	X^2=20.69	<0.0001**
Global PSQI Mean (SD)	7.6 (4.4)	5.5 (3.2)	McFadden's R^2=0.26	<0.001*
Quality Mean (SD)	1.3 (0.8)	1.1 (0.7)		0.03*
Latency Mean (SD)	1.1 (0.8)	0.79 (0.7)		0.003*
Duration Mean (SD)	1.0 (1.1)	0.7 (0.9)		0.02*
Efficiency Mean (SD)	1.1 (1.2)	0.7 (1.0)		<0.001*
Disturbance Mean (SD)	1.5 (0.6)	1.3(0.6)		0.04*
Medication Mean (SD)	0.6 (1.1)	0.2 (0.6)		0.03*
Daytime Dysfunction Mean (SD)	1.2 (1.0)	0.75 (0.8)		0.05*

Key: OND=Optic nerve disorders; PSQI=Pittsburgh Sleep Quality Index; R^2=McFadden's R-squared; SD=Standard deviation; χ^2=Chi squared value; *Significant to p≤0.05; **Significant to p≤0.0001.

Figure 7: Mean PSQI Scores in OND versus Controls



Key: PSQI=Pittsburgh Sleep Quality Index; OND=Optic nerve disorder; *Significant to p≤0.05.

Table 10: ESS and MEQ in OND versus Controls

Questionnaire		OND	Controls	Statistics	p Value
ESS	Mean (SD)	6.8 (4.7)	6.2 (4.2)	W=17409	0.3
	Normal Range <11 n (%)	99 (81.1)	235 (77.8)	-	-
MEQ	Mean (SD)	58.4 (10.7)	59.3 (9.6)	W=19724	0.4
	Season	-	-	X^2=0.4804 (df=3)	0.5

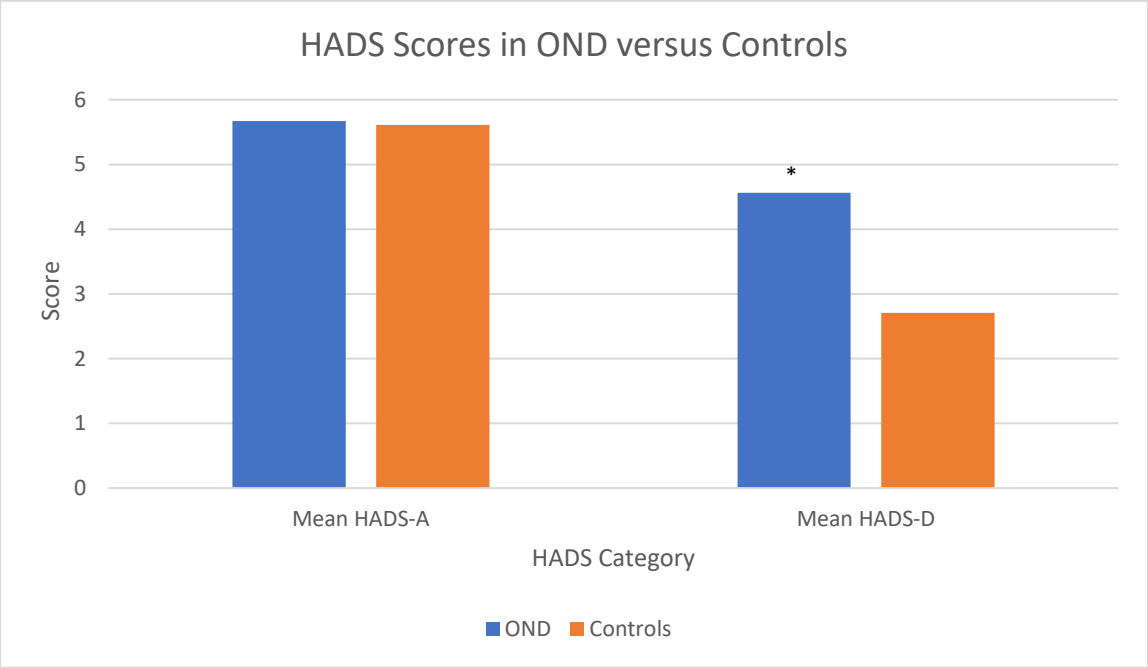
Key: df=Degrees of freedom; ESS=Epworth Sleepiness Scale; MEQ=Morningness-Eveningness Questionnaire; OND=Optic nerve disorders; n=Number; W=Wilcoxon test value; X^2=Chi squared value.

Table 11: HADS Scores in OND versus Controls

HADS Subscore	OND	Controls	Wilcoxon Test (W Value)	p Value
HADS-A Mean (SD)	5.7 (4.3)	5.6 (3.6)	19287	0.6
HADS-A Normal Range n (%)	88 (72.1)	221 (73.1)	-	-
HADS-D Mean (SD)	4.6 (4.0)	2.7 (2.6)	14162	0.04*
HADS-D Normal Range n (%)	99 (81.1)	286 (94.7)	-	-

Key: HADS=Hospital Anxiety and Depression Scale; HADS-A=HADS anxiety subscore; HADS-D=HADS depression subscore; n= Number; OND=Optic nerve disorder; SD=Standard deviation; *=Significant to p≤0.05.

Figure 8: HADS Scores in OND versus Controls



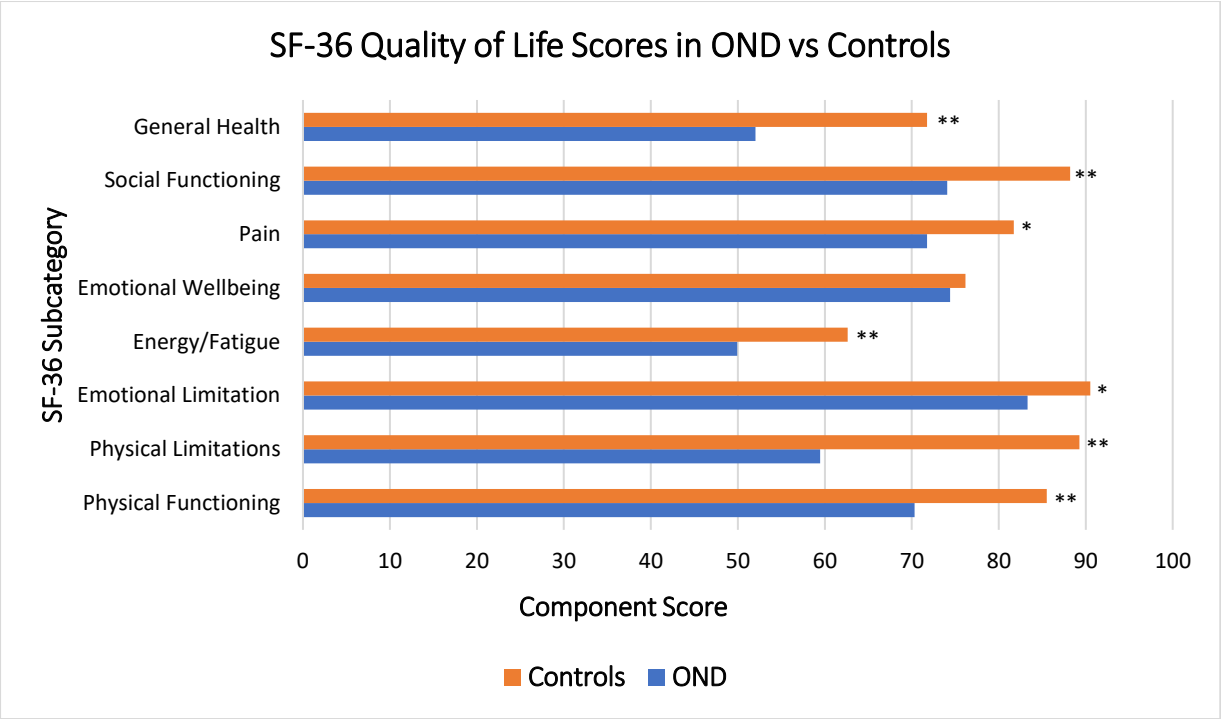
Key: HADS=Hospital Anxiety and Depression Scale; HADS-A=HADS anxiety subscore; HADS-D=HADS depression subscore; OND=Optic nerve disorder; *Significant at p≤0.05.

Table 12: Quality of Life Scores in OND versus Controls as Measured by the SF-36

SF-36 Subscore Mean (SD)	OND	Controls	Wilcoxon Test (W Value)	p Value
Physical Functioning	70.3 (29.4)	85.5 (20.2)	25033	<0.0001**
Physical Limitations	59.5 (44.0)	89.3 (36.9)	25555	<0.0001**
Emotional Limitation	83.3 (32.5)	90.5 (25.3)	20743	0.0084*
Energy/Fatigue	49.9 (23.6)	62.6 (19.4)	24377	<0.0001**
Emotional Wellbeing	74.4 (18.3)	76.2 (16.7)	19370	0.5
Pain	71.7 (28.5)	81.7 (21.9)	21524	0.003*
Social Functioning	74.1 (30.3)	88.2 (19.9)	23236	<0.0001**
General Health	52.0 (26.8)	71.8 (19.4)	26531	<0.0001**

Key: OND=Optic nerve disorder; SD=Standard deviation; SF-36=Medical Outcomes Study 36-Item Short Form Survey; *Significant at p≤0.05; **Significant at p≤0.0001.

Figure 9: SF-36 Scores in OND versus Controls



Key: OND=Optic nerve disorder; SF-36=Medical Outcomes Study 36-Item Short-Form Survey; *Significant to p≤0.05; **Significant to p≤0.0001.

5.6 Sleep Quality and Mood in OND Alone

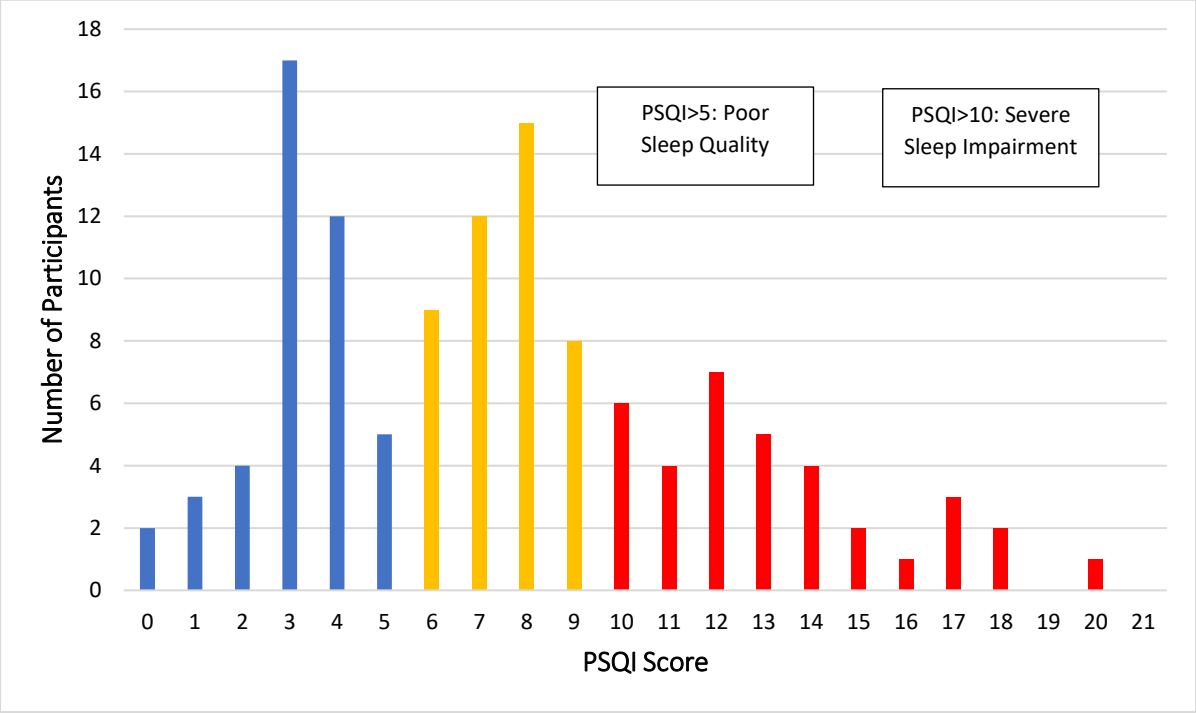
Out of the total 122 participants with OND, 44 participants had PSQI scores between 6 and 10 (36.1%). 35 participants had a PSQI score of 10 or more (28.7%). 43 participants had a PSQI score of five or less (35.0%) (see Figure 10).

Neither sex (p=0.6), caffeine (p=0.3), smoking (p=0.2) nor alcohol consumption (p=0.5) impacted sleep quality. There was a trend for sleep quality to worsen with increasing age (p=0.07) and BMI (p=0.06). As sleep quality worsened so did anxiety (p=0.002) and depression (p=0.002) scores. The spread of HADS anxiety and depression scores in participants with OND can be seen in Figures 13 and 14.

All 122 participants with OND had BVA recorded, and 47 participants with OND had complete HVF data available. The mean BVA in OND participants was 0.4±0.7LogMAR. Out of the 47 participants with HVF data available, the mean HVF MD of the better eye (and

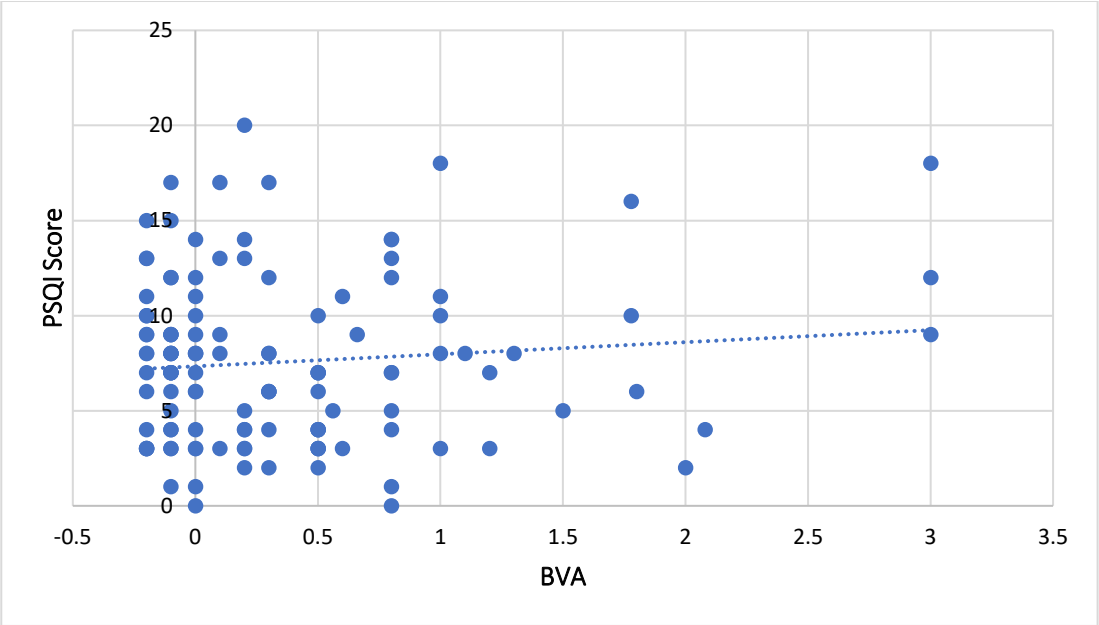
standard deviation) was -4.6(±5.2)dB. A Spearman's rho correlation was used to assess the relationship between sleep quality and BVA or HVF MD. There was no significant relationship between BVA and sleep quality (Rs = -0.033, p=0.7), nor between better eye HVF MD (BVF) and sleep quality (Rs=0.062, p=0.7) (see Figures 11 and 12).

Figure 10: PSQI Global Scores in OND



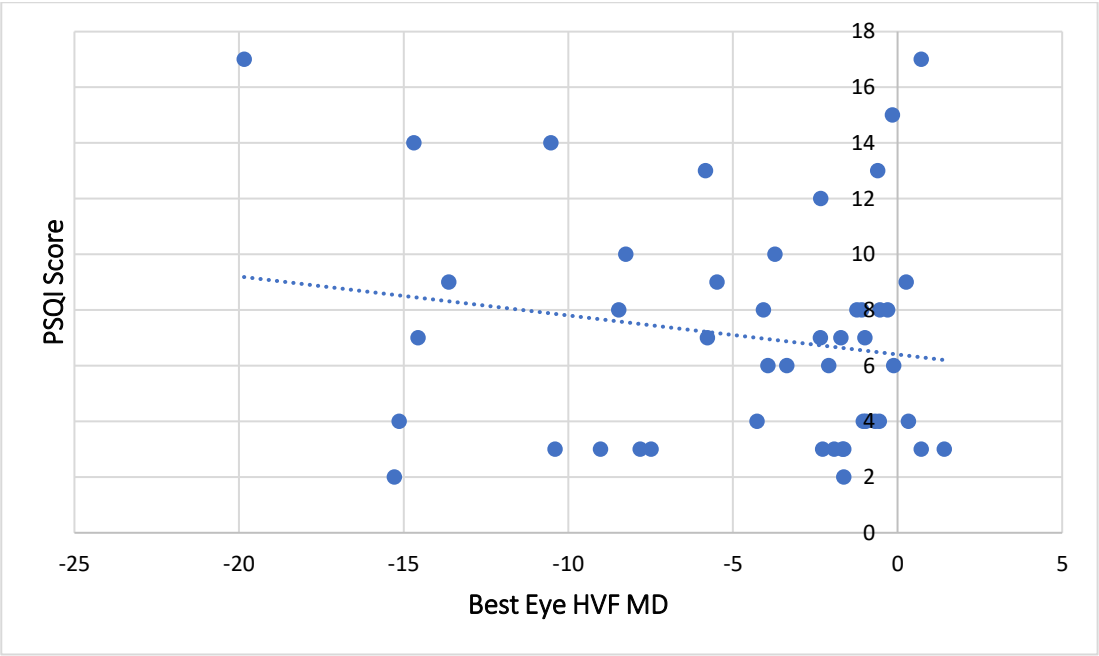
Key: OND=Optic nerve disorder; PSQI=Pittsburgh Sleep Quality Index.

Figure 11: BVA versus PSQI in OND



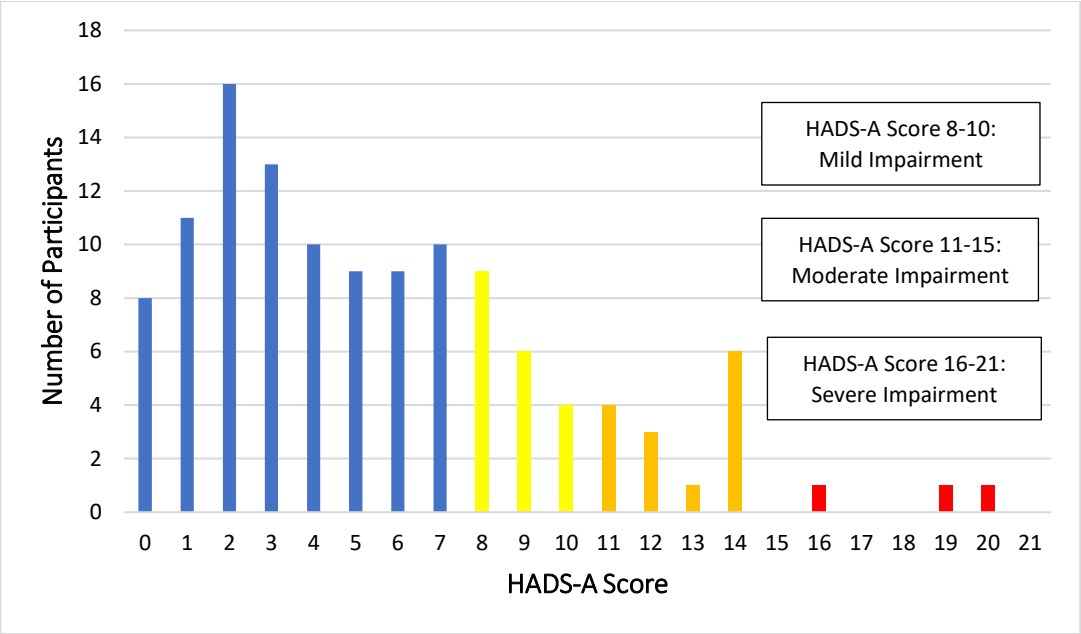
Key: BVA=Best visual acuity of the better eye; PSQI=Pittsburgh Sleep Quality Index; OND=Optic nerve disorder.

Figure 12: HVF versus PSQI in OND



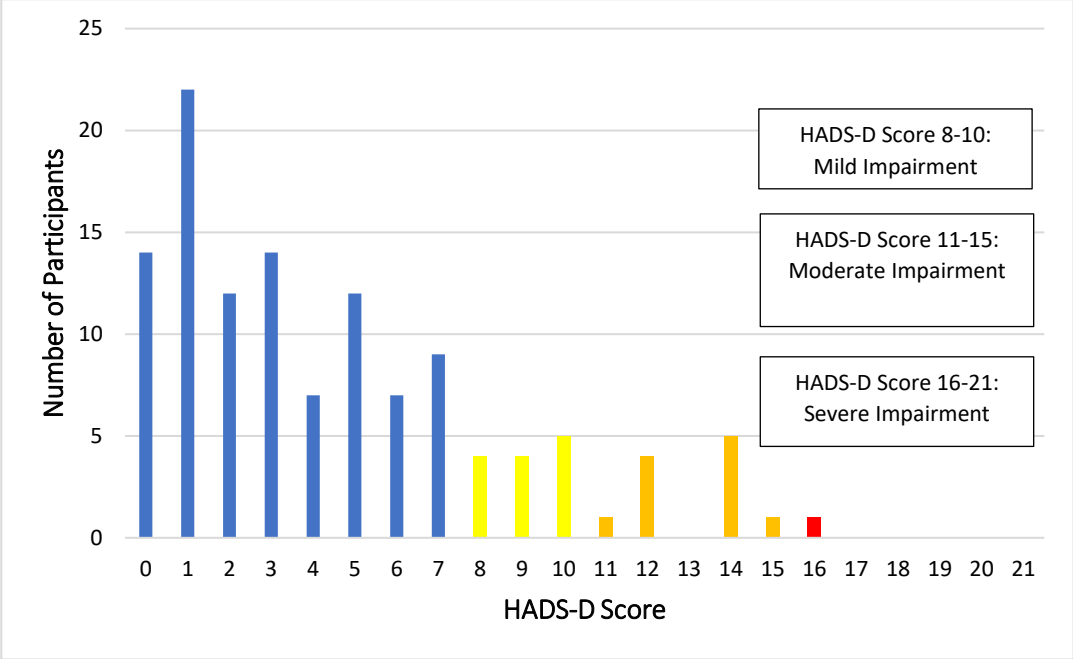
Key: HVF MD=Humphrey visual field mean deviation; PSQI=Pittsburgh Sleep Quality Index; OND=Optic nerve disorder.

Figure 13: HADS Anxiety Scores in OND



Key: HADS=Hospital Anxiety and Depression Scale; HADS-A=HADS anxiety subscore; OND=Optic nerve disorder.

Figure 14: HADS Depression Scores in OND



Key: HADS=Hospital Anxiety and Depression Scale; HADS-D=HADS depression subscore; OND=Optic nerve disorder.

5.7 OND Pathologies within My Study Population

Table 13 illustrates the categories of OND found within participants with OND in this study. Optic nerve pathologies identified within my study population were as follows:

The largest proportion (33 subjects) of the study population had OND associated with NMOSD (27.04%). MS-related optic neuropathy was found in eight subjects (6.6%), ADEM-related optic neuropathy in 2 subjects (1.6%), and sarcoid optic neuropathy in five subjects (4.1%). No patients with CRION were recruited.

A diagnosis of HON was found in 17 subjects (13.9%), seven of whom had LHON (5.7%), six of whom had DOA (4.9%), and four of whom had other causes of HON (3.3%). No subjects in this study had a diagnosis of WS.

IIH-associated optic neuropathy was present in five subjects (4.1%). Optic neuropathies subsequent to other causes of raised ICP were present in nine subjects (7.4%), including five subjects with meningioma (4.1%), one subject with glioblastoma (0.8%), and one subject with hydrocephalus (0.8%).

Optic nerve pathology due to compression of the intracranial, intracanalicular or intraorbital portions of the optic nerves was present in 14 subjects (11.5%). This comprised CP in four subjects (3.3%), PA associated with MEN type 1 in one subject (0.8%), PA in one subject (0.8%), NF1 in two subjects (1.6%), NF2 in one subject (0.8%), carotid artery dilation in two subjects (1.6%), orbital apex syndrome in one subject (0.8%), autosomal dominant osteopetrosis in one subject (0.8%) and optic nerve astrocytoma in one subject (0.8%).

Vascular optic neuropathies were found in nine subjects (7.4%). These comprised NAION in four cases (3.3%), and AAION in three cases (2.5%). Two subjects (1.6%) were found to have optic neuropathy in association with retinal haemorrhage.

One subject had toxic optic neuropathy (0.8%). No subjects with TON were present in the study population.

5.7.1 OND associated with Systemic Conditions

74 participants with OND (60.7%) were found to have a chronic systemic condition that was associated with their OND.

Table 13: OND in the Study Population

Diagnosis	Frequency
Multiple sclerosis optic neuropathy	8
Neuromyelitis optica spectrum disorder (NMOSD)	33
Acute disseminated encephalomyelitis (ADEM)	2
Sarcoid optic neuropathy	5
Leber hereditary optic neuropathy (LHON)	7
Dominant optic atrophy (DOA)	6
Inherited optic atrophy (non-LHON, non-DOA)	4
Neurofibromatosis type 1	2
Neurofibromatosis type 2	1
Meningioma optic atrophy	5
Astrocytoma of the optic nerve	1
Multiple endocrine neoplasia type 1 – pituitary macroadenoma	1
Pituitary adenoma optic atrophy	1
Craniopharyngioma	4
Glioblastoma optic atrophy	1
Idiopathic intracranial hypertension (IIH)	5
Optic neuropathy secondary to raised intracranial pressure (non-IIH)	2
Hydrocephalus optic atrophy	1
Compression optic neuropathy due to dilated carotid artery	2
Orbital apex syndrome	1
Autosomal dominant osteopetrosis	1
Non-arteritic anterior ischaemic optic neuropathy (NAION)	4
Arteritic anterior ischaemic optic neuropathy (AAION)	3
Optic neuropathy associated with retinal haemorrhage	2
Toxic optic atrophy	1
Optic neuritis	8
Optic atrophy	11
	Total: 122

5.8 Retrospective Analysis of Participants with Optic Neuropathy Recruited from Oxford

I performed a sensitivity analysis using the retrospective data that I collected from 110 subjects with OND from Oxford University Hospitals. This sample formed the majority of the population of my prospective study of 122 subjects. Sensitivity analyses that I conducted were for use of systemic glucocorticoids, shift work in the past year, transmeridian travel of greater than one time zone in the past 3 months, use of systemic glucocorticoids and positive OSA screen as per the GHQ, JMCQ, data front sheets and EPR (see Appendices D and G). This was based on the original prospective data analysis R codes.

My results were robust to all of the sensitivity analyses for shift work, transmeridian travel, systemic glucocorticoids and positive OSA screen. Estimate of the groups remained within the 95% CI for the full model (0.78-1.92) for all sensitivity analyses.

5.8.1 Aetiological Findings from Review of Oxford Retrospective Data

Of the eight subjects with unspecified ON recruited prospectively from 2016-2018 (see Table 13), review of EPR records revealed that three subjects were found to have NMO, three were found to have CIS, one was found to have MS and one was recruited from another site (UHW), so details were not available. Of the 11 subjects who had unspecified OA, four were recruited from sites other than Oxford (three from MEH, one from UHW), and raw data was not available for three subjects. Of the remaining four subjects, one was found to have LHON, one was found to have NMO, one was found to have CIS, and one was found to have an unspecified inherited OA.

5.9 Subset of Oxford Sample with Autoimmune and Demyelinating Optic Neuropathies

I analysed a subsection of participants recruited from Oxford University Hospital with autoimmune and demyelinating optic neuropathies in greater detail. This group comprised

34 participants with NMOSD, 10 with MS, two with ADEM and four with CIS. No participants with CRION were identified on retrospective searching of EPR or raw data packs.

5.9.1 Demographics of Subset with Autoimmune and Demyelinating Conditions

I have presented demographic information for this group of participants in Table 14. I conducted a descriptive analysis due to the small sample size.

Participants recruited with NMOSD and MS were predominantly female (58.8% in NMOSD, 70% in MS) with equal numbers of males and females with ADEM and CIS. Participants with ADEM tended to be younger with mean age 29.5y, in contrast to MS an NMOSD with mean ages of 49.5y and 45.9y respectively, with CIS intermediate at 39.3y. This is consistent with the aetiologies of these conditions, with ADEM onset typically in childhood and adolescence, and CIS a potential early precursor for MS. This may also be reflected in the mean time since diagnosis of this subset, the shortest time being for CIS at 1.4y, and the longest being for ADEM at 10.0y.

Time since diagnosis was categorised into <1 year, 1 to <3 years, 3 to <5 years and 5+ years as described in my Methods chapter (Wingerchuk et al, 2007(328)).

Information on time since diagnosis was available for 33 out of the 34 participants with NMOSD. 10 had been diagnosed under 1 year prior to recruitment (29.4%), 12 for 1 to <3 years (35.3%), four for 3 to < 5 years (11.8%) and seven for 5 or more years (20.6%). Two (20%) participants with MS had received a diagnosis less than 1 year prior to recruitment, four (40%) for 1 to <3 years, one (10%) for 3 to <5 years, and three (30%) for 5+ years. Both participants with ADEM had been diagnosed for 5+ years. Two participants with CIS had been diagnosed for <1 year 50%), one at 1 to <3 years (25%) and one at 5+ years (25%).

5.9.2 Antibody Status and Systemic Involvement

32 out of 34 participants with NMOSD had details of antibody testing available. 21 participants (65.6%) were AQP4 antibody positive, and 10 (31.3%) were MOG antibody positive, which included one participant who was positive for both AQP4 and MOG antibodies. Two participants (6.3%) were antibody negative.

Antibody details were not available in eight out of 10 participants with MS, and the remaining two participants were antibody negative. Both participants with ADEM were antibody negative. Two out of four participants with CIS had details of antibody testing, both of whom were negative, which likely to reflective of the clinical presentation and clinical suspicion in diagnosis of these participants.

Information gleaned from raw data packs and EPR regarding systemic involvement in subjects with NMOSD was sparse. Two participants were found to have transverse myelitis, and a further two were found to have other systemic involvement; one had multiple autoimmune conditions and joint pains, and one had central pontine myelinosis with associated unilateral deafness and epilepsy. This is likely to be an underestimate, as details of systemic involvement were not apparent in the remaining 30 participants with NMO.

Out of the 10 subjects with MS, seven were diagnosed with RRMS, one with primary progressive MS (PPMS), one with secondary progressive MS (SPMS) and one with optic-spinal MS. Details of systemic involvement were available in one out of the two subjects with ADEM, who had spinal involvement. By its classification, none of the four participants with CIS had systemic involvement.

Using data gleaned from timings of hospital admissions from EPR, two participants in this subset were inpatients at the time of recruitment, one of whom had NMOSD, and one of whom had MS.

5.9.2(a) Sphincter Dysfunction, Fatigue and Pain

I identified seven out of 34 subjects with NMOSD as having sphincter dysfunction (20.6%). This was also the case in five out of 10 subjects with MS (50%) (of whom one had PPMS, one had SPMS and three had RRMS) and in one out of two subjects with ADEM (50%). No subjects with CIS had sphincter dysfunction.

Three participants with NMOSD (8.8%) were recorded as having fatigue, in addition to four with MS (40%) (of whom three had RRMS and one had PPMS) and 1 with ADEM (50%). No participants with CIS were recorded as having fatigue as a notable feature of their presentation.

Bodily pain was reported in 12 subjects with NMOSD (35.3%), five with MS (50%) (of whom one had SPMS, one had PPMS and three had RRMS) and one with ADEM (50%). There were no reports of problematic pain in any subjects with CIS.

5.9.3 Ophthalmological Details

OND was bilateral in both subjects with ADEM (100%) and in the majority of subjects with NMOSD (n=20, 58.8%). 50% of subjects with MS had bilateral OND (of whom one had SPMS, one had PPMS and three had RRMS), and one subject with CIS (25%) had a bilateral presentation.

Mean BVA was 0.17 LogMAR in subjects with NMOSD, 0.1 LogMAR in subjects with MS, 0.4 LogMAR in subjects with ADEM and 0.23 LogMAR in subjects with CIS.

As described in my methods section, I used the RNIB criteria for SI and SSI registration to divide participants into categories of SI, SSI and not meeting CVI criteria. 14.0% of participants with NMOSD met the criteria for either SI or SSI, as did 10% of participants with MS, 50% with ADEM and 25% with CIS.

I obtained details of HVF for 17 (50%) subjects with NMOSD, with mean MD -4.84dB. 80% of subjects with MS had HVF details available, with mean MD -2.59dB. No HVF data was obtainable for either of the subjects with ADEM (0%), and three subjects with CIS (75%) had HVF data, with mean MD -0.57dB.

I categorised HVF MD into mild (>-6dB), moderate (-6 to -12dB) and severe VFD (<-12dB) as per Chin et al (2020). From the HVF data available, moderate to severe VFD was present in 35.3% of participants with NMOSD, 25% with MS and 0% with CIS.

Cataract assessment was available in five subjects with NMOSD (14.7%). One was stated to have no evidence of cataract (2.9%), two had unilateral cataract (5.9%) and two had bilateral cataract (5.9%). No details of cataract assessment were available in subjects with MS, ADEM or CIS.

Table 14: Demographics of Subset with NMOSD, MS, ADEM and CIS

	NMOSD n=34	MS n=10	ADEM n=2	CIS n=4
Mean Age (SD) (y)	45.9 (15.4)	49.5 (6.4)	29.5 (4.5)	39.3 (7.7)
Sex M/F (%M)	14/20 (41.2)	3/7 (30)	1/1 (50)	2/2 (50)
Mean BMI (SD) (kg/m^2)	28.5 (5.3)	25.68 (6.02)	26.4 (N/A)	26.7 (5.4)
Mean Time Since Diagnosis (SD) (y)	3.8 (4.8)	3.9 (3.4)	10.0 (0.9)	1.4 (1.3)
Time Since Diagnosis Category (y) n <1 / 1-<3 / 3-<5 / 5+	10/12/4/7	2/4/1/3	0/0/0/3	2/1/1/0
Unilateral/Bilateral (% bilateral)	14/20 (58.8)	5/5 (50)	0/2 (100)	3/1 (25)
AQP4+ n (%)	21 (61.8)	0 (0)	0 (0)	0 (0)
MOG+ n (%)	10 (29.4)	0 (0)	0 (0)	0 (0)
Antibody Negative n (%)	2 (5.9)	2 (20)	2 (100)	2 (50)
Antibody Status Unknown n (%)	2 (5.9)	8 (80)	0 (0)	2)50)
Mean BVA (SD)	0.17 (0.68)	0.1 (0.28)	0.4 (0.4)	0.23 (0.56)
CVI Criteria n None/SI/SSI (%SI+SSI)	29/1/4 (14.7)	9/1/0 (10)	1/1/0 (50)	3/0/1 (25)
Mean BVF MD (SD) n with HVF available (%)	-4.84 (9.19) 17 (50)	-2.59 (3.41) 8 (80)	N/A 0 (0)	-0.57 (0.55) 3 (75)
BVF n Mild/Moderate/Severe (% Moderate+Severe)	11/3/3 (35.3)	6/2/0 (25)	N/A	3/0/0 (0)
Sphincter Dysfunction present n (%)	7 (20.6)	5 (50)	1 (50)	0 (0)
Fatigue present n (%)	3 (8.8)	4 (40)	1 (50)	0 (0)
Pain present n (%)	12 (35.3)	5 (50)	1 (50)	0 (0)
Current smokers n (%)	6 (17.6)	1 (10)	0 (0)	1 (25)
Current alcohol n (%)	11 (32.4)	5 (50)	1 (50)	4 (100)
Caffeine ≥1/day n (%)	26 (76.5)	6 (60)	1 (50)	3 (75)
HADS-A positive n(%)	9 (26.5)	4 (40)	0 (0)	0 (0)
HADS-D positive n(%)	11 (32.4)	2 (20)	0 (0)	0 (0)
Inpatient/Outpatient (% Inpatient)	1/33 (2.9)	1/9 (10)	0/2 (0)	0/4 (0)
Mean PSQI (SD)	8.6 (4.2)	6.3 (4.5)	11.5 (0.5)	5.5 (1.5)
PSQI>5 n (%)	25 (73.5)	4 (40)	2 (100)	2 (50)
ESS>10 n (%)	7 (21)	5 (50)	1 (50)	1 (25)

Key: ADEM=Acute disseminated encephalomyelitis; AQP4+=Aquaporin 4 antibody positive; BMI=Body mass index; BVA=Better eye visual acuity; BVF=Better eye visual field; CIS=Clinically isolated syndrome; CVI=Certificate of visual impairment; HADS-A=Hospital Anxiety and Depression Score Anxiety Component; HADS-D=Hospital Anxiey and Depression Score Depression Component; MD=Mean deviation; MOG+=Myelin oligodendrocyte antibody positive; MS=Multiple Sclerosis; n=Number; NMOSD=Neuromyelitis optica spectrum disorder; OND=Optic nerve disorder; PSQI=Pittsburgh Sleep Quality Index; SD=Standard deviation; SI=Sight impairment; SSI=Severe sight impairment

5.9.4 Subjective Sleep Quality and Timing

The mean PSQI scores in NMOSD, MS, ADEM and CIS were 8.6, 6.3, 11.5 and 5.5 respectively. These were all higher than the threshold of PSQI>5 indicating poor sleep. Poor sleepers with PSQI>5 accounted for 73.5%, 40%, 100% and 50% of participants with NMOSD, MS, ADEM and CIS respectively. Of participants with MS with poor sleep, one had SPMS, one had PPMS and three had RRMS.

ESS>10 denotes excessive daytime sleepiness, which was found in 21%, 50%, 50% and 25% of subjects with NMOSD, MS, ADEM and CIS respectively. Of the participants with MS with excessive daytime sleepiness, one had SPMS, one had PPMS and three had RRMS.

5.9.4(a) Time Since Diagnosis and Sleep Quality

Data for time since diagnosis was available for 33 out of 34 subjects with NMOSD. Poor sleep, defined as PSQI >5 was found in 70% (7 out of 10) who were diagnosed less than 1 year prior to recruitment, 75% (9 out of 12) who were 1 to <3 years since diagnosis, 100% (4 out of 4) diagnosed between 3 and <5 years, and 57.1% (4 out of 7) diagnosed for 5+ years.

In the 10 subjects with MS, poor sleepers were identified as 0% (0 out of 2) diagnosed less 1 year before recruitment, 50% (2 out of 4) diagnosed between 1 to <3 years, 0% (0 out of 1) diagnosed from 3 to <5 years, and 66.7% (2 out of 3) diagnosed for 5+ years.

Both subjects with ADEM had been diagnosed for 5+ years, and both were poor sleepers (100%). Of the four subjects with CIS, two patients were diagnosed less than 1 year prior to recruitment, and neither had poor sleep (0%). One subject had been diagnosed for 1 and <3 years, and had poor sleep (100%), and one subject had been diagnosed for 3 to <5 years and had poor sleep (100%).

5.9.4(b) Sight Impairment and Sleep Quality and Timing

In subjects with NMOSD, 29 subjects did not meet criteria for CVI (85.3%), of whom 23 were poor sleepers (79.3%). One subject met the criteria for SI (2.9%) and did not have poor sleep quality. Four met SSI criteria (11.8%), of whom two (50%) were poor sleepers.

In the 10 subjects with MS, nine (90%) did not meet CVI criteria, of whom three had poor sleep (33.3%). One subject with PPMS met SI criteria (10%) and was a poor sleeper (100%).

One subject with ADEM (50%) did not CVI criteria and had poor sleep (100%). The other subject met SI criteria (50%) and had poor sleep quality (100%). Three out of the four subjects with CIS (75%) did not meet CVI criteria, of whom one was a poor sleeper (33.3%). One subject met SSI criteria (25%) and had poor sleep (100%).

Of the three subjects with NMOSD with confirmed cataract, one out of the two subjects with unilateral cataract was a poor sleeper (50%), and the subject with bilateral cataracts was also a poor sleeper (100%).

Excessive daytime sleepiness measured by ESS was found in 21% of subjects with NMOSD, all of whom had mild VFD and visual function better than CVI criteria. In subjects with MS, 50% had ESS>10, of whom 20% had SI and 20% had moderate VFD, with the remainder having mild VFD and better than CVI visual function. One subject with ADEM (50%) had excessive daytime sleepiness, who had better than CVI visual function, and 1 subject with CIS (25%) had ESS>10, who had SSI.

5.9.4(c) Visual Field Defects and Sleep Quality

17 out of 34 subjects with NMOSD had HVF data (50%), of whom 11 had mild (64.7%), three had moderate (17.6%) and three (17.6%) had severe VFD. Poor sleep found was found in six (54.5%), two (66.7%) and one (33.3%) subjects with mild, moderate and severe VFD respectively.

Eight out of 10 subjects with MS (80%) had HVF data available, with mild VFD found in six (75%) and moderate VFD found in two subjects (25%). Poor sleep was found in three subjects with mild VFD (50%) but was not found in either subject with moderate VFD (0%).

Neither subject with ADEM had VFD data available. Three out of four subjects with CIS had HVF data (75%), all of whom had mild VFD (100%). One subject had poor subjective sleep quality (33.3%).

5.9.4(d) Systemic Involvement and Subjective Sleep Quality

Of the four participants with NMOSD with confirmed systemic involvement, both subjects with transverse myelitis were found to have poor sleep quality (100%). Of the two subjects with other systemic pathologies, one was found to be a poor sleeper (50%). One subject with NMOSD screened positive for OSA using the JMCQ and was found to have poor sleep quality (100%).

Out of 10 subjects with MS, seven had RRMS, of whom two were poor sleepers (28.6%). Poor sleep quality was found in each of the subjects with PPMS and SPMS (100% in each). The subject with optic-spinal MS was not found to have poor sleep quality (0%).

Systemic involvement was present in one subject with ADEM (50%), who was found to have poor sleep quality (100%). No systemic involvement was present in any of the participants with CIS.

5.9.4(d)(i) Sphincter Dysfunction and Sleep Quality

Seven participants with NMOSD were found to have sphincter dysfunction (20.6%), of whom six were found to have PSQI>5 (85.7%).

Five participants with MS (50%) were found to have sphincter dysfunction, of whom four (80%) had PSQI >5. One participant with ADEM had sphincter dysfunction (50%) and was found to be a poor sleeper (100%). No participants with CIS had sphincter dysfunction.

5.9.4(d)(ii) Fatigue and Sleep Quality

Three subjects with NMOSD were confirmed to have fatigue (8.8%). All three had poor sleep quality (100%). Four subjects with MS (40%) had fatigue, of whom one (25%) had PSQI>5. One out of two subjects with ADEM (50%) had fatigue and poor sleep (100%). No subjects with CIS had fatigue.

5.9.4(d)(iii) Pain and Sleep Quality

12 participants with NMOSD were identified as having bodily pain (35.3%), of whom 10 had poor sleep quality (83.3%). Five participants with MS (50%) had pain, of whom three (60%)

had poor sleep. One participant with ADEM (50%) reported bodily pain and was found to have poor sleep (100%). No participants with CIS had any record of bodily pain.

5.9.5 Psychological Status

A positive psychiatric history was present in nine out of 34 subjects with NMOSD (26.5%), of whom eight had PSQI>5 (88.9%); five subjects with MS (50%), of whom two (40%) had poor sleep; one subject with ADEM (50%), who was found to have poor sleep (100%); and one subject with CIS (25%), who was found to have poor sleep (100%).

Using the HADS tool, nine subjects with NMOSD screened positive for anxiety (26.5%), of whom eight had poor sleep (88.9%). Four subjects with MS screened positive for anxiety (40%), of whom two (50%) had poor sleep. No subjects with ADEM or CIS screened positive on HADS-A. 11 subjects with NMOSD screened positive for depression using HADS-D (32.4%), all of whom had poor sleep (100%). Two subjects with MS (20%) screened positive for depression, both of whom had PSQI>5 (100%). No subjects with ADEM or CIS screened positive on HADS-D.

5.9.6 Medication History

Antidepressants and antipsychotics were prescribed for six participants with NMOSD (17.6%), of whom five (83.3%) were poor sleepers; Four participants with MS (40%), of whom three (75%) had poor sleep; and one subject with ADEM (50%), who had poor sleep (100%). No participants with CIS were taking antidepressants or antipsychotics.

Antiepileptics were taken by eight subjects with NMOSD (23.5%), of whom five (62.5%) were poor sleepers; 1 subject with MS (10%), who did not have poor sleep; and no subjects with ADEM or CIS.

Sleeping medications were taken by five subjects with NMOSD (14.7%), all of whom had poor sleep (100%), and were not taken by any subjects with MS, ADEM or CIS.

Baclofen was taken by two subjects with NMOSD (5.9%), both of whom had poor sleep (100%), and two subjects with MS (20%), one of whom (50%) was a poor sleeper. It was not taken by any subjects with ADEM or CIS.

NSAIDs were prescribed for one participant with NMOSD (2.9%), who was a poor sleeper (100%), and both participants with ADEM (100%), who were poor sleepers (100%). No participants with MS or CIS were taking NSAIDs.

Opiate medications were taken orally by one subject with NMOSD (2.9%) who had poor sleep (100%). One subject with MS (10%) (SPMS) used a combination of transdermal and oral opiates and had PSQI>5 (100%).

Systemic beta-blockers were prescribed for two participants with NMOSD (5.9%), both of whom had poor sleep (100%). No participants with MS, ADEM or CIS were taking systemic beta-blockers, and no subjects were taking topical beta-blockers.

Systemic glucocorticoids were taken by 23 subjects with NMOSD (67.6%), of whom 19 (82.6%) had poor sleep quality. They were not prescribed for any subjects with MS, ADEM or CIS. One subject with MS was taking inhaled glucocorticoids and had a normal PSQI score.

5.9.7 Caffeine, Smoking and Alcohol

76.5% of subjects with NMOSD had caffeine intake at least once daily, of whom 80.8% had poor sleep. In the 60% of subjects with MS with regular caffeine intake, 33.3% had poor sleep. One subject with ADEM (50%) had regular caffeine intake and poor sleep (100%), and three subjects with CIS had regular caffeine intake, with poor sleep in one subject (33.3%).

Six participants (17.6%) with NMOSD were current smokers, of whom four (66.7%) had poor sleep. One participant with MS (10%) (RRMS) was a current smoker and had poor sleep (100%). No participants with ADEM were current smokers, and one participant with CIS (25%) was a smoker and had poor sleep quality (100%).

11 participants with NMOSD were current drinkers (32.4%), of whom seven (63.6%) had poor sleep. Five participants with MS (50%) were current drinkers, of whom two (40%) had poor sleep. One participant with ADEM (50%) was a current drinker and had poor sleep (100%), and four participants with CIS (100%) were current drinkers, of whom two (50%) had poor sleep. Current alcohol intake of >14 units/week was found in one participant with NMOSD (2.9%) who had poor sleep (100%), and two subjects with MS (one with optic-spinal MS, one with RRMS), neither of whom had poor sleep (0%).

Chapter 6: Discussion

6.1 Introduction

The purpose of this chapter is to discuss the findings of this study and explore their context and relevance to the pool of existing research, and what they contribute to the care and overall management of patients with OND.

I will commence this chapter by summarising my findings in relation to my study aims and objectives. Next, I will contextualise the results of my study in the light of existing published literature. I then discuss the strengths and weaknesses of my study, and the factors that affect its application in practice. Following this, I will discuss the implications of this study for practice and policy and for research. Finally, I will use the themes discussed to draw conclusions.

6.2 Summary of Findings in Relation to Study Aims and Objectives

6.2.1 Study Aim

The aim of my research was to investigate the nature of the relationship between OND and sleep quality and timing. The PSQI was used to assess sleep quality in my study population, while subjective sleep timing was assessed using ESS and MEQ and component scores of the PSQI.

6.2.1(a) OND and Sleep Quality

In my prospective study population, individuals with OND had significantly worse subjective sleep quality, longer SL, worse SE, longer sleep duration and increased sleep disturbances as measured by the PSQI compared to the control group. The proportion of OND participants with a PSQI score greater than five was 65.6%, and those with a PSQI score greater than 10 made up 28.7% of OND participants. PSQI>10 is generally accepted as an marker of severe sleep impairment(43, 44, 1091, 1092). The McFadden's R^2 value was 0.26, indicating that the

independent variable (OND versus control) did not fully explain the dependent variable (sleep quality) and the goodness of fit was not high(1093). This suggests that factors other than the presence of OND are likely to account for differences in sleep quality seen in the participants in this study, which I will discuss later in this chapter.

There was no significant relationship between sleep quality score and better eye VA in subjects with OND and sleep quality; neither was there a significant correlation between BVF and sleep quality.

My sensitivity analysis for subjects with OND recruited from Oxford University Hospital did not show any change in significance after exclusion of shift work, transmeridian travel, systemic glucocorticoids or positive OSA screen.

In my retrospective study population of autoimmune and demyelinating OND, participants with NMOSD, MS, ADEM and CIS were all found to have mean PSQI>5, with values of 8.6, 6.3, 11.5 and 5.5 respectively. 73.5%, 40%, 100% and 50% of subjects with NMSOD, MS, ADEM and CIS respectively were defined as poor sleepers with PSQI>5.

With regard to visual function, subjects with NMOSD, MS, ADEM and CIS had mean VA of 0.17, 0.1, 0.4 and 0.23 converted LogMAR respectively. In terms of degree of VI, there did not appear to be any clear relationship between sleep quality scores and whether visual function was better than or met the CVI criteria of SI or SSI on descriptive analysis. Of subjects with NMOSD whose vision was better than CVI status, 79.3% were poor sleepers, while 0% of those with SI and 50% of those with SSI were poor sleepers, and the numbers of subjects with MS, ADEM and CIS were too small to draw any meaningful narrative.

17 subjects with NMOSD had HVF results available. 64.7% were found to have mild VFD, of whom 54.5% had poor sleep. 17.6% had moderate VFD, of whom 66.7% were poor sleepers, and 17.6% had severe VFD, of whom 33.3% had poor sleep. Again, these numbers are small, and no clear pattern was seen between the degree of VFD and sleep quality.

6.2.1(a)(i) Time Since Diagnosis and Sleep Quality

In my retrospective study of autoimmune and demyelinating OND, I evaluated time since diagnosis and its relationship to sleep quality. I identified poor sleep in 70% of subjects who were diagnosed less than one year, 75% diagnosed between 1 and <3 years, 100% diagnosed between 3 and <5 years, and 57.1% diagnosed at 5 years or more prior to recruitment. This does not indicate a clear pattern and corresponds to the findings in my systematic literature review, where no correlation between time since diagnosis and sleep disturbance was found(15, 1036, 1037, 1051). Of particular note is Turkoglu et al's study (2020)(1047), in which subjects with ON as the first presenting complaint in MS had the longest times since diagnosis but better sleep quality compared to patients with other forms of MS. My retrospective study population for autoimmune and demyelinating disorders was small, and results from a larger sample size are likely to be more applicable to population with autoimmune and demyelinating OND. Poor sleep is present in all categories of time since diagnosis, which may reflect anxiety of a new diagnosis, and depression and poorer QOL associated with increased time since diagnosis(19, 21, 22).

6.2.1(b) OND and Sleep Timing

In my prospective study, subjects with OND had longer subjective sleep times, worse daytime dysfunction and were more likely to take medications that assisted sleep compared to the control group, as measured by the PSQI. Subjective daytime sleepiness, as measured by the ESS, was comparable between OND and control groups, as was the MEQ measurement of chronotype which included similar MEQ scores, categories, and the season of questionnaire completion. The significance of these results did not change with my retrospective sensitivity analysis.

In my retrospective analysis of demyelinating and autoimmune OND, it was not meaningful to analyse PSQI component scores or MEQ due to small study numbers. Excessive daytime sleepiness with ESS>10 was confirmed in 21.2% of subjects with NMOSD which compares to 18.9% of subjects with OND in my prospective study. ESS>10 was present at higher levels in MS at 50%, although this was a small sample.

6.2.2 Specific Objectives

1) Review of Published Literature

My first objective was to review published literature evaluating the relationship between OND and sleep quality and timing. I conducted a systematic review of the literature examining OND and glaucomatous optic neuropathy in Chapter 3. Study design was heterogeneous with the 43 publications yielded comprising two self-controlled interventional studies, 39 cross-sectional studies, one case series and one case report. The studies were of level II-2 evidence and below(1094), and sample sizes in studies of OND tended to be smaller in comparison to glaucoma, which may be a reflection of prevalence in the general population. Additional themes included a lack of detailed ophthalmological data, particularly in studies of OND associated with systemic endocrine or neurological disease; the presence of uncontrolled studies; and use of unvalidated outcome measures. The overall picture given by my literature review is that people with OND appear to have worse sleep quality and timing compared to those with normal vision or other forms of ocular disease. This was reflected in subjective reduction in sleep quality and confirmed with objective disruption of rest-activity, altered sleep architecture, and altered melatonin levels and rhythms.

2) Collection of Subjective Data

My second objective was to collect subjective sleep quality and timing, general health, QOL and mood data from individuals with OND (with details of ocular history, time since diagnosis and visual function) and from a normally sighted control group. General health, QOL and mood can affect and be affected by sleep quality. As described in my methodology in Chapter 4, I collected subjective data using a set of seven questionnaires (see Appendix D) from patients with OND attending outpatient ophthalmology and neurology clinics across multiple sites. I obtained informed consent after allowing patients to read the information sheet (Appendix D) and answered any questions that they had. I recruited control participants which contributed to a bank of control data that was used for comparison

across all arms of the SOMNUS study. Study questionnaires were validated to collect subjective sleep data (PSQI and ESS), subjective chronotype (MEQ), screen for risk of OSA and RLS (JMCQ), mood (HADS) and QOL (SF-36). General health data was collected using the GHQ, an adapted form of the PHQ.

3a) Statistical Analysis

My third objective was to statistically analyse data collected from individuals with OND and controls to determine whether OND and other health and lifestyle factors have an impact on sleep quality and timing.

As detailed in my results in Chapter 5, I entered paper-based questionnaire outcomes and ophthalmological examination data from patient notes into an Excel csv spreadsheet. To do this, I anonymised and coded patient details. I analysed the raw data descriptively and with statistical modelling using R-2.15, with advice from Dr. Iona Alexander and Colm Andrews, team statisticians at ERGO. I conducted a retrospective power analysis for my study of 122 subjects with OND, the number of subjects required for 80% power being 100, which indicated that my study was sufficiently-powered. I conducted a sensitivity analysis for transmeridian travel, shift work, glucocorticoid use and positive OSA screen in 110 subjects with OND recruited from Oxford, which had formed the majority of my prospective study sample, and was deemed an acceptable analysis by team statisticians. I also conducted a descriptive analysis of the subset of patients with autoimmune and demyelinating OND who were recruited from Oxford.

3b) Summary of Mood, Quality of Life and Lifestyle Findings

My findings regarding interactions of OND, sleep quality and timing are outlined in Section 6.2.1. With respect to mood, significantly poorer HADS depression scores were found in the OND (mean 4.6) group compared to controls (mean 2.7) ($p=0.04$), although no significant differences in HADS anxiety scores were found. Worsening anxiety and depression scores in all subjects showed a direct correlation with sleep quality ($p=0<0.0001$, p0.04 respectively), as it did on analysis of the OND group alone ($p=0.002$, $p=0.002$ respectively). With the exception of emotional wellbeing, which was comparable ($p=0.5$), there were significant

differences in all QOL scores in OND compared to controls as measured by the SF-36, with worse scores in physical functioning, physical limitation, emotional limitation, energy/fatigue, pain, social functioning and general health ($p<0.005$ for all). With regard to general health, BMI, as reported in the GHQ, was significantly higher in OND compared to control subjects ($p=0.005$).

My analysis of the impact of lifestyle and other health factors on sleep wake found that sleep worsened with increasing age and BMI, and that females were more likely to report poor sleep than males. No significant differences were found in caffeine and alcohol intake between OND and control groups, and there was a trend for the number of cigarettes smoked per day to be comparable between groups. My sensitivity analysis did not reveal any changes in the significance of my study findings on exclusion of shift work, transmeridian travel or a positive OSA screen.

In the OND group alone, neither sex, caffeine, smoking nor alcohol consumption impacted sleep quality. A notable proportion of OND participants were taking glucocorticoid medications (30.7%), psychiatric medications (15.3%), benzodiazepines or other sleeping medications (8.1%), and beta-blockers (4.0%). These were not features of the control group, although my sensitivity analysis did not show any differences in significance of my study findings when systemic glucocorticoids were excluded.

The findings of my retrospective study of autoimmune and demyelinating OND also indicate a possible relationship between sleep and depression. In subjects with NMOSD, 32.4% screened positive for depression on HADS-D, all of whom (100%) were found to have poor sleep. This was also the case in subjects with MS, of whom 20% screened positive on HADS-D, and 100% of whom had poor sleep. Regarding HADS-A, 26.5% of subjects with NMOSD screened positive for anxiety, 88.9% of whom had poor sleep, and 40% of subjects with MS were above HADS-A threshold, of whom 50% had poor sleep. No subjects with ADEM or CIS screened positive for either HADS-A or HADS-D.

With respect to systemic symptoms, sphincter dysfunction was found in 20.6% and 50% of subjects with NMOSD and MS, of whom 85.7% and 80% had poor sleep respectively, which may indicate the contribution of dysfunctional sensory symptoms and motor control of bladder and bowels to poor sleep quality in autoimmune and demyelinating OND. Pain was

present in 35.3%, 50% and 50% of subjects with NMOSD, MS and ADEM, of whom 83.3%, 60% and 100% had poor sleep respectively, which may illustrate its impact on sleep quality. Fatigue was present in 8.8%, 40% and 50% of subjects with NMOSD, MS and ADEM, of whom poor sleep was identified in 100%, 25% and 100% respectively. This may point to an overlap of fatigue and sleep quality. Due to its aetiology, no subjects with CIS had associated sphincter dysfunction, fatigue or pain.

Concerning systemic medications, glucocorticoid use was found in 67.7% of subjects with NMOSD, of whom 83.3% were poor sleepers, which may indicate a high prevalence of glucocorticoid use in NMSOD coinciding with poor sleep. Antidepressant or antipsychotic medications were prescribed for 17.6% and 40% of subjects with NMOSD and MS, with poor sleep found in 83.3%, 75% respectively, which is in agreement with the association found between depression and poor sleep in my prospective study and with HADS-D scores in this subset.

4) Relevance to Practice and Policy

My fourth objective was to discuss the relevance of my findings to practice and policy with regards to management of patients with OND, taking into consideration their general health, QOL, lifestyle and mood. After contextualising my findings in the light of existing literature and evaluating strengths and weaknesses of this study, I discuss the implications of my findings to practices and policy in Section 6.5.

6.3 Contextualisation of Findings in the Light of Existing Literature

I hypothesised that individuals with damage to the optic nerves have poorer sleep quality and timing than individuals who have normal visual function and intact optic nerves.

My prospective study findings demonstrated that subjective sleep quality and timing was significantly worse in study participants with OND, which is in agreement with my hypothesis. Whether this sleep disturbance was due to circadian dysregulation is more difficult to ascertain. No significant relationship was found between BVA, BVF and PSQI score, and retrospective evaluation of BVA and BVF in autoimmune and demyelinating

conditions did not show a clear pattern in relation to sleep quality. BVA can serve as a weak, though flawed approximation of pRGC function(1095), which is intimately involved in entrainment of the internal circadian pacemaker to light and dark(1096). The lack of correspondence of BVA (as a weak inference of pRGC function) and PSQI suggests that disturbed sleep wake in this study population may be due to causes other than circadian dysrhythmia. Reduced RGC counts have been demonstrated to accurately correlate with VF loss even in the early stages of pathology(1097), and as no correlation of VF with sleep quality was found in my prospective study, it indicates that factors other than RGC damage may have contributed to poor sleep quality in participants with OND. This was also suggested by results of my retrospective study, in which there was no evident pattern between visual function or VFD and poor sleep.

Similarly, daytime sleepiness, as measured by ESS was comparable between groups in my prospective study. In my retrospective analysis of subjects with autoimmune and inflammatory optic neuropathies, there was no clear trend between severity of visual function and excessive daytime sleepiness. As daytime sleepiness could indicate a desynchronised sleep wake cycle, a significantly different ESS in the OND group could support circadian dysfunction over other causes of sleep disturbance, which was not the case in my study. Similarly, there was no difference in MEQ scores or chronotype categories between OND and controls in my prospective data. MEQ scores indicating excessive morningness or eveningness could point to advanced or delayed phasing of the circadian clock respectively, which was not evident in OND participants in my study, and also implies that other factors may have produced the differences in sleep quality observed between OND and control groups.

In my literature review, the quality of studies was generally low and many had small sample sizes, reducing their power and generalisability. Several studies were uncontrolled. Most studies were observational in nature, meaning that causation could not be proved, although the subjective and objective findings gathered could provide support for or against the impact on OND on circadian function. There are myriad other factors which may also contribute to poor sleep quality and timing, which I will discuss in the following sections. These comprise other non-circadian sleep disorders, including OSA, PLM and RLS; chronic systemic disease, which may give rise to endocrine abnormalities, pain, fatigue and

sphincter dysfunction; psychiatric conditions and mood; prescribed medications and lifestyle factors such as caffeine, nicotine and alcohol.

6.3.1 Obstructive Sleep Apnoea and Sleep Wake

In my prospective study, analysis of the JMCQ indicated that 4.3% of participants with OND were at risk of OSA. The reported prevalence of OSA is approximately 3-7% in adult males and 2-5% in adult females(1090), although calculations of risk, a prospective evaluation of a disease-free individual developing a condition over time, and prevalence, an evaluation of the presence of disease in a population at a point in time, are separate assessments(1098). In my retrospective analysis, only one subject with NMOSD (2.9%) screened positive for OSA, who was found to have poor sleep quality. My sensitivity analysis indicated that a positive OSA screen did not influence the significance of my study results, as OSA was present in a small proportion of participants in my study. This concurs with published studies in my literature review, in which OSA was present as a confounder in one patient in Pan et al's (2015)(1050) PSG study of 33 patients with NMOSD, and three were found to have reduced peripheral oxygen saturations in association with worse fatigue and depression scores.

In my prospective study population, BMI was significantly higher in the OND group. High BMI and obesity are associated with OSA, although the mechanism by which this occurs is not fully defined. Increased neck girth and adiposity can cause upper airway obstruction, particularly in a reclined position, and there may be altered neural signalling to musculature of the upper respiratory tract(1099). However, OSA can occur in the absence of a high BMI, although its underlying pathophysiology is considered to be phenotypically distinct(1100).

Factors within the OND group in this study which would predispose to high BMI include the use of glucocorticoid, beta-blocker and antidepressant medications(1101), which were identified in participants with OND using the GHQ, and which were significantly different to the control population. Reduced physical functioning can also contribute to high BMI(1102), which was also found to be significantly worse in the OND group compared to controls on SF-36 measurement; as can depression(1103), which was found to be significantly higher in the OND group on HADS scoring.

Subjects in my prospective OND study group who may be at higher risk of obesity include those who had chronic systemic conditions, which was present in 60.7% of the group. NMOSD, MS, sarcoidosis, intracranial compression of the optic chiasm by PA and CP (hypothalamic obesity), and AAION caused by GCA, as found in the OND group, can all cause physical limitation and may require glucocorticoid therapy. Their chronicity may also impact on mood(1104-1111). Additionally, OSA has been reported in association with NAION, a condition found in four participants with OND in my prospective study, and is likely to be related to the overlap of risk factors between the two conditions, such as hypertension, diabetes and hyperlipidaemia(1112). Depression and OSA have been found to have a bidirectional relationship, which again depicts a possible predisposition towards sleep-disordered breathing in the OND group in this study(1113). IIH has been reported to correlate with high BMI and low mood(1114, 1115), and was found in five participants with OND in my prospective study.

In my retrospective analysis of autoimmune and inflammatory OND, mean BMI in NMOSD was higher than mean BMI for OND in my prospective study, which was not the case in MS, ADEM or CIS. Increased glucocorticoid use was present in subjects with NMOSD, which has been found to be associated with increased BMI in NMOSD(1116). OSA has found to have a higher prevalence in NMOSD, and it can be aggravated by high BMI(820, 1117).

6.3.2 Periodic Limb Movements, Restless Leg Syndrome, Parasomnias and Sleep Wake

61.20% of participants with OND in my prospective study were found to be at risk of RLS in comparison to 18.15% of control participants, both of which are higher than the reported prevalence of RLS in the general population of 5.5 to 11.6%(1118). 29.3% of participants with OND were found to be at risk of parasomnias. The prevalence of parasomnias in the general adult population of approximately 4%(199), although risk, which is the proportion of a disease-free sample developing a disease, and prevalence, which is the proportion of individuals within a population with a condition at a defined time point, are distinct measurements(1098, 1119).

PLM can reduce sleep quality in patients independent of OSA(1120), and PLM and RLS are associated with OND pathologies in this study as discussed in my background chapter, which include MS(808), NMOSD(820) sarcoidosis(835). A higher prevalence of PLM and RLS have also been found in major depression(786), which may correspond to the OND participants in my study, in whom HADS depression scores were significantly higher compared to control participants (mean scores 4.6 compared to 2.7 respectively, p=0.04). The control group in my study also had a risk of RLS that was higher than the reported prevalence of RLS in the general population (18.2% of control subjects were at risk of RLS, compared to a population prevalence of 5.5-11.6%), although as stated above, risk refers to prospective development of a condition over time whereas prevalence denotes the proportion of a population with the condition at a designated point in time, so are discrete calculations(1098). RLS and PLM have been found to be more prevalent in women than in men(1121, 1122). As the control group had a significantly greater proportion of women participants (72.6% compared to 50.8% respectively, p=<0.01), this may have contributed the elevated risk of RLS in the control group.

Parasomnias have been found to be associated with psychiatric conditions including depression, and with neurodegenerative conditions such as PD(1123, 1124). As participants with OND in my study were found to have significantly higher mean scores for depression, it is possible that this may be associated with the high proportion at risk of parasomnia (29.3%) in the OND group.

6.3.3 Endocrine Dysfunction and Sleep Wake

A total of six participants with OND in my prospective study had OND associated with possible endocrine dysfunction (four with CP, two with PA). Endocrine dysfunction in isolation can cause changes in sleep wake. When associated with disorders that cause OND, it may be difficult to differentiate between the impact of endocrine abnormalities and pRGC damage (which may lead to circadian dysregulation) on sleep wake. I will describe combined OND and endocrine pathologies which are relevant to my literature review and study population in this section.

6.3.3I Pituitary Dysfunction

It is relevant to examine individual hypothalamic and pituitary hormonal contributions to sleep wake, as there can be numerous permutations in HPA hormonal excesses or deficiencies in PA and CP. ACTH deficiency is a severe, life-threatening condition, and observations of sleep parameters are not well documented, although fatigue is one of its presenting features(1125, 1126). In contrast, the effects of ACTH hypersecretion in the form of Cushing Disease on sleep is well documented, which include increased stage 1 sleep, SL, night time awakenings, WASO and REM density, and reduced SE, TST, SWS and REML(1127).

GH insufficiency has been found to reduce subjective sleep quality and REM sleep and increase daytime sleepiness, stages 1 and 2 sleep, SWS and TST(1128, 1129). Acromegaly, in which there is hypersecretion of GH and IGF-1 is associated with OSA(1130) and poor subjective sleep quality(841). Hypothyroidism is related to OSA(1131), however the impact of TSH insufficiency on sleep is less clear. In normal conditions, a TSH surge occurs during sleep, and the absence of this TSH surge has been found in major depression and rapid-cycling bipolar disorder(1132, 1133).

The effect of LH or FSH deficiencies on sleep is not widely evidenced; however, intermittent sleep disturbances have been found to induce pulsatile LH secretion(1134), and during the luteal phase of the menstrual cycle, at which time both LH and FSH are low, REM sleep has been found to decrease, and sleep spindle frequency and daytime sleepiness are increased(884). Prolactin secretion is upregulated during sleep, although this falls during REM sleep, on which it appears to have a modulatory effect(1135, 1136). Sleep disturbance in pituitary insufficiency following treatment of pituitary macroadenoma and resolution of visual field defects has been reported by Biermasz et al's study (2011)(1137), with findings including reduced SE and REM sleep, and increased stage 1 sleep and night time awakenings.

Excessive ADH production can lead to hyponatraemia and cerebral oedema(1138), while ADH deficiency can lead to hypernatraemia, an inability to concentrate urine and excessive urination, which may lead to sleep disturbance(1139).

6.3.3(d) Pituitary Tumours

Romeijn et al (2012)(1042) studied patients with pituitary tumours, all of whom had pituitary insufficiency on at least one axis, divided into a group with a history of OCC and another where there had been no signs of visual dysfunction. Patients with a history of OCC had later reported bedtimes, indicating a possible later chronotype, and lower proximal daytime temperature. Borgers et al(1043) compared patients with pituitary insufficiency due to tumours, comprising 38 with OCC (30 macroadenoma, 8 CP) and 18 without OCC (10 macroadenoma, 3 microadenoma, 2 CP, 2 dysgerminoma, 1 ependymoma). Subjective sleep quality did not differ between groups, but patients with OCC had later bedtimes and sleep onset, and shorter TST compared to those without OCC. Although OCC was confirmed with ophthalmological testing in both of the above studies, no VA, VF or pupil response data was included in either publication. Clearly, endocrine dysfunction in both studies could have affected sleep parameters, although a phase delay in patients with OCC is suggested by the available data. Sagan et al (2021)(1041) evaluated sleep quality pre- and post-transsphenoidal resection of PA in 29 subjects, 15 of whom had OCC, which resolved post-resection. 59% of the study population had functioning PA, and 41% had non-functioning PA. Post-resection, there was improved sleep quality, duration and SE in subjects with OCC, but alteration in secretion of HPA hormones pre- and post- surgery may have contributed to these results. Joustra et al (2014)(1040) evaluated sleep in 29 patients with NFMA, 82% of whom had OCC pre-surgery which resolved post-resection, and found impaired subjective sleep quality on follow-up several years later, which may have been due to historical OCC or hormonal deficiencies.

6.3.4(e) Craniopharyngioma

Endocrine dysfunction is a common presentation in CP. Deficiencies of gonadotrophins, GH, ACTH, ADH and TSH have been found in up to 85%, 75%, 71%, 38% and 24% of patients at presentation respectively. DI has been found in 76% at presentation, while hypersecretion of prolactin has been found in up to 50% with CP. Surgery can exacerbate endocrine deficiencies, with further depletion in ACTH, GH and gonadotrophins being reported postoperatively, and disordered melatonin secretion and high BMI due to hypothalamic obesity are also associated with CP(401, 1140, 1141).

Pickering et al (2014)(974) conducted an actigraphic study and melatonin assay in 15 patients with CP compared to 15 healthy controls. Subjectively worse mental fatigue, increased SL and daytime dysfunction were found in patients with CP, with poorer general health. Reduced melatonin secretion was observed in CP, and low night-time melatonin correlated with reduced TST, lower SE, poor sleep quality, increased daytime sleepiness, lower general activity levels and increased fatigue. Of note, TSH and free thyroxine levels were lower in CP patients compared to controls, as were FSH and LH, and measures of visual function were not reported. Clearly, there is a marked potential contribution of endocrine dysregulation to sleep wake in this study. Joustra et al (2014)(1040) studied eight subjects with CP, seven of whom had pre-resection OCC, all of which resolved post- resection. All eight subjects had HPA hormonal insufficiency and sleep quality scores were impaired several years post-resection, with the presence of at least two mechanisms (HPA dysregulation and damage to pRGCs) which may have contributed to poor sleep.

6.3.4 Pain and Sleep Wake

In my prospective study, the mean pain score, as measured by the SF-36, was significantly worse in OND than in controls (mean scores 71.7 and 81.7 respectively, p=0.003). Within the OND sample there was a substantial proportion of participants with diagnoses in which there is a predisposition to pain, such as MS, NMOSD, neurosarcoidosis, elevated intracranial pressure, AAION and isolated ON, which will be discussed in this section. Pain can impact on sleep wake, and there is often an interrelationship between the two: pain can cause poor sleep and poor sleep can exacerbate pain(640, 699).

6.3.4(a) Demyelinating, Autoimmune and Inflammatory OND

Eight participants in my prospective study had a diagnosis of MS. Newland et al (2009)(710) found that pain in women with RRMS had a deleterious effect on sleep, fatigue and mood and had higher intensity and interference with daily life than in healthy controls, which concurs with Amtmann et al's (2015) report of increased levels of fatigue, anxiety, disordered sleep and depressive symptoms with worsening pain scores in MS.

33 participants in my prospective study had a diagnosis of NMOSD. Published studies have found that pain has a marked impact on QOL in patients with NMOSD. Kanamori et al (2011)(714) found pain to be of greater frequency and severity in NMOSD than in MS, while Asseyer et al (2018)(715) found that pain in NMOSD was not adequately managed with analgesia, suggesting that pain may be a confounder in this group of study participants.

In my retrospective study of autoimmune and demyelinating OND, pain was present in 35.3% of subjects with NMOSD, 50% with MS and 50% with ADEM, of whom 83.3%, 60% and 100% were poor sleepers respectively, with no pain symptoms recorded in subjects with CIS. Neuropathic, nociceptive pain and headache are prevalent in NMOSD(1142). Neuropathic pain has been found to be associated with sleep disturbance in almost 70% of individuals(1143), which may be reflected by the numbers of subjects with NMOSD who had pain in conjunction with poor sleep quality in this subset.

Five participants with OND in my prospective study had a diagnosis of neurosarcoidosis. Ocular pain has been observed in 9.6% of patients with neurosarcoidosis in a study by Joseph and Scolding (2008)(1144), with facial pain also reported. Acute ON due to neurosarcoidosis can present with painful visual loss(1145), and chronic pain in sarcoidosis is widely described, often in the form of small fibre neuropathy(1146, 1147).

6.3.4(b) Raised Intracranial Pressure

A total of 23 participants in my prospective study had OND in the context of confirmed or possible raised ICP. Five participants in the OND group had CNS meningioma, four had CP, and two had PA (one MEN-1 macroadenoma, and one sporadic PA), and one had glioblastoma. Two participants had NF1 and one had NF2. Two participants had raised ICP due to other causes, one had hydrocephalus OA, and five had IIH.

Headache is frequently associated with isolated raised ICP and also in association with space occupying lesions of the CNS(1148, 1149). Abe et al (1998)(1150) reported the presence of headache in 37% of patients with PA. In Pereira-Neto et al's (2010)(1151) study of PA, 56% of subjects reported severe HA symptoms. Recurrent headaches have been described in 77% of individuals with NF1(1152) with migraine reported in 65%(1153). Headaches have been reported as the presenting symptom of NF2, and have been recorded in 50% of cases where

vestibular schwannoma was present(1154). Headache has been noted in one third of patients with hydrocephalus(1155), and it is the most frequent presenting symptom in IIH(1156), having been found in 94% of cases(1157). Headache in IIH has been reported to cause night time waking, in addition to back pain and muscle aches(699, 720).

6.3.4(c) Arteritic Anterior Ischaemic Optic Neuropathy

Three participants in my prospective study had AAION, which is associated with GCA, and frequently presents with headache, scalp pain and jaw claudication(1158). Symptoms of GCA tend to be alleviated following treatment with glucocorticoids(1111), meaning that this group is less at risk of reporting pain as they are unlikely to have been recruited to my study prior to acute medical management.

6.3.4(d) Isolated Optic Neuritis

Eight participants in my prospective study had isolated ON. The optic nerve is insensate, and it is the inflammation of the optic nerve sheath in acute ON that can lead to ocular and retrobulbar pain, which is often aggravated by ocular movement. This was found in 92% of cases of ON with visual loss in the Optic Neuritis Treatment Trial(1159, 1160). Glucocorticoid therapy is used with discretion in ON, depending on the presence and degree of visual loss, and results in resolution of pain(1161, 1162). None of the participants with ON in my prospective study were in the acute stages of management with intravenous glucocorticoids, and pain was unlikely to be a prominent symptom at the time of data collection in this group.

No participants with CIS in my retrospective study were recorded as experiencing problematic pain. The mean time since diagnosis in this group was 1.4 years, meaning that subjects were unlikely to have been recruited during the acute stages of presentation, and that pain due to inflammation was likely to have been controlled.

6.3.5 Chronic Disease and Sleep Wake

60.7% of OND participants in my prospective study were found to have an associated chronic disorder. SF-36 evaluation of OND and control participants found significantly worse physical functioning (mean scores 70.3 and 85.5 respectively, $p<0.0001$), physical limitation (mean scores 59.5 and 89.3 respectively, $p<0.0001$) and energy and fatigue (mean scores 49.9 and 62.6, $p<0.0001$) in participants with OND compared to controls.

In my retrospective study, four subjects with NMOSD (11.8%) were found to have systemic involvement, thee of whom were poor sleepers (75%). Of the subjects with MS, seven had RRMS, one had SPMS and one had PPMS of whom 28.6%, 100% and 100% had poor sleep respectively. Of the two subjects with ADEM, one had spinal involvement and concurrent poor sleep.

Short duration (six hours or less), long duration (nine hours or more), and disturbed sleep are more prevalent in chronic disease states (1163, 1164), particularly in the presence of multiple pathology and in older age(1164, 1165). Reduction in physical function, the presence of pain and mental health challenges including anxiety and depression are morbidities that can result from chronic illness which themselves may impact on sleep(1166-1170), which may be confounders when determining whether OND have an impact on circadian timing in the presence of chronic disease.

Patients with chronic disease are more likely to have a sedentary lifestyle due to their physical limitations, and this can impact on BMI, as reflected in the significantly higher mean BMI in participants with OND in my prospective study(1171-1173) and the high mean BMI in participants with NMOSD in my retrospective study. Sleep wake disturbances have been found to be more prevalent in sedentary adults with mobility limitations compared to those with physical disabilities who participated in structured physical activity(1174).

6.3.6 Psychiatric Conditions and Emotional Impact

HADS depression scores were significantly increased in participants with OND compared to controls in my prospective study (mean 4.6 and 2.7, respectively, $p=0.04$). In all participants,

poor sleep was associated with increased anxiety and depression ($p<0.0001$, $p=0.04$ respectively), and as sleep scores worsened, so did anxiety and depression scores ($p<0.0001$, $p=0.0009$ respectively). In OND, worsening sleep scores were also found to correlate with worsening anxiety and depression scores ($p=0.002$ for both). In the OND group, 36 participants (29.5%) had a history of anxiety, depression or other mental health condition, as measured by the GHQ.

Emotional limitation, measured by the SF-36, was significantly worse in participants with OND compared to control participants (mean scores 83.3 and 90.5 respectively, $p=0.008$), although emotional wellbeing scores were comparable between OND and controls (mean 74.4 and 76.2 respectively, $p=0.5$).

In my retrospective analysis of subjects with autoimmune and demyelinating OND, 26.5% of subjects with NMOSD and 40% of subjects with MS screened positive for anxiety on HADS-A, of whom poor sleep was found in 88.9% and 50% respectively. HADS-D screen was positive in 32.4% of subjects with NMOSD and 20% of subjects with MS, all (100%) of whom had poor sleep quality, which may indicate the strong correlation that has been found with depression and sleep quality and timing, with sleep disorders a core symptom in the clinical diagnosis of depression(1175).

6.3.6(a) Depression and Sleep Wake

Depression has been found to correlate with increased sleep disturbance and SL, reduced sleep quality and daytime napping in older adults(1176). It appears that the relationship of depression with sleep is bimodal: sleep duration greater than 8 hours and less than 6 hours is associated with depressive mood; in addition, the subjective perception of feeling rested after sleep is reduced in depression(1177). Moreover, insomnia and hypersomnolence in the context of MDD correlate with elevated suicidality(1178), which illustrates the grievous implications of sleep disturbance in depressive disorders. Depression has been reported in association with MS, NMOSD, endocrine tumours, neurosarcoidosis, NF1, NF2, DOA and IIH, all of which were found within my prospective OND study population, in addition to glucocorticoid therapy.

Eight participants with OND in my prospective study had MS, and 33 had NMOSD. In my retrospective study, 34 participants had NMOSD and 10 had MS, of whom 32.4% and 20% screened positive for depression respectively. Depression in MS has a lifetime prevalence of 50%, and may occur due to the impact of the disease process on the CNS leading to cognitive impairment, as well as due to pain, physical limitations and fatigue(1179, 1180). Depression in NMOSD and MS has been found to be comparable and to strongly correlate with mental composite scores, fatigue, physical functioning and health-related QOL(1079). Shi et al (2016)(1048) described a correlation between depression and sleep disorders in NMOSD. Pan et al (2015)(1050) found that depression scores correlated with fatigue, which was higher in participants with NMOSD than in control participants, which agrees with Seok et al's (2017)(1026) findings that depression and QOL scores were worse in female patients with NMOSD and were associated with fatigue. Miao et al (2017)(1049) found that poor sleep quality was significantly associated with depression in NMOSD, and Barzegar et al (2018)(812) found worse cognitive fatigue and worse cognitive, somatic and total depression scores in NMOSD compared to MS.

In my retrospective analysis, two subjects had a diagnosis of ADEM, both of whom screened positive for depression and had poor sleep quality. ADEM has been reported to present as a severe depressive episode in both children and adults, which can impact on sleep(1181), and is also associated with hypersomnia and narcolepsy with low hypocretin/orexin levels(821, 822).

Six participants in my prospective study had endocrinological tumours. Depression in pituitary disorders such as PA and CP can be due to the presence of the CNS tumour itself as well as the impact of this on the individual. Additionally, excessive GH production, causing obesity, disruption of the HPA-axis and hypersecretion of ACTH, or deficiency in TSH and central hypothyroidism can lead to depressed mood(1182-1184).

Major depression has been observed to be the primary presentation in neurosarcoidosis(832), which was the cause of OND in five participants in my prospective study. Cognitive failure was found by Voortman et al (2019)(828) to be present in 55.7% of neurosarcoidosis patients, and was associated with depression and fatigue.

Two participants in my prospective study with OND had a diagnosis of NF1, and one had a diagnosis of NF2. Cohen et al (2015)(1185) found a 55% likelihood of clinical depression in patients with NF1, which had a strong impact on QOL. Wang et al (2012)(1186) found that emotional function in the neurofibromatoses did not correspond to severity of condition but did relate to the number of visits to health professionals, as did low self-esteem and subjective stress. Of note, increase in healthcare attendance could also correspond to increased likelihood of recruitment to this study, as OND participants were recruited from outpatient clinics. Merker et al (2016)(1187) observed reduced emotional function scores in NF2 compared to the general population.

Glucocorticoid therapy may be used in all of the above conditions (MS, NMOSD, endocrine tumours, neurosarcoidosis, NF1 and NF2), which can independently contribute to changes in mood(1188), including depression(1189). Systemic glucocorticoids were taken by 67.7% of subjects with NMOSD in my retrospective study, of whom 82.6% had poor sleep quality, which may have contributed to the presence of low mood and poor sleep quality found in my observational study as a whole.

Six participants with OND in my prospective study had DOA, which has been found to be associated with depression(1190), as has IIH (found in five study participants), which impacts on QOL and is not fully explained by its association with high BMI(1115). Antidepressant therapy also alters sleep parameters and sleep architecture as described later in this chapter.

6.3.6(b) Anxiety and Sleep Wake

Insomnia is present in 70-90% of individuals with anxiety. Sleep quality can also be compounded by sleep panic attacks and sleep paralysis. Cataplexic episodes (loss of muscle tone and sudden collapse) are higher in anxiety than in the general population(1191). Sleep impairment in anxiety is associated with worsened disability and poorer mental health-related QOL(768). PSG evidence of lighter sleep, increased microarousals and less REM density was reported in GAD by Fuller et al(1997)(771). Anxiety has been reported in association with a number of OND diagnoses found in this study, including MS, NMOSD,

neurosarcoidosis, PA, NF1, DOA and IIH, and glucocorticoid medications can exacerbate anxiety. Sleep wake can also be affected by anxiolytic medications.

In my retrospective study, 40% of subjects with MS had anxiety, of whom 50% had poor sleep. Anxiety disorders are common in MS, and are often under-diagnosed(1192). Younger female patients who are less impaired and who experience pain and fatigue are more likely to suffer from anxiety in the context of MS(1193). Anxiety has been found to three times more prevalent in MS than depression, and the two frequently co-exist(1194). It has been associated with poorer sleep quality and increased variability in sleep timing in MS(805).

In my retrospective study, 26.5% of subjects with NMOSD were found to have anxiety, of whom 88.9% had poor sleep. Shi et al (2016)(1048) found that anxiety correlated with depression, fatigue, disability and health-related QOL in NMOSD. Miao et al (2017) also found that anxiety in NMOSD was associated with poor sleep(1049), and comparable anxiety scores have been reported in NMOSD and MS(735).

Anxiety has also been observed to be a presenting feature of ADEM(825, 1195). Neither subject with ADEM screened positive for anxiety in my retrospective analysis, although this sample is too small to be a reflection of typical presentation. In childhood onset ADEM, emotional symptoms such as anxiety, hyperactivity and aggression are more prevalent when the onset of the condition is at a younger age(1196, 1197). Anxiety and cognitive symptoms can be apparent in neurosarcoidosis(1198), and in general, anxiety has been found to be present in one third of sarcoidosis sufferers, with a measurable impact on emotional wellbeing(1199).

Anxiety traits have been noted in patients with PA(1200). GH-producing adenomas(1201), and increased ACTH production (Cushing disease) have been associated with increasing anxiety prevalence, which are reflected in a reduction in novelty-seeking behaviour and exploratory activities and a preference for obviating harm(1202). Anxiety traits are present at higher levels in CP, and its consequences such as risk avoidance may be related to obesity levels(1203), which, in combination with negative life events may further increase anxiety(1204). Oxytocin deficiency has been found to be associated with increased anxiety in adults following surgical excision of CP in childhood(1205).

Doser et al (2020)(1206) reported that 15% of NF1 patients had clinical anxiety, and that the degree of impact of NF1 on physical appearance and its overall severity corresponded to its psychosocial impact. Pasini et al (2012)(1207) also noted worse anxiety in children and adolescents with NF1 compared to healthy controls. Horingold et al (2012)(1208) found that 53% of patients with NF2 had anxiety symptoms, which was worse than in the general population and in those with isolated vestibular schwannomas.

Glucocorticoid therapy was prevalent in participants with NMOSD in my retrospective study and is used in several of the systemic pathologies found in participants in my prospective study. An association of glucocorticoids with anxiety and panic disorder has been found, which may be due to their action on hippocampal glucocorticoid receptors. This can lead to a defective stress and fear response, heightened anxiety and freezing of activity(1189, 1209).

DOA has been found to be associated persistent anxiety, which may be due to its slowly progressive and highly visually disabling nature(1190). Higher anxiety has been found in IIH in comparison to BMI-matched controls and controls with chronic headache(1210). Mild cognitive impairment in multiple domains including executive function, attention, problem solving, and processing speed has been found in patients with IIH(1211), which may also contribute to these symptoms.

Therapies for anxiety include benzodiazepines, which are anxiolytics and hypnotics and also have an impact on sleep, which may act as confounders in the OND group in this study(1212, 1213). Cannabidiol (CBD) has also been proposed as an anxiolytic and has been found to improve sleep in anxiety-related insomnia(1214-1216). No information about use of CBD or related substances was collected in my questionnaire data, so this is an unknown quantity.

6.3.6(c) Emotional Regulation and Sleep Wake

Emotional limitation was found to be significantly worse in OND than in controls, although emotional wellbeing was comparable ($p=0.008$ and $p=0.5$ respectively). Goldstein and Walker (2014)(1217) in a review of the role of sleep and emotional function describe REM sleep as a vehicle for recalibration of emotions, including emotional memory resolution, and as a means of “affective brain homeostasis”, noting the negative emotional sequelae of

sleep deprivation, and the restorative social and emotional effects following good quality sleep.

Participants with OND in my prospective study had worse sleep quality than control participants, which may have affected their QOL and emotional functioning. Emotional state can also be influenced by chronic disease, which was present in the OND population, and physical symptoms can be altered due to emotional state(1218). Pain consists of sensory, physical, psychological and emotional responses, and can impact on emotional functioning(700), while emotional state can also influence pain(1219). VI can affect emotional wellbeing(1220), although emotional state has not always been found to be altered in individuals with visual limitation compared to those who are unimpaired(1221). Emotional lability is a feature of MS, with increased emotional experience reported in patients, although an impaired ability to recognise emotional facial expression of others may be present(1222). Emotional lability is also a feature of NMOSD, although it has been found in a significantly lower proportion of patients than in MS(1223). These clinical features may have contributed to poorer emotional limitation scores in OND subjects in this study.

6.3.7 Medications and Sleep Wake

It was not feasible to exclude subjects on the basis of medication history in the OND group of my prospective study, as I aimed to obtain a sample of subjects that was representative of the spectrum of OND in the general population, and there is a predominance of medication use in systemic disorders associated with OND. This section describes the numbers of participants within the OND group who were taking medications which may have affected their sleep, including psychiatric medications, benzodiazepines and sleeping medications, beta-blockers, glucocorticoids, NSAIDs, opiates and antispasmodics, with an evaluation of the effects of these drugs in published literature.

6.3.7(a) Psychiatric Medications

In my prospective data, 19 participants in the with OND (15.6%) were taking psychiatric medications, and in my retrospective study they were prescribed for six participants with

NMOSD (17.6%), four with MS (40%) and one with ADEM (50%), of whom five (83.3%), three (75%) and one (100%) were poor sleepers respectively. Psychiatric medications are a heterogenous group of drugs, with varied effects on sleep. Most antidepressants (SSRIs, SNRIs, MAOIs, TCAs) suppress REM sleep. Increased PLM can occur with SNRI use, and increased SWS and dream intensity is associated with SSRIs(661, 663-670). Antipsychotics increase TST and SE and reduce WASO and REM sleep. Typical antipsychotics can have a sedative effect and atypical antipsychotics are associated with sleep-disordered breathing(676, 678-681). Mood stabilisers increase SWS, suppress REM sleep and can assist in circadian entrainment(684, 685). Psychiatric medications can influence sleep wake, either by increasing sleep disturbance, or conversely by directly improving sleep quality or by indirectly alleviating psychiatric symptoms. Psychiatric medications may therefore have contributed to the difference in sleep quality found in subjects with OND in this study.

6.3.7(b) Benzodiazepines and Sleeping Medications

In my prospective study, 10 participants (8.2%) with OND were taking benzodiazepines or other sleeping medications, while in my retrospective study of autoimmune and inflammatory OND, five subjects with NMOSD (14.7%) were taking sedative or hypnotic medications, all of whom had poor sleep. Benzodiazepines are GABA agonists and have anxiolytic and hypnotic properties. They suppress REM sleep and SWS and increase stage 2 sleep(672-675), but can also lead to a rebound next-day insomnia(1224). Other classes of sedatives and hypnotics include GABA-selective agents such as Zaleplon, which have been found to reduce SL and WASO, and increase TST, although altered sleep architecture may ensue(1225). Barbiturates such as phenobarbital, produce postsynaptic augmentation of GABA(1226). Exogenous melatonin has been used as a sedative, and can be used as a weaning agent for hypnotic medications(1227). These medication properties may have led to altered sleep quality and duration in some individuals in my study and may have amplified or diminished (via alleviation of symptoms) any differences between subjects with OND and controls.

6.3.7(c) Beta-Blockers

In my prospective study, five participants with OND (4.1%) were taking oral beta-blockers and one participant with OND (0.8%) was taking a topical beta-blocker (eye drops). In my retrospective study, two subjects with NMOSD were taking systemic beta-blockers (5.9%), both of whom had poor sleep. Beta-blockers antagonise β1-adrenergic receptors, and via this mechanism also reduce melatonin secretion from the pineal gland, which in animal studies has been found to produce melatonin in response to stimulation of β1-adrenergic receptors in addition to α and P-adrenergic receptors(1228, 1229). Subjective sleep disturbance has been reported with metoprolol, a second generation beta-blocker(1230), and exogenous melatonin has been demonstrated to improve PSG sleep measures in individuals with hypertension taking either atenolol or metoprolol(1231). Lipophilic beta-blockers such as pindolol and propranolol are more likely to affect the CNS and have been associated with depressed mood(1232), although one study(1233) found that neither metoprolol nor atenolol altered affect, but that higher levels of fatigue were reported with both. These pharmacological features may have affected sleep quality in my study population.

6.3.7(d) Glucocorticoids

In my prospective study, 38 participants in the OND group (31.1%) were taking glucocorticoid medications. In my retrospective study of subjects with autoimmune and demyelinating OND, 23 participants were taking systemic glucocorticoids (67.6%), of whom 82.6% had poor sleep, and one participant with MS was prescribed inhaled glucocorticoids and had a normal sleep score. Only five subjects had cataract data available; the presence of cataract in this sample was likely to be an underestimate in view of the high prevalence of glucocorticoid therapy. My sensitivity analysis for systemic glucocorticoids did not show any change in the significance of study findings, although glucocorticoids have been found to have a marked influence on sleep timing and quality. Sarnes et al (2011)(1234) reported sleep disturbances in 30% of publications in a systematic literature review, and dexamethasone has been found to decrease REM sleep and SWS(1235). Glucocorticoids modulate serotonergic activity in the CNS in a bell-curve relationship, with excessively low endogenous glucocorticoids and excessively high glucocorticoid doses causing negative

effects(1236). It is hypothesised that high-dose glucocorticoids cause hippocampal damage which in turn can affect cognition, in particular verbal and declarative memory, and cause depressive affect, bipolar symptoms and psychosis(1188, 1237).

6.3.7(e) Non-Steroidal Anti-inflammatory Drugs

NSAIDs are frequently taken in chronic inflammatory conditions and inhibit the production of prostaglandin D2 via their suppression of cyclo-oxygenase 1 and 2. Prostaglandin D2 induces adenosine secretion, whose action is to reduce arousal and promote sleep. Inhibition of prostaglandin D2 and adenosine may indirectly reduce melatonin secretion(1238). Ibuprofen has been found to reduce SE and increase night time awakenings on PSG(704). With respect to mood, NSAIDs have been found to decrease suicidal ideation in males and females and reduce depression in osteoarthritis patients and women, which is postulated to be due to its reduction of CNS inflammation, which is attributed to depressive states(1239, 1240). In my retrospective study of autoimmune and demyelinating OND, one participant with NMOSD (2.9%) was taking NSAIDs, and was a poor sleeper, and both participants with ADEM were prescribed NSAIDs and were poor sleepers, which may have contributed to worse subjective sleep quality in these individuals.

6.3.7(f) Opiates

In my retrospective study of autoimmune and inflammatory optic neuropathies, one participant with NMOSD was prescribed oral opiate medication (2.9%), and had poor sleep, and one subject with MS (10%) (with a diagnosis of SPMS) was taking a combination of transdermal and oral opiates and had poor sleep. As pain is associated with several aetiologies of OND, it is possible that opiate analgesia was also used by subjects with OND in my prospective study.

Opiate medications generally increase the timing of light sleep stages and decrease SWS. They suppress REM sleep and reduce SE, although paradoxical effects are seen in addiction, withdrawal and dependence(642-644).

With longer-term opiate use, dependence, tolerance and withdrawal and their impact on sleep wake may need to be considered(648, 1241, 1242). These factors may have influenced sleep quality in subjects with NMOSD and MS in my retrospective analysis and in my prospective study population.

6.3.7(g) Antispasmodics

Baclofen is a centrally acting antispasmodic agent and is a GABA-B agonist(709). It is delivered orally, although it can be administered intrathecally in conditions where severely increased muscle tone causes functional impairment and pain, including MS, NMOSD and PD(1243-1245). Baclofen has been found to increase TST, REM and NREM sleep and reduce WASO, with a slight decrease in nocturnal oxygen saturation observed(709). In my retrospective study, baclofen was taken by two subjects with NMOSD (5.9%), both of whom had poor sleep, and two subjects with MS (20%), one of whom was a poor sleeper. As an agent which generally improves sleep parameters, it may have led to relatively better sleep scores in these subjects although it not have been sufficient to normalise scores due to many other systemic and medication factors.

6.3.8 Caffeine, Smoking and Alcohol

Caffeine, alcohol and nicotine intake were comparable between OND and control groups in my prospective study (p=0.9, p=0.07, p=0.2 respectively). All three substances can interfere with sleep parameters and sleep architecture. In view of my results, intake in this sample is unlikely to have accounted for the differences in sleep wake and mood between groups. However, for completeness, I will examine caffeine, alcohol and nicotine with regard to neurodegeneration and chronic pain and their risks within the OND categories in this study. All three substances can impact on psychological status and mood, which could amplify the effects of visual loss, chronic disease and pain on mood and sleep in OND.

6.3.8(a) Caffeine and Sleep Wake

In my retrospective study of autoimmune and demyelinating OND, 76.5% of subjects with NMOSD had at least once daily caffeine intake, of whom 80.8% had poor sleep. In contrast, of the 60% of subjects with MS with at least once daily caffeine intake, 33.3% had poor sleep. One subject with ADEM (50%) had daily caffeine exposure and had poor sleep, and three subjects with CIS (75%) had regular caffeine intake, one of whom had poor sleep (33.3%). There appears to be no overall pattern in this data, although the sample is small and timing of caffeine intake (whether in the morning or closer to bedtime) was not recorded. There is scant published evidence regarding caffeine as a risk factor or its prevalence in OND pathologies. In essence, adenosine induces physiological sleep via its action on A_{2A} receptors, on which caffeine has an antagonistic effect. As a result, caffeine can suppress REM and NREM sleep stages(1246). Although caffeine may improve overall performance in sleep-deprived individuals, it may weaken cognitive inhibitory functions in this population(1247). Long-term caffeine consumption has been associated with poorer sleep quality and reduced pineal parenchymal volume in older adults, and has been found to have a greater effect in the elderly than in the young(513, 1248).

Males have a greater susceptibility to the anxiety-generating effect of caffeine(514). The OND group in my prospective study had a significantly higher proportion of males than the controls (49.2% compared to 27.4% respectively), which may have influenced anxiety and mood findings, although in my retrospective analysis of demyelinating and autoimmune OND, there were more female than male participants. Caffeine is metabolised at a slower rate during the second half of the menstrual cycle in females(1249), meaning that its effects may have been more pronounced in the control group in my prospective study, which had a significantly greater proportion of female participants, despite caffeine intake being comparable between groups. Chronically high caffeine intake can produce symptoms of tolerance and dependence, while withdrawal can cause rebound fatigue and mood changes, although historical caffeine use was not assessed in this study(526, 528, 1250).

6.3.8(b) Smoking and Sleep Wake

Nicotine has been found to act on nAChRs of the CNS and inhibit sleep-promoting GABA neurones in the VLPO, leading to increased arousal. It has sedative properties in low

concentrations, and in higher concentrations increases wakefulness, with impact on sleep parameters and architecture including increased SL, REML, stage 2 sleep, sleep fragmentation and early morning wakening, and reduced TST, SWS and REM sleep, with increased risk of sleep-disordered breathing and OSA in smokers(532, 533, 539-542, 548, 549). Nicotine can cause a phase advance, but if consumed at night can delay the circadian clock(535-538). Premenopausal women, particularly those taking oestrogen-related contraceptives metabolise nicotine at a faster rate than men(1251).

Although cigarette smoking was comparable between OND and control groups in my prospective study, there was a significantly higher ratio of women to men in the control group (72.6%) than in OND (50.8%), which may have affected outcomes. In my retrospective analysis, six (17.6%) subjects with NMOSD were current smokers, 66.7% of whom had poor sleep. One subject with RRMS and one with CIS were smokers, both of whom had poor sleep. As nicotine is metabolised at a more rapid rate in women, its overall impact on sleep may have varied between my prospective and retrospective studies, as my retrospective study had a higher proportion of female participants. Caffeine also has the effect of increasing nicotine cravings and use in the short term(552), although this interaction was not assessed. Similarly, the effects of nicotine tolerance, dependence and withdrawal, which can also impact on sleep architecture, quality and timing, could not be evaluated(535, 539, 540, 545, 547).

6.3.8(c) Alcohol and Sleep Wake

In my retrospective study of demyelinating and autoimmune OND, 32.4% of participants with NMOSD were current drinkers, of whom 63.6% had poor sleep quality. In subjects with MS, 50% were current drinkers, of whom 40% had poor sleep. One subject with ADEM was a current drinker and had poor sleep, and four subjects with CIS had current alcohol intake, of whom 50% had poor sleep. Numbers in this analysis are small, and no overall pattern was evident from the data. In addition, of the three participants with weekly alcohol intake of >14 units/week, one subject had poor sleep quality, and two had normal sleep scores. Alcohol has stimulatory effects via the dopaminergic system and soporific effects via facilitation of the GABA inhibitory system and antagonism of the glutaminergic system, including NMDA receptors, which are implicated in REM sleep(563, 565, 566). Alcohol

consumption has been found to increase SWS, WASO, stage 2 sleep and REM sleep during the second half of the night and reduce SL, TST and REM sleep in the first half of the night(579-581). Alcohol has a greater effect on reduction in subjective sleep duration and next day tiredness in the young than in the elderly(606), and is eliminated at a slower rate in females compared to males(583, 584). In my prospective study, age and alcohol consumption were comparable between groups; however, the proportion of females in the control group was significantly higher, meaning that the impact of alcohol consumption on sleep wake may have differed between groups. Similarly, my retrospective study of autoimmune and demyelinating OND comprised a higher proportion of female subjects, which may have led to differences in results between the OND populations in my prospective and retrospective studies.

Nicotine consumed with alcohol counters its sedating effect, maintains wakefulness and normalises REM sleep(572, 573). The dual impact of nicotine and alcohol on sleep could not be elicited in this study; neither could the impact of caffeine in attenuating the hypnotic properties of alcohol(576-578). Additionally, the impact of alcohol tolerance in normalising sleep architecture(585, 586), and subsequent dependence producing a disruption in NREM and REM sleep, increased SL, reduced TST and SWS, and increased PLM could not be assessed in this study(587, 588); neither could any impact of alcohol withdrawal such as disordered sleep and wake timing, increased daytime sleep propensity, reduced SWS and sleep fragmentation(592, 593).

6.3.8(d) Neurodegeneration and Chronic Pain

Caffeine has been found to have a protective effect against neurodegeneration(1252), which may be relevant to the systemic neurological conditions associated with OND in this study. Smoking is a risk factor in an array of neurodegenerative diseases(1253), although the evidence for alcohol consumption is more patchy.

As described earlier in this chapter, chronic pain may be a feature of chronic systemic conditions, which were present in 60.7% of the OND group in my prospective study, in addition to isolated OND such as AAION and ON, which were found in three and eight participants with OND, respectively. Current smoking and nicotine dependence are of

markedly higher prevalence in chronic pain sufferers(1254), with higher cigarette consumption correlating with more severe pain(1255). In my retrospective study, problematic pain was recorded in 35.5% of subjects with NMOSD, 40% with MS and 50% with ADEM. Among patients receiving treatment for chronic pain, 16-25% have been reported to have history of alcohol misuse, and 43-73% of patients receiving treatment for alcohol misuse have a history of chronic pain(1256). This is information that could not be derived from the GHQ or SF-36 questionnaire data but are elements that may relevant clinically or in future research.

6.3.8(e) Demyelination, Autoimmune and Inflammatory Conditions

Eight participants in my prospective study had MS, although an analysis of tobacco consumption in aetiological subgroups was not performed. In my retrospective study 10 participants had MS, of whom one was a current smoker. Smoking is a modifiable risk factor for the development of MS, and for more rapid development of MS lesions and disease progression once its diagnosis is established(1257-1259). Palacios et al (2011)(1260) reported increased the risk of MS onset in smokers. Friend et al (2006)(1261) found that smoking rates in MS were less than in the general population, but that those with MS who did smoke tended to be heavy smokers. In contrast, Kvistad et al (2016)(1262) found no relationship between smoking and disease activity in MS. Caffeine and alcohol have not been implicated in the onset of MS(1263), and caffeine intake has been found to be protective(1264); however misuse of alcohol has been found in 13.6% of patients with MS compared to 7.4% of the general population(1265).

Tobacco consumption within the subgroup of 33 participants with NMOSD in my prospective study was not analysed. In published literature, the prevalence of smoking in NMOSD has been found to be lower than in MS, and an inverse relationship between smoking and disease incidence has been hypothesised(1253). However, in a study of environmental risk factors for NMOSD, Eskandarieh et al (2018)(1266) found increased odds of developing NMOSD in passive smokers, water pipe smokers and use of alcoholic spirits.

There is very little evidence regarding the impact of smoking on and alcohol on neurosarcoidosis (a diagnosis in five participants with OND in my prospective study),

although smoking may lead to long-term functional impairment(1267). A negative association between smoking and sarcoidosis has been reported(1268, 1269), and no association of caffeine with the presentation of sarcoidosis has been found(1270).

6.3.8(f) Compressive Optic Neuropathies and Idiopathic Intracranial Hypertension

In my prospective study, subjects with compressive OND aetiologies included five subjects who had CNS meningioma and two with PA. Five participants had a diagnosis of IIH. Smoking has not been found to be related to the risk of PA in one study, and has been found to reduce its risk in another(1271, 1272). Fan et al (2013) conducted a meta-analysis and found no association between smoking and meningioma(1273), although a reduced risk of meningioma in female smokers has been found by Claus et al(2013)(1274), which agrees with Claus et al's (2012)(1275) findings, although they also reported an elevated risk of meningioma in male smokers. Increased risk of requiring a CSF shunt has been found in smokers with IIH(1276), although no relationship between smoking and IIH onset has been identified(1277).

6.3.8(g) Hereditary Optic Neuropathies

Seven participants with OND had a diagnosis of LHON in my prospective study. Smoking(1278, 1279) and heavy alcohol intake have been found to correlate with increased phenotypic penetrance in LHON(1280). Due to the impact of nicotine intake on sleep, its combination with RGC loss could have a more detrimental effect. However, this is countered by Kerrison et al (2000)(1281) who did not find a correlation of vision loss in LHON with smoking, and conversely found a reduced risk of phenotypic penetrance with alcohol use.

6.3.8(h) Ischaemic Optic Neuropathies

Four participants with OND had a diagnosis of NAION in my prospective study. Smoking has been found to be associated with NAION in some studies(1282, 1283), while in others, no association has been found(1284, 1285). An association with alcohol consumption was not identified in NAION when compared to risk factor-matched controls(1286); however

bilateral NAION has been reported in a patient with alcoholic liver disease(1286). As an analysis of caffeine, alcohol and tobacco intake in ischaemic optic neuropathies was not performed in my prospective study, comparative data is unavailable. However, the presence of the same risk factors for the development of a disease (such as smoking and alcohol intake) could also amplify any deleterious effects of the disease (such as contributing to worsened sleep quality in the presence of circadian disorders due to RGC damage).

6.3.8(i) Toxic and Nutritional Optic Neuropathy

One participant in my prospective study had toxic optic neuropathy. There are a range of causes of toxic optic neuropathy, which involves exposure to substances that can cause mitochondrial injury and degeneration of RGC axons in the optic nerve. Similarly, nutritional deficiencies cause depletion of certain metabolites, which can also cause mitochondrial damage and optic neuropathy. Both toxic and nutritional optic neuropathies present with a characteristic loss of papillomacular nerve fibres(1287). Specific classes of drugs (for example, anti-tuberculosis medications, quinines, amiodarone, methotrexate, vincristine), solvents, heavy metals, carbon monoxide, methanol and ethylene glycol (antifreeze) can cause toxic damage to optic the optic nerves, as can smoking. Deficiencies of thiamine, riboflavin, vitamin B12, folic acid and amino acids are implicated in nutritional optic nerve damage, which may be associated with alcohol intake(469, 1288, 1289), and excessive alcohol consumption has been found to be a risk factor in the onset of bilateral OA(1290). Depending on the cause of toxic optic neuropathy, precipitating factors may have a notable exogenous impact on sleep wake as well as damaging pRGCs and potentially causing circadian dysrhythmia.

6.3.9 Selective Preservation of Photosensitive Retinal Ganglion Cells

Although there are many non-circadian reasons for the association of OND with poor sleep quality in this study, it is appropriate to consider the impact on circadian mechanisms due to pRGC damage in OND, and conversely the relative sparing of pRGCs in certain classes of OND

which exhibit degeneration of other RGC subtypes. Both pRGC degeneration and sparing may impact on circadian regulation in OND.

pRGCs make up approximately 0.8% of the total number of ganglion cells distributed throughout the retina, of which there are approximately 30 known subtypes. Some RGCs are motion sensitive, with subtypes including those that are direction selective and identify movement along a visual axis, those that can detect looming dark objects, and those that stabilise eye movements in response to visual stimuli. Other RGCs are orientation-selective, and others are edge detectors, identifying light or dark borders of objects. Another subgroup is able to detect centres and surrounds of objects. pRGCs, as described earlier, are identifiable by the photopigment melanopsin, and are intrinsic to the pupillary light response and entrainment of the SCN(1291, 1292).

As found by La Morgia et al (2010)(1034) in their study of individuals with mitochondrial optic neuropathies, there appears to be preferential sparing of pRGCs in comparison to other ganglion cells and photoreceptors, with subsequent maintenance of circadian entrainment. This may account for Munch et al's (2015)(280) study in which subjects with HON had comparable PLR, melatonin suppression and subjective sleepiness to controls. Prihodova et al's (2021)(1028) study of LHON and DOA found that PSQI, ESS and PSG outcomes were comparable to controls. Similarly, in Czeisler et al's (1995)(916) study of serum melatonin levels in patients with NPL, one patient with bilateral optic neuropathy, undetectable VEPs and PLR demonstrated a normal ERG and showed suppression of melatonin on exposure to bright light and normal circadian entrainment. Moura et al (2013)(1293) found PLR, although attenuated, were still present in a study of patients with LHON versus controls, despite severe optic atrophy and very poor VA, which suggests enhanced survival of pRGCs, which form the afferent arc of the pupillary light reflex(1291). Perez-Rico et al (2009)(116) found positive melatonin suppression in response to light in two subjects with DOA and three subjects with AION, suggesting that in addition to mitochondrial optic neuropathies, ischaemic optic neuropathies may also display selective preservation of pRGCs, which is consistent with Tsika et al's (2015)(1045) findings of comparable PSQI scores between subjects with AION and controls and preservation of some PLR at lower light intensities in AION.

Animal studies have shown injury-resistance in pRGCs(107). Perganta et al (2013)(1294) found no difference in circadian entrainment in a mouse model of DOA, while de Sevilla Muller et al (2014)(1295) found prolonged survival of M1 pRGCs in the rat retina following optic nerve transection. DeParis et al(2012)(1296) found that mouse pRGCs were resistant to excitotoxicity caused by NMDA injection, whereas other RGCs showed attrition.

In a study of crush injury to the optic nerve in mice, Daniel et al (2018)(1297) found that Wallerian degeneration affected all RGC axons regardless of subtype, but that pRGCs demonstrated the most effective survival. Wallerian degeneration is the process of "dying back" of neuronal axons following transection due to the interruption of axonal transport of metabolites from the cell soma to the terminal axon, resulting in the degeneration of the terminal axon and its sheath(1298). Although animal models of AION have been developed, no published studies have described the specifics of pRGC function(1299-1301).

6.3.9(a) Glaucoma

In glaucoma, the picture of pRGC vulnerability or resistance is less clear, and there is some disparity between human and animal models. Gracitelli et al (2015)(1067) reported reduced pupillary responses and increased night time arousals, implicating reduced pRGC function in glaucoma patients. Gracitelli et al (2016)(1054) found increased daytime sleepiness as measured by the ESS, poor SE on PSG and impaired pupillary responses in patients with glaucoma in comparison to healthy controls. A lack of melatonin suppression in patients with advanced bilateral POAG after bright light exposure has been described(116, 1302), as has a marked loss of pRGCs in postmortem eyes of subjects with severe glaucoma(1303).

In animal models, Li et al (2006)(1304) found that a greater proportion of pRGCs survived in the presence of chronic ocular hypertension in comparison to other RGC cell types. Rovere et al (2016) in a further rat model of acute ocular hypertension found that pRGCs were less susceptible to damage than other forms of RGC. In contrast, Zhang et al (2013) found significantly more pRGC loss in comparison to other RGCs in a mouse model of pigmentary glaucoma.

Of note, the process of axonal loss in AD and glaucoma are analogous, and there is a preponderance of patients with AD with glaucoma(1305). In glaucoma, loss of VF, with characteristic scotomas tends to precede any loss of VA. Loss of VF is more likely to be related to pRGC functional decline than loss of VA, and this may correspond to the early loss of pRGCs seen in AD(1097). La Morgia et al (2016)(115) found reduced RNFL thickness and worse SE on actigraphy in patients with AD, with reduced pRGC density and abnormal pRGC morphology found in postmortem AD subjects compared to controls. In contrast to the pattern of visual loss in glaucoma, mitochondrial optic neuropathies, such as LHON, are characterised by a more rapid loss of VA, indicating a discrete pathological process(1306).

6.3.9(b) Survival of Photosensitive Retinal Ganglion Cells in Hereditary versus Acquired Optic Neuropathies

It has been theorised that pRGC resistance to injury in mitochondrial optic neuropathies is due to their larger volume, indicating higher mitochondrial reserve and activity in contrast to the smaller calibre RGCs, including midget RGCs which are preferentially lost from the papillomacular bundle in LHON, in addition to parasol and bistratified RGCs in DOA. Protection from cytochrome c-oxidase, PI3K and PACAP may be greater in pRGCs in mitochondrial optic neuropathies(158). In unilateral ischaemic optic neuropathies, there is speculation that dopaminergic modulation of retinal pRGC receptors plays a role in preservation of pupil responses, with adaptive upregulatory processes post unilateral ischaemic insult being the cause of the altered pRGC function observed bilaterally, alongside possible amplification of SCN activity preserving circadian functioning(1307, 1308). Mitochondrial dysfunction is a feature of glaucomatous and toxic optic neuropathies, in which larger RGCs, such as pRGCs are affected more readily, which may be due to their higher metabolic demand, with withering of RGC axons evident in toxic optic neuropathies. The prevalence of glaucoma increases with age, which is associated with reduction in mitochondrial function and density and slower RGC recovery, which could amplify IOP-induced pRGC injury(1309). In cases of trauma to the optic nerve, reduction in pRGC survival may be mediated by dysfunctional expression of the microRNA miR-204, which has a regulatory role in optic nerve function, neurogenesis, neuroprotection, oxidative stress and metabolism. Abnormal expression of miR-204 may induce apoptosis of pRGCs via

suppression of growth-associated proteins, notably GAP-43, which promotes neural plasticity, growth and regeneration, and its inhibition may reduce the likelihood of preserved pRGC function(1310-1312).

6.3.10 Sex and Sleep Wake

In my prospective study, females were more likely to report poor sleep than males and had worse sleep scores than males. Females have reported poorer subjective sleep quality of shorter duration, and longer SL than males(869, 870). This has been confirmed objectively with actigraphy, with increasing age in females also having an effect(872). A meta-analysis has found that insomnia has a female preponderance(871). Females are more likely to have shorter endogenous circadian cycles(873), and to be more sensitive to artificial desynchronisation of circadian rhythms, with higher levels of sleep disturbance than males(875). Later chronotypes are associated with depression in young adult females, which may lead to further sleep disturbance(876). Sex was not comparable between groups in my prospective study, with a significantly higher proportion of females in the control group (72.6%) compared to the OND group (50.8%). As females are more likely to report disturbed sleep, this may have reduced any divergences that might otherwise have been observed in sleep timing in the OND group. In my retrospective study of subjects with autoimmune and demyelinating OND, there was a higher proportion of female participants, which may have contributed to the prevalence of subjective sleep impairment.

6.3.11 Age-Related Changes

In my prospective study, sleep worsened with increasing age across the whole population, and there was a trend for sleep quality to worsen with increasing age in the OND group, although this did not reach significance (p=0.07). There was no significant difference in age (p=0.4), chronotype (p=0.4) or season of completion of questionnaires (p=0.5) between groups. Therefore, age was unlikely to have contributed to group effect in OND versus controls.

In children, adolescents and young adults, increased age has been associated with reduction in sleep duration and shift to a later chronotype(891); conversely in older adults, advancing age has been associated with a longer sleep duration and earlier chronotype(893, 1313, 1314). Chronotype has also been influenced by season in higher latitudes(1313, 1315), although season of questionnaire completion was comparable between subjects with OND and controls in my prospective study. With advancing age, there is degeneration of RGC axons, with depletion of oestrogen associated with premature aging of the optic nerve, which may have implications for circadian regulation in older females(1316).

In animal models, survival of RGCs following excitotoxic stimulus has been found to be greater in adult compared to immature mice(1317). With advancing age, however, animal models of glaucoma and subsequent optic neuropathy have shown increased ganglion cell loss(1318), although this can demonstrate variability(1319).

6.3.12 Summary

In summary, in addition to damage of pRGCs in OND, there is selective preservation of pRGCs in some optic nerve pathologies. This could mean that there is a lesser impact of OND on circadian function than expected. Resistance to injury of pRGCs has been demonstrated in observational and experimental studies(107). This has included sparing of pRGCs in inherited optic neuropathies in humans and in mice with *OPA1* mutations (1034, 1294). pRGCs have exhibited less vulnerability to cell death with induced ocular hypertension in rats(1304), and resistance to the excitotoxic cell death implicated in glaucoma has been found after intravitreal injection of N-methyl-D-aspartic acid in mice, irrespective of genotype or the presence of photoreceptor cells(1296), although findings in human studies of glaucoma have not reflected this(116). pRGCs have shown greater resistance to axonal injury than other RGC types in rats following optic nerve transection(1295), and in optic nerve compression(1320), although DelRosso et al (2014)(468) demonstrated clear evidence of circadian disruption following bilateral optic nerve trauma in a human subject. Non-circadian influences on sleep wake may arise from the presence of OSA, PLM, factors associated with chronic disease and pain, psychiatric comorbidities (which may also

manifest circadian disturbances in some cases) and psychiatric and other medications. The picture in this study is multi-faceted and suggests a variety of circadian and non-circadian influences on sleep in individuals with OND.

6.4 Strengths and Weaknesses of This Study

There are manifold strengths and limitations of this study, which may impact on the validity of my findings. In this section, I will explore these strengths and limitations. I will specifically consider my study design, the questionnaire information, clinical information, and study population (the prospective OND and control groups and my retrospective study population). I will then discuss the missing data in my study and how this could have been mitigated. Finally, I will outline what would be an "Ideal study" for evaluating the impact of OND on sleep quality and timing, based on what I have learned in the process of conducting this study.

6.4.1 Study Design

This was an epidemiological observational cross-sectional study(39). It had the advantage of providing a snapshot of the prevalence of sleep quality and timing in the study population, and allowed measurements of general health, chronotype and emotional, physical and social functioning in addition to screening for RLS and OSA. My study had public health and clinical implications as it assessed sleep function in the OND population. As a point-in-time study, no follow-up data collection was required, so there was no loss of data on re-measurement, which also had a favourable implications for study cost(40), although missing data was present prospectively, and the nature of retrospective data collection means that not all data was complete, as discussed in the following sections.

Although my cross-sectional prospective study allowed data collection from a large number of individuals with OND and control participants, its design limited generalisability due to its short-term nature: Had my study been conducted repeatedly at stipulated time intervals in a longitudinal manner, the outcomes may have been at variance to the current study findings.

According to EBM, establishing a causal relationship between a pathology and its outcome requires high-ranking evidence, such as a RCT. The nature of this study was observational, so associations can be identified, but defining cause and effect is beyond its scope(1321).

6.4.2 Study Recruitment

6.4.2(a) Numbers Recruited versus Missing Data

158 OND participants were recruited in my prospective study, but data sets were only available for 122 participants. Data from 36 participants were insufficient to use in my analysis. Most of the missing data arose from participants who signed informed consent forms but took questionnaire packs home for completion, alongside with a stamped addressed return envelope. This data is likely to have been missing not at random (MNAR)(1322), which may have introduced bias. According to Kearney(1323), reasons for missing data include losing contact with patients in 61% of cases, missed measurements in 25% of cases, patients being too ill to complete the study in 20%, and data not being provided by clinical staff in 20%.

6.4.2(b) Road Map to Mitigate for Missing Data

A patient-centred approach has been found to be essential in achieving a good rate of retention in clinical studies. Clear communication of study objectives with well-designed brochures and patient information leaflets is an important step in recruitment, but also assists in retention of participants. Content could be piloted and reviewed by a patient support group, with easy-to-understand language free from jargon, that is age-appropriate and addresses key concerns a participant may have about safety and their ability to attend study appointments. Recording detailed contact information such as Email addresses, telephone numbers, home address and Email and telephone details of a close friend or relative can ensure that contact can be made with participants and that they can be updated with study progress newsletters which also give details of its benefits, and feel engaged with the process(1324, 1325).

Providing participants with a clear timeline of clinic visits and text message or telephone reminders prior to appointments can help participants know what to expect and feel

involved with the study process(1325). Reducing the participant burden can improve retention, for example by arranging transport to clinical appointments and covering transport and childcare costs, and conducting questionnaires over the telephone or sending them via Email if participants are too unwell or unable to attend clinic appointments(1324, 1326). Questionnaires that are available in large print, or electronic questionnaires where text size, colour and contrast can be adjusted or braille or audio format questionnaires could assist in reducing a bias towards participants who had better vision. An electronic format questionnaire that only submits once data is complete could also reduce bias by increasing the number of complete cases. In addition, shortened versions of questionnaires could be considered as these have a higher response rate(1327, 1328).

Telephone and text message reminders can assist in collection of outstanding data from recruited participants, as can clinician-assisted completion of outstanding questionnaires via telephone or online. Personal touches, such as providing a safe clinic space, hot or cold drinks, snacks or meals and designated parking spaces can also create a welcoming environment that participants are more likely to return to, as can a flexible approach, working around participant needs and schedules(1326).

Research teams which provided a positive environment with a good work ethic and who adapted to participants' needs were found to have high participant retention rates(1326). Developing good relationships with clinicians across active study sites and arranging informative site initiation visits to give clear details of study objectives and the data required, with regular site contact could also improve future study retention and data collection.

6.4.2(c) Considerations for Improving Recruitment

Improved recruitment to clinical trials can be assisted by clinician enthusiasm and communication, as can developing a trusting partnership with patients, showing empathy and adapting information and explanations to meet patient needs. If recruitment is not to plan, evaluation of patient information-seeking behaviour and social activities may be useful to adapt recruitment strategies. Continuous evaluation and modification of methods may assist in recruiting a wider and more diverse study population, and publishing positive and

negative points of strategies employed can assist in refinement of future study protocols(1329, 1330).

Use of electronic media, such as Facebook, Twitter and Google ads as well as advertising on local radio, in newspapers and in community groups and support groups can reach a wider demographic. In minority communities, availability of clinicians who speak patients' first languages and who have minority backgrounds themselves may improve patient confidence and recruitment, as can reassurance regarding anonymity and maintenance of dignity and reduction of patient burden in attending research visits as detailed in the previous section(1326, 1331). Other factors that facilitate patient recruitment include perceived personal benefit, which should be clearly described in any study information, as well as how the study will benefit other patients and scientific progress, as feelings of altruism are often motivators(1330, 1331).

6.4.3 Questionnaire Data

Five validated questionnaires were used, all of which have been described and utilised in peer-reviewed studies, with PSQI findings comparable to those of PSG, and the reliability and validity of the ESS, MEQ, HADS and SF-36 having been discussed in published literature. Additionally, the JMCQ, which has been used in reported studies, but has not been validated(918), allowed me to screen for features of RLS, parasomnias and OSA. Baseline information with regard to age, sex, BMI, medical, psychiatric and social history were collected using an adapted general health questionnaire (GHQ), which allowed comparison of demographics and factors which may have affected sleep including alcohol, caffeine and nicotine intake.

All data obtained in this study were subjective. No objective measurements of sleep-wake such as actigraphy or PSG were obtained, which could have provided stronger evidence of sleep timing and architecture and circadian function(1332), and no longitudinal assays of melatonin were available to give primary information about internal circadian rhythm.

6.4.3(a) The Pittsburgh Sleep Quality Index

The PSQI (see Appendix D) has been found to have high test-retest reliability(1333) with a Cronbach's alpha of 0.83(1334). It has been found to be orthogonal to objective sleep data and more closely related to subjective psychological symptoms(953), although it has also been found to correlate strongly with actigraphy(1335). Correlation of PSQI with objective SL on PSG has been found, however, no association of PSQI and PSG was found in a study of elderly subjects of 80y and over(43, 952). The age range of the OND group was 19-85, with three OND participants aged 80 years and over. The age range of the control sample was 19-91 years, with six control participants aged 80 years and over, which may have affected PSQI outcomes in both groups. The PSQI relies on recall of sleep and daily activities in the past month(43), which may have introduced recall (or rumination) bias into my results(1336). As I was present with study participants to assist completion of questionnaires, obsequiousness bias, or a participant giving information that they think the researcher wants to hear, cannot be ruled out(1336).

6.4.3(b) The Epworth Sleepiness Scale

There is no gold standard measurement for sleep propensity, which is situational, and is represented discordantly by different objective measures. In the MWT, subjects are instructed to sustain wakefulness, whereas in the MSLT, subjects are advised to sleep. In contrast, the ESS (see Appendix D) measures self-report of sleep propensity in multiple settings, and has been shown to have reliable re-test results, but to only correspond to the MSLT on three out of its eight items(1337), although it has been found to have good internal consistency(1338). Thus, the ESS was satisfactory measurement tool for this study, although certain aspects of daytime sleep propensity may not have been captured and may require objective evaluation in future studies.

6.4.3(c) The Hospital Anxiety and Depression Scale

The HADS (see Appendix D) has been found to have acceptable sensitivity and specificity in both major and minor depression(1339). In UK normative data, median HADS anxiety scores are higher in women than in men(1340). The proportion of female participants in the control group was significantly higher than in the OND group in this study, which may have obscured any real-world differences in anxiety scores that may exist between individuals with and without OND once sex is accounted for. A difference in depression score between the OND and control groups was detected using the HADS, which is reflective of the increased rates of depressive states in VI and chronic disease in reported studies(767, 1341).

6.4.3(d) The Morningness-Eveningness Questionnaire

Although the MEQ (see Appendix D) measures diurnal psychological preference, and broadly indicates circadian function, it is not a particularly specific marker of circadian phase, of which DLMO is the gold standard, and with which the MCTQ has a somewhat improved correlation(961). Zavada et al (2005)(959) found that the MEQ had good correlation with the MCTQ and its measurement of sleep timing, but that the MCTQ provided a more thorough analysis of sleep-wake activity. Hence, MEQ data obtained in this study is an approximation of circadian rhythmicity, and more detailed subjective and objective measures would be useful in confirming circadian phase in future studies.

6.4.3(e) The Medical Outcomes Study 36-Item Short Form Survey

The SF-36 (see Appendix D) has been found to have good internal consistency, construct and content validity(1342-1344). However, its normative values vary between and within national populations. For example, normative data for Wales has shown worse QOL domain scores compared to other UK areas, including Oxfordshire, Berkshire and Buckinghamshire(975, 1342, 1345-1347), and UK norms are different to those in Canada(1348) and Queensland, Australia(1343). I recruited OND participants from five UK sites, one of which was in Oxfordshire, one in Buckinghamshire and one in Wales, and

control participants were recruited from all of the active sites for SOMNUS. This may have led to discrepancies between QOL scores influenced by region. Conversely, as a multicentre study, QOL scores obtained in this sample may be more representative of the UK population.

6.4.3(f) The Jupiter Medical Center Questionnaire

The JMCQ(1349) (see Appendix D) is not widely used, and has been created for assessment of sleep parameters in a healthcare, rather than an academic setting. Although it is a useful tool in this study to evaluate OSA and RLS, it has not been validated, and does not have a standard itemised tally(918). It has been used in published studies of sleep wake in age-related cognitive impairment in comparison to actigraphy and sleep diaries, and in AD and brain cancer in comparison to actigraphic and EEG measurement(918, 966). As the data obtained by the JMCQ in this study cannot be compared to normative data, it has limited external validity and its representation of other OND populations cannot be evaluated.

6.4.3(g) The General Health Questionnaire

The GHQ (see Appendix D) was adapted from the PHQ and was used as a screen to collect data on demographic, sociodemographic and health factors (see Appendix D). Extensions to questions regarding medical and medication history, such a history of mental health problems and use of blood pressure medication ("yes/no" answers followed by "please give details") increased the ambiguity of the questionnaire. This meant that responses were likely to be less precise, and information gleaned regarding anxiety, depression and other mental health issues in the sample was less reliable, as was the precise number of participants who used beta-blockers. Open questions about other features of medication history (such as questions 17 and 18) may have yielded less definitive replies concerning psychiatric medications, medications to aid sleep, opiates, and glucocorticoids, so these were more likely to be missed. Closed yes or no questions regarding a history of anxiety, a history of depression and current use of beta-blockers would have generated more specific and reliable feedback(1350). The GHQ asks closed, quantitative questions to determine alcohol, nicotine and caffeine consumption, allowing these components to be included in

statistical analysis of data between the OND and control groups. Self-report of smoking and alcohol status and consumption may correlate poorly with objective toxicology findings(1351-1356), although caffeine intake self-report has been found to be more reliable(1357, 1358). A further flaw of the GHQ is that it is not a validated questionnaire. This reduces the generalisability of the data yielded.

Question 28 of the GHQ asks whether participants have undertaken shift work in the past year. Five participants with OND in my prospective study answered yes, however this question does not clarify whether an individual is currently performing shift work, or when their last episode of shift work was. If several months had elapsed since the last episode of shift work, circadian rhythms could have normalised in this interval. La Morgia et al (2010)(1034) in their study of mitochondrial optic neuropathies excluded shift work in the past month, which may be a more appropriate marker.

15 participants with OND answered yes to question 29 of the GHQ, which asks whether participants have travelled across more than one time zone in the past three months. Travel across one time zone may not have sufficient impact on circadian alignment to be relevant. La Morgia et al (2010)(1034) excluded participants who had travelled over three or more time zones in the past month, which agrees with Inder et al (2016)(1359) who found that travel over three or more time zones led to an impact on mood. Asking whether three time zones had been crossed in the past month may have been more relevant in determining the circadian impact of transmeridian travel.

6.4.4 Clinical Information

In view of the size of the study and participant time, collection of baseline clinical data from medical notes as an adjunct to questionnaire data was reasonable and enabled me to obtain a more complete data set. Constraints existed in the clinical information available, which may have impacted on the clarity, quality and generalisability of my findings. Clinical information was obtained from OND participants' medical records with their informed consent, and included VA, VF (where available), ophthalmological, medical and medication history to supplement questionnaire information.

My retrospective analysis provided more in-depth insights into subjects with NMOSD and demyelinating OND; however due to the nature of retrospective studies, in which the available data has been recorded for a different purpose, missing data that could not be gleaned from EPR, questionnaire front sheets or a review of answers from the GHQ is likely to have introduced bias into my results(1322).

6.4.4(a) Visual Acuity

6.4.4(a)(i) Conversion of Snellen to LogMAR

I collected VA data from OND participants' medical records in LogMAR or Snellen format. Where required, conversion of Snellen VA to LogMAR VA was performed to allow stratification for statistical analysis using a standardised conversion chart (see Appendix F). Inaccuracies of conversion between the two systems exist, particularly when the patient is unable to read an entire line of a Snellen chart(1360), or in conversion to the LogMAR equivalents of low vision and hand movements(1361). In addition, parametric stastistical analyses of Snellen values converted to LogMAR VA may compromise the validity of findings, as fewer Snellen optotypes are used on lines testing lower vision, which leads the data produced having a skewed, rather than normal distribution, which does not change on conversion of Snellen values into LogMAR(161). Use of a LogMAR chart and ETDRS protocol has been found to produce markedly better scores for best-corrected visual acuity (BCVA) than Snellen measurement(1362).

In participants with OND, BVA was compared to PSQI score. One participant with OND had BVA of PL. As per guidelines by Holladay(2004)(1361), the LogMAR equivalent values of CF and HM vision are 2.0 and 3.0 respectively, which then allows for statistical analysis. However, as per Holladay's guidelines, PL vision is not classified as a measurement of acuity, but rather a response to a stimulus, and therefore cannot be analysed numerically. The recommendation is that visions of PL and NPL should be discussed separate to the data analysis. This meant that one patient with poor vision was excluded from the analysis of BVA in the OND group, which narrowed the spread of data as results of their BVA versus PSQI could not be included in correlational analysis.

6.4.4(a)(ii) Best-Corrected Visual Acuity

BCVA measurement can be compromised by assumption that a participant's current glasses or contact lens prescription is accurate or that their unaided vision cannot be improved. In elderly populations, the presence of undercorrected refractive errors has been found to be 26% in Armenia and 38.8% in France, with higher prevalence if individuals require domiciliary visits for sight testing(1363, 1364). This can mean the difference between good visual function and VI, and can lead to loss of two lines on a vision chart or 0.20 LogMAR(1365). Due to its prevalence, undercorrected refractive error is likely to have impacted on SI grading in my retrospective study of subjects with autoimmune and demyelinating OND. Elliott's (2016)(161) recommendations for ensuring that VA in clinical studies is genuinely best-corrected include performing subjective refraction with details of how this was conducted and references; recording the specifics of the vision test including chart type (LogMAR) and luminance, test distance; and consistency in scoring and termination of the test (patient motivation, and number of letters missed on a line), in addition to details of the clinicians scoring the test and their experience.

6.4.4(b) Visual Fields

There was limited VF data available in OND participants' medical notes. HVF mean deviation of the better eye was collected from 47 (37.9%) OND participants in my prospective study, and showed an inverse trend with PSQI score, but this was not significant. In my retrospective study of autoimmune and demyelinating OND, HVF data was available in 28 out of 50 participants (56%), with no obvious correspondence between severity of VFD and sleep quality. In my retrospective study of autoimmune and demyelinating OND, HVF data was missing in 22 participants, one of whom had GVF, two had SI and two had SSI. The remaining 17 participants had vision better than CVI, and no clear reason for the absence of HVF testing was detailed on data front sheets or EPR. It was not apparent whether HVF data were missing at random (MAR) or missing not at random (MNAR), as a complete case analysis with HVF for each participant was not possible(1366). If data was MNAR, it is likely to have led to bias in my prospective and retrospective studies, although omitting every case with incomplete data in this study would have led to loss of statistical power and bias due to

small sample size(1322). Sensitivity analyses that can be performed for missing data include analysing complete cases only and then comparing these to the data set, and also imputation of missing data with repeat statistical analysis(1367).

VF data was the most accurate assessment of pRGC function that was clinically available in my study as ERG is time-consuming with requires dark adaptation, and expertise in setting up, carrying out and analysing the test, and is therefore not a routine assessment in the majority of individuals with OND(1368). VF data is a more acceptable proxy measurement of pRGC function than VA(1097, 1369). However, due to the limited numbers of OND participants with VF data in their medical notes, the spread of results may have been reduced, and it may not have been representative of the OND sample as a whole, or the wider population with OND.

6.4.4(c) Optical Coherence Tomography and Electrophysiology

Neither OCT nor electrophysiological testing data were routinely acquired from OND participants recruited to this study. OCT of RNFL thickness and analysis of the GCL can provide an accurate analysis of RGC concentration and RGC loss. Function of RGCs can be assessed using electrophysiological measures such as VEPs, pattern ERG, photopic negative responses and mfERG(1370-1373). Electrophysiological testing is useful in patients with no conscious visual perception as it can confirm true blindness and lack of RGC function(1374). As stated in the previous section, electrophysiological testing is time-consuming, and requires staff with expertise, so it was not pragmatic to test OND participants in this study(1368). However, this data would be useful to collect in future studies of sleep wake in OND.

6.4.4(d) Age at Visual Loss and Duration of Visual Loss

The age at which participants with OND developed VI was not included in my prospective study, and neither was the time since loss of vision. In my retrospective study of autoimmune and demyelinating OND, there was no observable correspondence between time since diagnosis and sleep quality on descriptive analysis, although the sample size was small. Lockley et al (1997)(1036) evaluated time since onset of VI in their study of melatonin

rhythms and visual loss in blind subjects. In this study, no effect of duration of blindness on circadian rhythmicity was observed; however the circadian timing system has been found to develop prenatally, with early photic exposure being important for the foundation of entrained circadian rest-activity rhythms(1375). In individuals who are blind from an early age, this could potentially impact on their circadian development, and may have been useful information to have collected.

6.4.4(e) Assessment of Cataract

The presence of cataract was not assessed in my prospective study, and information gathered retrospectively regarding the presence of cataract was sparse. It is likely that cataract was present in my prospective and retrospective study populations in larger numbers than that collected in retrospectively, as use of systemic glucocorticoids was prevalent in participants. Glucocorticoids can predispose to development of cataract, particularly in doses of >10mg/day for long periods, and in individuals under 50 years(1376, 1377). As increased lens opacity reduces light transmittance, this could affect circadian function and sleep quality(1378), and reduced visual function could impact on QOL and mood(1379), which in turn may affect sleep quality and timing.

6.4.4(f) Medical History and Medication History

Medical and medication history from OND participants' notes was beneficial in clarifying some participants' drug histories as recorded by the GHQ, particularly if they could not remember the exact names of their medical conditions or prescribed medications. However, medical and medication history was not always easy to clarify if the medical notes were extensive. There was no information with regard to recreational drug use obtained by the GHQ, and the accuracy of self-reported recreational drug use can be questionable(1380-1382), although their use has been described candidly in patients with chronic disease and pain(1383-1385), which is relevant to my study population.

6.4.5 Study Population

This study is the largest study of sleep quality in individuals with OND published to date, with a total of 158 individuals recruited and viable questionnaire data collected from 122 participants. A notable proportion of studies of OND and sleep in my systematic literature review literature were small in size, in contrast to the studies of glaucoma, which may be due to study design and to their relative prevalence(1386, 1387). I recruited control participants which formed part of the bank of data from 302 normally sighted individuals used for comparisons for all arms of the SOMUS study. This contrasts with several of the studies in my systematic review, in which no control group was present. There were, however, several shortcomings in my study population, recruitment of participants, and in the questionnaire completion process. In this section I will discuss strengths and weaknesses of the OND and control groups.

6.4.5(a) Participants with OND

My aim was to recruit a large, representative sample of participants with OND, and my sample size was sufficient for 80% power. However, the number of OND participants with NMOSD in this study was high compared to other OND disorders, although this does not reflect the prevalence of OND pathologies in the real world(1388). Oxford is a specialist referral centre for NMOSD, which facilitated recruitment of participants with this condition. Eight participants with ON due to MS were recruited to my prospective study, in comparison to 33 participants with NMOSD, although the ratio of MS:NMOSD in the general population is approximately 43:1(1389). As NMOSD is a chronic systemic condition, and is frequently associated with pain and altered mood(713, 1079), this may have had a bearing on the results of my study and its representativeness. The control group in my prospective study was large, and control subjects had independent sleep parameters to those in the OND group as spouses and carers were excluded, which improves its generalisability and external validity.

Since NMOSD was over-represented in my sample, I conducted a retrospective study of the participants with NMOSD and demyelinating optic neuropathies who were recruited from Oxford, and gathered additional information from EPR, raw data front sheets, and reviewed GHQ questionnaire data (Appendix D). This allowed a focused study of 34 participants with NMOSD, 10 with MS, two with ADEM and four with CIS. This sample was too small for statistical analysis, so I conducted a descriptive analysis of the data, with reference to time since diagnosis, sphincter dysfunction, pain and fatigue, medication history and mood, the presence of cataract, inpatient vs outpatient status, VA and VF.

A high proportion of subjects with NMOSD and demyelinating conditions were found to have poor sleep in the presence of sphincter dysfunction, pain, depression, and glucocorticoid use. There did not seem to be a clear pattern between loss of visual function or disease duration and sleep quality, although the sample size was small, so results may not be generalisable.

Minimisation of bias is the aim of the most rigorously structured studies in the evidence hierarchy(1321). Neyman bias, or incidence-prevalence bias may have existed in participants with OND who agreed to participate in my study. As these participants were clinic attendees at multiple UK sites, it would be necessary for their condition to be sufficiently severe or requiring ongoing monitoring or management to be selected. Similarly, those with OND as a result of severe pathology which resulted in the patient either being too unwell to attend clinic or to have died as a result of their pathology would not have been included in the OND sample(1336, 1390, 1391). Ascertainment bias within the OND sample is also likely, as all of the OND participants were attending a healthcare setting, which may have been an inappropriate definition of the whole population of individuals with OND, hence my results may not be representative or generalisable(1336, 1392).

Due to the fact that OND are less prevalent than ocular conditions such as age-related macular degeneration, diabetic retinopathy and glaucoma, which formed other arms of the SOMNUS study(1076, 1393, 1394), it was expedient to include participants with OND who had positive psychiatric and OSA histories, who were taking glucocorticoids, beta-blockers, psychiatric medication and medications to improve sleep, and who had travelled across time zones and undertaken shift work. However, this reduced comparability of the OND group

with the control group, as these features had been excluded from the control group. This could have led to increased discrepancy between the two groups in analysis of mood; it could also have erroneously reduced discrepancies in sleep quality if sleeping medications were being taken in the OND group, or conversely have worsened the discrepancy in sleep scores due to the presence of psychiatric diagnoses and other medications that affected sleep quality, timing, and architecture. Glucocorticoid therapy and analgesics in the OND group had the potential to improve physical functioning and pain scores but may also have led to sleep alteration. Therefore, it was necessary to conduct a sensitivity analysis to ascertain whether baseline differences between the OND and control populations had led to differences in study outcomes(1395). My sensitivity analysis for glucocorticoids, shift work, transmeridian travel and OSA was robust and did not show any changes in significance.

6.4.5(b) Control Participants

I recruited control participants via their attendance at ophthalmology clinics with relatives or friends. Additionally, ophthalmology staff and study volunteers who responded to advertisement by the hospital trust were recruited as controls if they met the inclusion criteria. Questionnaire information collected from control participants formed a bank of data which could be compared with the groups of ocular pathology from the five arms of the SOMNUS study. Use of unmatched controls was appropriate for this size of study and I adjusted the analysis of my prospective study for age and sex(1077).

Control participants were normally sighted, did not have a history of psychiatric illness or use psychiatric medication; had not engaged in shift work in the past year or transmeridian travel for three months prior to data collection, and were not partners of patients with ocular pathology. However, there may have been some similarities between control participants and those with OND which were unaccounted for in the selection process, particularly those who had attended clinic with OND patients. This may have introduced contamination bias(1336), which may have reduced the divergence between OND and control groups, leading to differences between groups not existing or not reaching the level

of significance. To address this, a larger sample of both OND and control participants would be needed(1396).

Significant demographic differences were present between OND and control groups. The percentage of female participants was 72.6% in the control group, in comparison to 50.8% in the OND group, which may have skewed the results. As discussed earlier in this chapter, differences in self-report of sleep wake varies with sex. Mean BMI was significantly lower in the control group (26.5kg/m^2) compared to the OND group (28.3kg/m^2). Higher BMI is associated with increased prevalence of sleep disturbances(1397), which may have augmented the divergence of reported sleep quality between the groups.

6.4.5(c) Retrospective Study Population

In general, retrospective studies can provide useful information when examining diseases and exposures that are less prevalent, or in the formation of a hypothesis that can be more thoroughly tested in a well-structured prospective study later on. However, the validity of retrospective studies is threatened by numerous forms of known and unknown bias(1398, 1399), with notable limitations of my retrospective study population described below.

Baseline characteristics of the of participants with OND recruited from Oxford University Hospitals may have compromised validity of my sensitivity analysis, as participants with OND recruited to my prospective study from sites other than Oxford could not be included in my retrospective data collection, and data from 10 additional participants from Oxford University Hospital who had consented to recruitment in SOMNUS, but whose questionnaire or diagnosis data was not available at the time of prospective data collection were included. These were added to the sample of 100 participants with OND whose data was analysed in the prospective component (and who formed the majority of the overall prospective OND study population). Subject selection bias may have been present, as the additional participants with more recently available data and OND population recruited from Oxford may have possessed different characteristics to the prospective group. This may also have

impacted on my descriptive analysis of the subset of participants with autoimmune and demyelinating optic neuropathies.

Retrospective data collected from EPR may have been affected by a lack of homogeneity, as different clinicians recorded patient information at different times. Instrumentation is also likely to have affected my findings, as clinical information available on EPR was not designed for the purpose of SOMNUS data collection, and invariably, some features of medical history relevant to my study will have been missed. Additionally, the subset of participants with autoimmune and demyelinating OND was a single-group sample, and the absence of a control group may also have led to bias.

In summary, over-generalisation of the results of the retrospective component of my study should be avoided, due to several sources of bias present in the study population and the process of data collection(1398, 1399).

6.4.6 The "Ideal" Study Design: Lessons Learned

Clearly, although it provides an insight into sleep quality and timing in OND, with additional evaluation of general health, mood, QOL and lifestyle, the study that I conducted was far from perfect, and there are many elements of its design that could be improved, particularly if practicalities were not an issue, and time and resources were unlimited. In this section I describe the "ideal" prospective cross-sectional questionnaire-based study to evaluate sleep quality and timing in OND with the aim of gleaning minimally biased data that is representative of the population OND with a study design that can be replicated and form a component of a meta-analysis. This is informed by my background and systematic review chapters, and the practical experience I gained from conducting my observational study.

6.4.6(a) Study Subjects

I would use a community-based recruitment strategy across multiple clinical sites to engage a representative sample of participants with OND and unrelated control participants with no

ocular disease and good vision using an encryption and deidentification algorithm to ensure anonymity of patient records in the raw data as per Zimmerman et al (2018)(1400). This study would need to be sufficiently large for subtypes of OND to be evaluated due to the differing pathophysiologies of RGC injury. I would divide OND participants into subgroups, including those with HON, vascular OND, traumatic OND, compressive OND, autoimmune and demyelinating OND. I would age- and sex-match control participants and conduct a prospective power analysis for the whole OND group and subgroups(1401).

I would invite potential study participants for an ophthalmological assessment at a clinical centre and to complete a set of questionnaires on subjective sleep quality, sleep timing, sleep disorders, mood and QOL. I would provide a standardised patient information sheet and provide online, Email, telephone and face-to-face contact details should potential participants wish to make any enquiries. I would ensure that informed written consent was obtained from participants taking part in the study and make them aware that they were free to withdraw their clinical information at any time with full removal of their raw data and details from study databases.

6.4.6(a)(i) Exclusion Criteria

I would apply the same exclusion criteria to subjects with OND and to control subjects, which would include visually significant cataract (with the presence and type of cataract assessed and graded using slit lamp biomicroscopy and with duplicate photograph gradings as per the Beaver Dam Eye Study(1402)) and any history of posterior pole pathology; transmeridian travel>3 times zones in the past month as this threshold has been shown to impact on mood(1359), and as per La Morgia et al (2010)(1034); shift work in the past three months as per Chin et al (2020)(1057); use of hypnotic or sedative agents or agents used to assist sleep, such as benzodiazepines, Z drugs, antihistamines and melatonin or its analogues. As systemic disease is often associated with OND, and I would aim for my recruitment to be representative of the spectrum of OND disorders in the population I would not exclude corticosteroid, antidepressant or analgesic medication from either the OND group or controls but would statistically adjust for their inclusion and conduct sensitivity analyses.

6.4.6(b) Evaluation of Optic Nerve Function

6.4.6(b)(i) Visual Acuity, Chromatic Vision and Contrast Sensitivity

I would perform the following ophthalmological examinations in both OND participants and controls: I would check BCVA with subjective refraction and details of methods and references provided, as per Elliott (2016)(161). I would test vision using a standardised protocol with an ETDRS LogMAR chart at a set distance and luminance and scoring/termination rule with details and experience of examining clinicians recorded(161). I would use an Ishihara test with standardised plates and luminance to evaluate chromatic vision, as it has good sensitivity and specificity in detecting defects of red-green colour vision which is appropriate for OND, is simple to use, and is the most widely used chromatic vision assessment in the published literature(1403). I would measure contrast sensitivity using the automated Freiburg visual acuity and contrast test (FrACT) at a standardised luminance and distance which is a psychophysical sine wave contrast test using a standardised protocol and has good correlation with the Pelli-Robson test(1404, 1405).

6.4.6(b)(ii) Visual Fields

I would conduct 30-2 HVF using a Swedish interactive threshold algorithm and standardised protocol (including background illumination and target size) to assess VF, as automated static perimetry is the gold standard for visual field examination(1406). The 30-2 programme tests the central 30 degrees of the VF and includes a greater sample of peripheral stimulus locations (total 76 points per eye, including 22 additional peripheral locations) compared to the 24-2 programme (total 54 points per eye). 30-2 HVF is the recommended static VF programme in the assessment of neurological VF, as it has been found to be more sensitive in detecting VF loss in neuro-ophthalmological conditions(1407). Moreover, the 30-2 programme has good agreement with Goldmann kinetic perimetry, which is also recommended in the neuro-ophthalmology setting(151) and has the advantage of providing numerical values for statistical analysis(1408).

6.4.6(b)(iii) Pupillary Light Reflexes, Fundal Examination and Electrophysiology

I would assess chromatic PLR using a computerised pupillary light reflex device, such as the RAPiDo, which has been found to have good sensitivity and specificity, using a standardised protocol(1409, 1410). I would perform a dilated fundal examination to examine optic disc diameter, cup-to-disc ratio and disc appearance, and to rule out any other posterior pole pathology, with details of persons performing the clinical examination and their experience. I would also perform spectral domain OCT of the peripapillary RNFL, optic nerve head volume, peripapillary retinal pigment epithelium and basement membrane, macular ganglion cell complex and RNFL and OCT angiography as per Malhotra et al (2020)(377).

I would conduct electrophysiology including flash and pattern-reversal VEP, PERG, photopic negative responses, full-field flash ERG and mfERG as per Marmoy and Vishwanathan (2021)(443) using a standardised protocol.

6.4.6(c) Outcome Measures for Sleep Quality, General Health, Mood and QOL

I would collect questionnaire data from study participants using a standardised protocol. I would provide this on computerised tablets, with adjustable size text and contrast and an audio option, using a programme that automatically saved questionnaire details. I would ensure that clinicians were available to answer queries or to fill in the tablet on a participant's behalf in the case of VI or other difficulties. Self-administered questionnaires have been found to be reliable and can elicit more information of a more sensitive nature compared to face-to-face consultations(1411, 1412). I would therefore record whether questionnaires were self-administered, or whether assistance was required for completion so this could be adjusted for on data analysis if necessary.

I would collect subjective sleep quality, sleep timing, sleep disorders, general health, mood and QOL data using the following outcome measures:

6.4.6(c)(i) Subjective Sleep Quality

As the PSQI is the most commonly used measure of subjective sleep in clinical and research settings, and is valid and reliable, I would continue to use this to assess subjective sleep quality(951).

6.4.6(c)(ii) Subjective Sleep Timing

The ESS is a widely used, validated measure of daytime sleep propensity, which I would continue to use in my ideal study(919). To evaluate chronotype, I would use the MCTQ, as this is comparable to the MEQ in evaluation of chronotype, but also assesses the impact of social jetlag(958).

6.4.6(c)(iii) Screen for Sleep Disorders

I would use the SDQ to screen for OSA, PLM and narcolepsy, as it is a validated tool(921), and has been more widely used in published literature than the JMCQ.

6.4.6(c)(iv) General health

I would use a published health questionnaire so that my methods would be repeatable. The Lifestyle and Clinical Survey assesses general health, medication history, social history and cardiovascular risk, and would collect comprehensive general health data(1413).

6.4.6(c)(v) Mood

I would continue to use the HADS for assessment of mood, as this is a validated and widely used screen for anxiety and depression(50).

6.4.6(c)(vi) Quality of Life

I would assess HRQOL using the SF-36, as this has high consistency and construct validity in VI(47, 973). I would asses VRQOL using the NEI-VFQ-25 with its NOS, which has been validated for assessment QOL in neuro-ophthalmic disorders(932). I would also assess SRQOL using the FOSQ, which has been found to be valid and reliable(923, 989).

6.4.6(d) Objective Evaluation

Ideally, for a comprehensive evaluation of sleep wake, objective outcome measures, including PSG, which is the gold standard for sleep evaluation, and can confirm the presence of OSA, RLS and parasomnias would be used(1414). In addition, sleep diaries, actigraphy,

melatonin rhythm and clock genes could be used in analysis of sleep timing and circadian function.

6.4.6(e) Statistical Analysis

I would seek advice from a team statistician to ensure that the most appropriate model was used for analysis of my data, for example, a generalised linear regression model(1415), and ensure that adjustment for confounders was made(1064). I would plan a sensitivity analysis to account for any missing data, outliers, clustering, distributional assumptions or baseline imbalance(1367).

6.5 Implications for Practice and Policy

My fourth study objective was to discuss the relevance of my findings to practice and policy regarding holistic management of patients with OND, taking into consideration patient experience and engagement with healthcare, their sleep, general and psychological health and lifestyle. In the next sections, I will address clinical practice considerations, in addition to sleep hygiene recommendations that could form a guideline to promote healthy sleep in patients with OND.

6.5.1 Sleep, General Health, Mood and QOL

As the participants with OND in my study were more likely to have poor sleep quality, worse SE and daytime dysfunction, and increased SL, sleep duration and use of sleeping medications, it is likely that individuals with OND are more likely to have sleep disturbance than the general population and this should be evaluated in clinical settings. This may also impact on mood and QOL, which should also be addressed.

6.5.1(a) Evaluation of Sleep in the Clinical Setting

Patient with OND can be asked about sleep quality, duration and timing during consultations or other interactions with clinicians. Simple outcome measures, such as the PSQI, which is

widely used, valid, reliable and easy to complete either as a self-assessment or with a clinician could be used routinely to evaluate a patient's sleep in the past month(43, 951).

6.5.1(a)(i) Patient-Reported Outcome Measures

Involving the patient with their own health management and gaining their perspective on challenges faced in everyday life is important to nurturing good patient-clinician partnerships, and use of patient-reported outcome measures (PROMs) may assist with this. PROMs have been found to improve patient engagement and may assist in giving patients permission to raise difficult issues and self-reflect on the impact of disease or other lifestyle factors on their wellbeing. They can help clinicians to raise relevant topics in a discussion, particularly those which may not be clinically obvious but may have an impact on QOL, and to then put measures in place to address these issues(1416). PROMs can also improve overall patient satisfaction with their care(1417).

Use of a shortened 10-Item version of the FOSQ, which is a patient-reported outcome measure may be a practical assessment of SRQOL in the clinical setting, and it has been found to be responsive and robust in its assessment of the impact of excessive daytime sleepiness on QOL(1418).

6.5.1(b) Calculation and Monitoring of BMI

BMI was found to be associated with worse sleep quality and mean BMI was higher in OND than in controls in my prospective study. In my retrospective study, mean BMI was higher than in the OND group in my prospective study. This implies that taking weight and height measurements and calculating BMI may be a useful baseline in subjects with OND. In patients with higher than recommended BMI, a screen for medical causes of raised BMI such as thyroid function can be carried out. Strategies can be implemented to assist with weight loss, for example simple advice, internet programmes and self-help books, involvement of a dietician, a physical exercise plan with a certified personal trainer, or engagement with a specialist clinical team(1419). Weight loss can improve sleep quality, and is particularly effective in reducing sleep fragmentation related to OSA(1420). Improving nutritional behaviours to reduce BMI can also help to improve sleep quality(1421). BMI could be monitored at subsequent visits, and sleep and QOL measures re-evaluated.

6.5.1(c) Risk Factors for OSA

A screen such as the SDQ could be used clinically to evaluate risks of OSA, which is suitable for triage in the clinical setting and has been found to have good validity, sensitivity and specificity(921, 1422). Risk factors for OSA include high BMI, smoking and high alcohol intake, and although it can affect children and adolescents, risk is higher aged over 35 years. OSA is associated with increased risk of hypertension, diabetes, stroke and cardiovascular disease. Assessment of blood pressure, serum lipids, HbA1c and asking about smoking and alcohol history may help to identify modifiable risk factors and develop strategies to reduce OSA risk, such as smoking cessation programmes, schemes for reducing alcohol intake and referral to primary care for management of hypertension and diabetes(1423).

6.5.1(d) Risk Factors for RLS

The SDQ can also be used as a screen for RLS and PLM(921). Factors that may contribute to the presence of RLS include iron deficiency, CNS dopamine imbalances and uraemia. Testing serum ferritin and kidney function may direct management. Aggravating factors include antidepressant, neuroleptic and dopamine-blocking medications in addition to smoking, caffeine and alcohol. Conservative management may entail techniques to lower anxiety before bedtime, keeping to a regular sleep routine, moderate exercise, and leg massage and warm baths, while medical management may include use of dopamine agonists, iron therapy with supplementary vitamin C, and alpha-2-delta calcium channel ligands such as gabapentin(1424, 1425).

6.5.1(e) Mood

Depression was found to be associated with poor sleep quality in OND in my prospective study, and a high proportion of subjects with depression had poor sleep quality in my retrospective study. Depression in chronic neurological disease may be a consequence of neurocognitive changes that are part of the disease process, or secondary to the effects of the disease on physical, emotional and social functioning(622). The HADS measurement tool is a simple and useful screen for the presence of depression and anxiety in the clinical setting and could be used to quantify depression anxiety in OND, particularly in the context

of chronic neurological disease(50). A thorough medical, medication, psychiatric and social history is required for identifying organic and drug-related factors which may give rise to depression and assessment of suicide risk. Identification and management of depressive symptoms may assist in improving sleep quality, and non-pharmacological management such as cognitive behavioural therapy and interpersonal therapy may be appropriate first lines. Pharmacological management may include SSRIS, SNRIs or TCAs(1426).

6.5.1(f) Health-Related Quality of Life

All SF-36 QOL scores were worse in OND in my prospective study, with the exception of emotional wellbeing, while in my retrospective analysis of autoimmune and demyelinating OND, a high proportion of subjects with sphincter dysfunction, fatigue and pain had poor sleep.

PROMS that evaluate the emotional, social, physical and psychological impact of chronic global neurological disease include the MS-QOL-54, which assesses HRQOL including fatigue and sphincter dysfunction(1427), and the Neuro-QOL, which addresses fatigue, sphincter dysfunction and pain(1428), both of which could be used in the clinical setting.

6.5.1(f)(i) Sphincter Dysfunction

Faecal incontinence can lead to anxiety, social isolation and impaired QOL(726). Any concerning signs such as blood in the stools should be investigated appropriately. Typical management of constipation due to neurogenic bowel problems includes methods to normalise stool consistency in the case of constipation, including laxatives, bulking agents, osmotic agents and stimulant laxatives, with some benefit shown from abdominal massage(726). Faecal incontinence may be improved by sacral neuromodulation, or posterior tibial nerve or spinal cord stimulation(1429).

Urinary retention or incontinence can impact on activities of daily living, travel plans, the need to change clothing and fatigue(1429). Urinary retention is most frequently treated with clean intermittent self-catheterisation(622), and urinary incontinence may be managed by planning fluid intake and toilet visits, bladder retraining, pelvic floor exercises,

anticholinergic medications and botulinum toxin injections to the detrusor muscle(622, 1429).

6.5.1(f)(ii) Pain

Neuropathic pain is highly prevalent in NMOSD and common in MS, and can impact on sleep(810). Treatment includes TCAs, SNRIs, alpha-2-delta calcium channel ligands, antispasmodics, antiepileptics and opiates such as tramadol. Management of pain is likely to lead to improved sleep quality and SWS(810, 1142).

6.5.1(f)(iii) Fatigue

Fatigue in chronic neurological disease can arise as a result of the disease process itself, or secondary to antispasmodic and analgesic medication, which it may be possible to titrate down to reduce its morbidity. Other means of managing fatigue include light exercise, progressive muscle relaxation techniques, hydrotherapy and stimulant medications such as modafinil(622, 1429, 1430).

6.5.1(g) Medication History

Taking a thorough medication history including psychiatric medications, glucocorticoids, opioids, NSAIDs and other analgesics, beta-blockers and the use of recreational drugs should be taken for patients with OND. In my study, there was a high prevalence of glucocorticoid use, particularly in NMOSD. These are known to affect sleep quality, and in view of other health risks of sustained use, including metabolic syndrome, patients should be transferred to steroid-sparing agents as soon as practicable after an acute episode(622, 1431).

6.5.2 Ophthalmological Assessment

In addition to a thorough ophthalmological, medical and social history, evaluation of VRQOL using the NEI-VFQ-25 and NOS(932) may appropriate to gain an understanding of patient experience of the impact of VI on their daily life. This could be used in parallel with SRQOL

outcome measures to evaluate whether there is any correspondence between the impact of VI and sleep.

In addition to a standard clinical evaluation of optic nerve function, a qualitative assessment of pRGC damage in OND could be undertaken using PLR, PERG, VEP, photopic negative responses and mfERG. Spectral domain OCT of peripapillary RNFL, optic nerve volume, retinal pigment epithelium and basement membrane, macular RNFL and ganglion cell complex and OCT angiography could provide a quantitative assessment of RGC injury(377). These may be a relevant tool at baseline and for disease monitoring(1371, 1373, 1432).

6.5.3 Objective Sleep Assessment Genetic Analysis

In patients with clear evidence of pRGC damage and desynchronised sleep wake, it may be relevant to arrange objective analysis of sleep using sleep diaries, actigraphy, melatonin assessment and PSG in a sleep laboratory(1433). Analysis of clock genes and for known genetic associations of DPSD and APSD may also be indicated in patients with clear evidence of SCRD(942, 1016, 1020), as this may help direct management of circadian sleep dysfunction, for example with melatonin supplementation or phototherapy(181).

6.5.4 Sleep Hygiene

Sleep hygiene was first described by Hauri in 1977 as a practical means of promoting somnolence in individuals with difficulty initiating and maintaining sleep(1434). Use of zeitgebers such as regular exercise and a regular bedtime and rising time can assist in regulating sleep patterns. Short daytime naps have been found to be beneficial if they do not interfere with habitual bedtimes(547, 736). Avoidance of alcohol, caffeine and tobacco products is also advised(1435). A light snack or milk products and a hot bath before bedtime can improve sleep onset, as can avoidance of use of the bedroom for working or watching television and extremes of room temperature(1436). Scheduling an evening “worry time”(1437), in which a person sets time aside to write down concerns and consider resolutions prior to bedtime can offset waking at night with anxious thoughts. Ensuring the

absence of clocks in the bedroom and relaxation and meditation techniques have been found to be helpful in creating an environment to improve subjective sleepiness and sleep quality(1437). These interventions could be suggested to individuals with OND who are experiencing disturbed sleep as a means of initial management and could serve as a guideline for promoting healthy sleep.

6.6 Implications for Research

In this section, I briefly mention future directions of research relating to clock genes. I explore published research in relation to melatonin, phototherapy and other external zeitgebers and their impact on circadian timing and ocular conditions. I also discuss their use in systemic, psychiatric and neurodegenerative conditions, as OND can co-exist with these. I discuss gaps in the existing research and the need for greater knowledge in these areas so that therapy can be delivered safely and effectively.

6.6.1 Clock Genes

One notable feature of my review of existing literature is that no published studies of clock genes (as described in Section 2.15.5) in relation to OND and circadian rhythms exist at this point in time (one out of the 43 studies in my systematic review conducted clock genotyping in subjects with glaucoma), although they have been used in other analyses of sleep wake in humans(1438). This may be a direction for future research in OND.

6.6.2 Melatonin and Sleep Wake

Melatonin is a marker of biological night that is universally secreted in living organisms and is produced primarily by the pineal gland in mammals. It is both highly water and lipid soluble and is derived from serotonin via the actions of serotonin-N-acetyltransferase (NAT) and hydroxindole-O-methyltransferase (HIOMT). Serotonin itself is derived from tryptophan, the availability of which can impact on production of both serotonin and melatonin.

Tryptophan levels are influenced by factors such as folate production and vitamin B6(1439). Melatonin has been found to have an extensive range of effects. Enhancement of the immune response by melatonin has been observed via interactions at retinoid orphan receptors and retinoid Z-receptors, and immune effects include augmented antibody responses, T cell cytotoxicity, helper T cell activity and IL-2 generation; elevated gamma-interferon (IFN-γ) secretion and natural killer cell activity(1440, 1441). The mediation of melatonin by MT1, MT2 and GPR50 receptors influences seasonal variations in sleep wake in addition to circadian and endocrine functions, and it has antioxidant properties. Through its action on M3 receptors and intracellular interaction with calmodulin, melatonin assists in detoxification and modulation of enzyme activity(1439, 1442, 1443). Melatonin acts as a scavenger of free radicals and has shown protection against alcohol, drug and heavy metal toxicity, ultraviolet and ionising radiation and ischaemia independent of its action on target receptors(1441, 1444). It has also displayed anti-carcinogenic and anti-neurodegenerative characteristics(1445). Melatonin is mostly (90%) metabolised by the liver; a small amount is secreted unchanged in the kidneys and its urinary metabolite aMT6s corresponds to serum melatonin levels. 3-hydroxymelatonin is also excreted in the urine(1439). Metabolites of melatonin include cyclic-3-hydroxymelatonin (c30HM), N1-acetyl-N2-formyl-5-methokynauriamine (AFMK) and N1-acetyl-5-methoxykynauramine (AMK), which also have roles in the scavenging of free radicals(1441).

6.6.2(a) Exogenous Melatonin

Exogenous melatonin therapy has been used to improve circadian alignment in individuals with circadian dysfunction due to shift work, jet lag and a range of conditions in which sleep disturbance is a feature, including in ocular conditions and blindness(1443). In transmeridian flights of five or more time zones, melatonin of dose 0.5-5mg has been found to improve sleep quality and timing when taken soon before the desired new sleep time, although slow release preparations were found to be less effective(1446). Other zeitgebers - mealtimes, social events and exercise - have been found to assist in circadian adjustment(1447). 1.8mg sustained release melatonin taken 30mins prior to daytime sleep in simulated night work was found to increase sleep duration and reduce WASO, although endogenous entrained circadian rhythms which were aligned to day and night did not alter(1448). Similarly, in a

real-world study of shift workers, 3mg melatonin taken 30 minutes before usual bedtimes at night for 2 weeks led to improved SE and decreased SL(1449). In adults with primary insomnia, melatonin therapy was found to be effective and safe in improving sleep architecture and increasing TST (1450), and melatonin analogues have been found to be effective in the treatment of patients with depression(1451) and in other psychiatric and neurodegenerative conditions(1452, 1453). I will consider the impact of melatonin in ocular, systemic, psychiatric and neurodegenerative conditions, as this is relevant to future directions for research in the OND population.

6.6.2(b) Melatonin in Ocular Conditions

Ocular conditions associated with oxidative stress have been shown to benefit from melatonin therapy: reduction of cataract formation, dampening photoreceptor damage in macular degeneration and reduction apoptosis of photoreceptors in retinitis pigmentosa have been reported(1454). In an experimental model of ON, preservation of blue light PLR and circadian rest-activity has been described with administration of melatonin(1455). In a second model of ON, melatonin was found to have a neuroprotective effect, reversing PLR and VEP deficiencies(1456). In an animal study of oxidative stress induced by ischaemia/reperfusion injury, melatonin was found to prevent mitochondrial apoptosis through induction of *OPA1*. Deletion of *OPA1* eradicated the antioxidant effects of melatonin(1457).

OPA1 is found in mitochondrial membranes and is mutated in DOA. Defective mitochondrial phosphorylation is known to be present in DOA, and oxidative stress has also been implicated in the pathophysiology of RGC loss in LHON; similarity of mitochondrial processes in both conditions is thought to lead to a shared pathway of visual loss(1458-1460).

In Zotter et al's (2001)(1461) case report of a child with ONG and learning disabilities with a severely disrupted sleep pattern, 6mg melatonin administered at 8pm improved TST and sleep timing. In a study of individuals with no conscious visual perception and FR circadian rhythms, Lockley et al (2000)(1462) found that four out of seven subjects treated with 5mg melatonin at 21.00h subsequently displayed circadian entrainment. Hack et al (2003)(1463) reported that administration of 0.5mg melatonin at 21.00h subjectively improved sleep in

nine out of 10 subjects and entrained circadian phase in 7 out of 10 subjects, however, these effects did not continue following cessation of treatment. Sack et al (2000)(1464) studied seven visually blind subjects with FR circadian rhythms. Six out of the seven subjects were found to have circadian entrainment when taking 10mg melatonin one hour prior to their preferred bedtime. A step-down protocol was used to gradually reduced melatonin dose prior to its cessation. Some subjects continued in an entrained state for several weeks prior to reverting to their endogenous circadian period.

6.6.2(c) Melatonin in Systemic Conditions

Use of melatonin therapy in MS has been found to improve psychological wellbeing and QOL(1465). Melatonin levels have been reported to negatively correlate with relapses in MS(1466), and dysregulation of melatonin has been implicated in its pathogenesis(1467), particularly in view of its inflammatory nature and the trends in seasonality and latitude that it displays(1468).

In a mouse model of NMOSD, abnormal expression of the clock genes *PER1* and *PER2* has been observed, as have alterations in rest-activity patterns and production of TNF-α and IL-10(1469). However, there is a lack of published literature regarding melatonin therapy in either human subjects or in animal models of NMOSD.

Successful melatonin therapy has been reported in pulmonary sarcoidosis, with improved lung function, radiological appearance and normalisation of ACE levels which is hypothesised to be due to its immunomodulatory and antiproliferative effects(1470). Melatonin has also been reported to be a safe and effective treatment in extrapulmonary sarcoidosis with resolution of skin manifestations and reduction in ACE levels to within normal limits(1471). There is little published literature of therapeutic outcomes of melatonin in neurosarcoidosis.

Muller et al (2006)(404) conducted a study of 10 children with CP, in whom low night time melatonin levels were associated with excessive daytime sleepiness and high BMI (hypothalamic obesity). Daily administration of 6mg melatonin improved daytime activity levels and ESS scores in all subjects. Decreased endogenous melatonin levels and circadian dysregulation have been found in Cushing syndrome and in prolactin-secreting pituitary

microadenomas respectively(1472, 1473), although there is a paucity of literature regarding melatonin supplementation in PA. Altered tryptophan metabolism has been found in human studies of meningioma, tryptophan being a component of melatonin synthesis(1474). Melatonin has been implicated in conditions presenting with skin pigmentation and skeletal abnormalities including NF1, as it is a factor that produces skin lightening and induces differentiation of osteoblasts and formation of the bony matrix(1475).

6.6.2(d) Melatonin in Psychiatric Conditions

Melatonin and its analogues has been found to alleviate insomnia symptoms in depression(1476). Claustrat et al (1984)(1477) found that melatonin rhythms were entrained but of lower amplitude in patients with depression compared to healthy subjects, although phase delay has also been found in MDD(1478, 1479). Major depression has been successfully treated with agomelatine, a melatonin analogue with SSRI properties at 5-HT_{2C} receptors. This has been found to reduce anxiety, improve sleep quality and circadian function and reduce WASO without influencing serotonin titres(1480). Lewy et al (1998)(1481) found that symptoms of winter depression were alleviated in a pilot study of five patients with administration of 0.125mg of melatonin twice daily in the afternoon, with the second dose four hours following the first dose. Melatonin has also been found to reduce low mood in patients with breast cancer(1482). In treatment-resistant depression, 10mg melatonin per day taken at unspecified times was found to improve sleep but not affect(1483).

Conversely, Carman et al (1976)(1484) found that melatonin given at peak doses of 150-1600mg/day worsened symptoms of unease, reduced sleep and body temperature and increased CSF 5-hydroxyindoleacetic acid and calcium. Timing of melatonin administration was not specified, and the doses administered were high.

Melatonin has been found to have short-term anxiolytic effects pre- and postoperatively in gynaecological, gastrointestinal, hand and cataract surgery(1485, 1486). Agonism at MT2 receptors has been found to produce anxiolytic and hypnotic results, and these receptors are also thought to mediate neurodegenerative disorders and pain(1487). In animal models,

melatonin analogues have been shown to reduce anxiety(1488), or potentiate the anxiolytic effects of benzodiazepines(1489).

Reduced melatonin levels have been found in all phases of BPD(1490), and attenuated melatonin suppression on light exposure has been observed(1491). Melatonin has been found to reduce the metabolic side effects of atypical antipsychotics(1492). Reversal of insomnia has been reported with melatonin therapy in a child with BPD(1493), although other studies have found that exogenous melatonin had no advantage over placebo or no treatment in BPD(1494, 1495). Low endogenous melatonin levels with normal rhythmicity have been found in schizophrenia(1496), with melatonin supplementation reported to improve sleep quality(1452).

6.6.2(e) Adverse Effects of Melatonin

Although very few or no adverse effects of melatonin have been described in most studies, it can have an impact on serotonergic and dopaminergic functions. As described earlier, melatonin is a derivative of serotonin. Concomitant use of melatonin with an SSRI and a high protein diet (both of which can lead to serotonin depletion) has been reported to cause a toxic optic neuropathy, which was reversed on discontinuation of melatonin and the high protein diet. Melatonin is produced by the retina, and it was theorised that exogenous melatonin affected dopamine activity, which can affect RGCs(1497).

In animal models of rheumatoid arthritis, melatonin has been found to worsen inflammation, which may be related to its enhancement of T helper cells and lymphocyte precursor cells as well as pro-inflammatory cytokines such as IL-2, IL-6, IFN-γ and TNF-α(1498). Forrest et al (2007)(1499) found that melatonin increased erythrocyte sedimentation rate and plasma kynurenine levels with no observable effects on clinical presentation or in IL-1β, IL-6 or TNF-α titre. Melatonin supplementation at very high doses has historically been found to worsen depressive symptoms and reduce sleep(1484).

6.6.2(f) Melatonin Therapy in Future Research

The published literature to date shows that in general, melatonin is safe and can be effective in aligning internal circadian timing with light and dark. However, little is known about optimum dosing, which is noticeable from the variation in dosing regimes in published studies. The optimum timing of administration also requires clarification, as do the long-term effects of melatonin therapy(1441, 1443). The use of melatonin in OND with associated SCRD may be promising in view of the results obtained in subjects with blindness.

6.6.3 Phototherapy and Sleep Wake

Light is the principal zeitgeber of the circadian clock in mammals(1500). pRGCs respond to light stimuli and relay this to the SCN, which allows entrainment of the internal circadian pacemaker to environmental night and day. A 460nm wavelength blue light has been shown to be most effective in eliciting phase adjustment, with melatonin suppression occurring at 400-500 lux and above(1501) and intensities of 2,500-10,000 lux producing improvements in sleep and mood(1502). Bright light alone is able to shift FR rhythms in human subjects by four hours, while in combination with other time cues, a shift of six hours has been observed(1503).

Appropriately timed exposure to bright light can assist in adaptation to shift work(1504). Olsen et al (2020)(1505) developed a protocol to assist adaptation to shift work for nurses using a portable light box to deliver 40minutes of bright light prior to night working, and light shielding with dark glasses following shifts, with structured advice with regard to sleep and nap scheduling. Dark goggles or glasses and bright light have been used by Eastman et al (1994)(1506) and Crowley et al (2003)(1507).

Bright morning light has been found to advance the circadian clock, whilst evening exposure can produce a phase delay reflected by plasma melatonin levels(1508). In preparation for transmeridian flight eastwards, continuous or intermittent exposure to morning light at >3000lux for 3 days has been found phase advance the circadian clock by 2h and 1.5h respectively(1509). In preparation for westward flight, phase delay can be achieved by delaying sleep schedule by 2h daily for several days and exposure to bright light prior to

sleeping(1510). Czeisler et al (1986)(1511) in a laboratory study exposed one subject with markedly advanced sleep phasing to four hours of bright light and rest and activity zeitgebers every evening for seven days, leading to her phase being delayed by six hours.

6.6.3(a) Ocular Conditions and Phototherapy

In blind children with learning disabilities, phototherapy was not found to be effective in circadian entrainment(1512). Circadian dysfunction is prevalent among individuals with NPL vision(15, 1035). Czeisler et al (1995)(916) studied patients with ERG-confirmed blindness, who were exposed to 90-100 minutes of bright light coinciding with peak plasma melatonin concentrations, which led to melatonin suppression in the absence of functioning photoreceptors. Similar circadian responses in the absence of conscious vision were reported by Klerman et al (2002)(1513) and Hull et al (2018)(1374), implicating pRGC involvement in photic entrainment of circadian phasing. Therefore, even in patients with low vision, treatment with phototherapy may be an appropriate intervention in some cases.

6.6.3(b) Demyelination and Phototherapy

Phototherapy at 10,000lux for 1 hour twice a day in the morning and evening for 4 weeks was found to improve fatigue scores, but not sleep quality or daytime sleepiness in patients with MS in a randomised phase II trial(1514). There are few published reports of phototherapy intervention in other chronic systemic conditions relevant to my study.

6.6.3(c) Psychiatric Conditions and Phototherapy

SAD has found to improve with phototherapy at 10,000 lux for 8 days in an Icelandic study(1515). Two hours of phototherapy for 7 days improved seasonal depression, but not MDD in a U.S. study(1516). Morning light exposure has been found to have a more powerful antidepressant effect and can advance circadian phase in SAD in comparison to evening light exposure, which causes a phase delay(1517). In a study of patients with MDD and BPD, exposure to 1000-2000lux bright white light from 0500-0600h improved depressive symptoms the following day(1518). Bright light of 10,000lux for 30 minutes between 0900

and 1230h for five days has been reported to improve depressive symptoms in institutionalised older adults with MDD(1519). In a study of patients with BPD with depressive symptoms, 15-60mins of bright white light at 7000lux between 12.00 and 14.30 led to symptom alleviation(1520).

Exposure to 5000lux from 0800-0830h for five days did not affect positive or negative symptoms in a study of hospitalised patients with schizophrenia(1521), although reduction in depressive symptoms in schizophrenia has been reported(1522).

In animal studies, bright morning light at 2500lux for 1h reduced anxiety and depression behaviours(1523). In contrast, 1h light exposure before lights off at 13.00-14.00 increased anxiety and depression symptomatology(1524). Light exposure of 600lux of unspecified duration and timing has also been found to increase anxiety in rats(1525).

6.6.3(d) Adverse Effects of Phototherapy

Morning bright light exposure has been implicated in the onset of mania in a schizophrenic patient(1521); hypomania has been precipitated by bright light exposure in a patient with winter depression(1526). Other negative side effects include headaches, nausea and agitation, sleep disturbance on exposure to evening light and mild eye irritation, although a general reduction in skin and eye irritation, skin rashes and blurred vision has also been described(1527, 1528).

6.6.3(e) Future Research in Phototherapy

From the variation in dose, duration, timing and length of treatment, it is clear that no general consensus has been arrived at regarding the optimum method for delivering phototherapy. Depending on an individual's internal circadian phasing, different protocols will be needed to advance or delay the circadian clock. In most studies, bright white light is used, although pRGCs and circadian entrainment are most sensitive to blue wavelength light(1501). Further research of the overall impact of blue light on sleep quality, timing and mood, its therapeutic ranges and adverse effects is required, as is further research into the most favourable dosing regimen for BLT.

6.6.4 Phototherapy and Exogenous Melatonin in Combination

Phase response curves for BLT and melatonin have been developed. These are specific to an individual's internal circadian timing but are useful in determining the optimum timings for therapy depending on whether a phase advance or delay is intended. Interventions tend to be recommended on the steep phases of the curve, in dim evening light conditions or early morning in the case of phototherapy, and when endogenous melatonin levels are low in the case of exogenous melatonin(1529-1532). BLT and melatonin therapy have been used in combination to entrain the endogenous circadian pacemaker, or to create phase shifting to adapt to other conditions.

Early morning light therapy (3000-5000lux for 2-3h, pulsed or continuous) in combination with 0.5-5mg melatonin administered 5.0-5.75hr before usual bedtime has been used to re-set the circadian clock in healthy individuals in a laboratory setting(1533, 1534). DPSD has been successfully managed with morning/midday light of 10,000lux and 3mg fast-release melatonin 12 hours later(1535). Burgess et al (2002)(1536) developed a suggested protocol for adaptation to shift work using phototherapy, dark sunglasses and melatonin supplementation (when the aim was to advance the circadian phase), with phototherapy shown to have a more potent phase shifting effect, and melatonin shown to have a more rapid impact(1537).

In children with chronic sleep onset insomnia, BLT combined with exogenous melatonin has been found to reduce SL, improve SE, increase TST and advance circadian phase, although WASO was not affected(1538). Phototherapy combined with melatonin has also been found to be effective in normalising rest-activity patterns in patients with AD(1539).

6.6.4(a) Future Research

As yet, few studies exist examining both BLT and phototherapy in combination in ocular and systemic conditions. As described for exogenous melatonin and phototherapy, precise dosing, specifics of the treatment dose (for example blue light vs white light; fast release melatonin vs sustained release) timing and duration of treatment are yet to be determined.

A qualitative and quantitative analysis of other bodily circadian rhythms, zeitgebers such as exercise, mealtimes, working hours and social events in combination with BLT and melatonin requires investigation(1443).

Chapter 7: Conclusion

OND are a heterogeneous, complex group of conditions that have a multi-faceted impact on the daily lives of those who experience them: visually, psychologically, socially, emotionally, physically, on sleep wake and in their clinical management.

7.1 General Literature Review

In my general literature review of the physiology of normal and abnormal sleep, exogenous and endogenous influences on sleep, the measurement of sleep and discussion of OND, I found that sleep is influenced by a variety of factors. Sleep and wake timing is under circadian control, which can be affected by the function of pRGCs and the optic nerves which input to the SCN via the RHT, and circadian misalignment can have a profound effect on wellbeing. Non-circadian sleep disorders also exist, such as OSA, RLS, PLM and narcolepsy. Caffeine, alcohol, nicotine and prescribed medications can impact on sleep quality and timing, as can chronic disease, pain, levels of physical activity, fatigue, social and lifestyle influences, age and sex. Psychiatric morbidity can lead to poor sleep quality and can itself be exacerbated by impaired sleep. Validated subjective and objective measures of sleep quality, duration and timing have been used in numerous published studies, and circadian rhythm can be established using melatonin assay. Circadian preference may have a genetic basis, and clock genes are a developing area of research.

Consideration of sleep quality in the clinical setting is important because of the health benefits of good quality sleep and the detrimental effects of sleep impairment. Evaluating factors that contribute to poor sleep may assist in its management.

7.2 Systematic Literature Review

My systematic literature review demonstrated that OND and glaucomatous conditions had a measurable association with sleep wake, with manifestations such as altered sleep quality, efficiency, duration and timing, daytime napping and daytime sleepiness. It also revealed that objective measures of circadian function were different in OND, although

generalisability of findings were marred by small sample sizes, uncontrolled studies, dissimilar control groups and insufficient assessment of visual function in several of the studies reviewed. This provided the basis for undertaking a large-scale controlled observational study of sleep quality and timing in OND which included assessment of visual function and use of validated outcome measures of sleep quality and timing, with exploration of general health, mood, and lifestyle with adjustment for confounders.

7.3 Observational Study – Prospective Component

In my prospective observational study, sleep disturbance was experienced by a higher proportion of participants with OND than control participants with normal visual function. Higher depression scores were associated with OND, and QOL scores were lower in OND. This supports the consideration of sleep quality and timing in the holistic management of patients with OND.

7.4 Observational Study – Retrospective Component

In my retrospective study, a high prevalence of poor sleep was observed in participants with autoimmune and demyelinating OND who screened positive for depression, used systemic glucocorticoid and psychiatric medications and who had sphincter dysfunction, pain and fatigue, suggesting that endogenous and exogenous influences other than circadian dysfunction are likely to contribute to OND in the presence of systemic conditions.

7.5 Summary

In my observational study, factors other than the pRGC damage and circadian dysfunction are likely to have contributed to poor sleep quality, such low mood, emotional, physical and social limitations and pain. Individuals with OND in the clinical setting may have worse subjective sleep quality than those without ocular pathology, and should be asked about this, in addition to their mood, QOL, systemic pathology, and medication history. Use of simple validated assessments of sleep quality and timing, sleep disturbance and mood in

addition to PROMs to evaluate the impact of HRQOL, VRQOL and SRQOL could engage patients in the management of their condition, give the clinician valuable insights into patient experience and identify areas that require attention to improve QOL. Good sleep hygiene may provide an initial step in alleviation of symptoms of poor sleep quality in some instances.

Selective preservation of pRGCs in some forms of OND have been demonstrated in several animal and human studies, meaning that circadian entrainment may be preserved in some individuals with OND, despite loss of visual function. Exogenous melatonin and phototherapy have been demonstrated to be effective in re-setting the circadian clock in some individuals with disorders of sleep and wake. Further research is needed into the impact of melatonin therapy and BLT in patients with OND. Use of subjective, objective, biochemical and genetic markers of sleep wake and assessing patient-related experience and outcomes would provide a comprehensive picture of a patient with OND as well as assessing pathology at a cellular level and provide a detailed baseline for comparison following intervention.

From a personal viewpoint, the experience of conducting this study has been an essential insight into the anatomy of clinical research. The necessity for a clear hypothesis, aims and objectives, and an understanding of the clinical context and recent evidence are fundamental steps in designing a clinical study which is scientifically robust, consistent with my aims and objectives and can feasibly provide an answer to my hypothesis. The ability to critically appraise study findings and identify sources of bias for meaningful interpretation and appropriate application of results in the real world has been a cornerstone in my development as a researcher and will provide a foundation for my involvement in future research.

Appendix A: PRISMA 2020 Checklist(1031)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	

Section 3.1

Section 3.2

Section 3.2.1

Section 3.5

Section 3.7

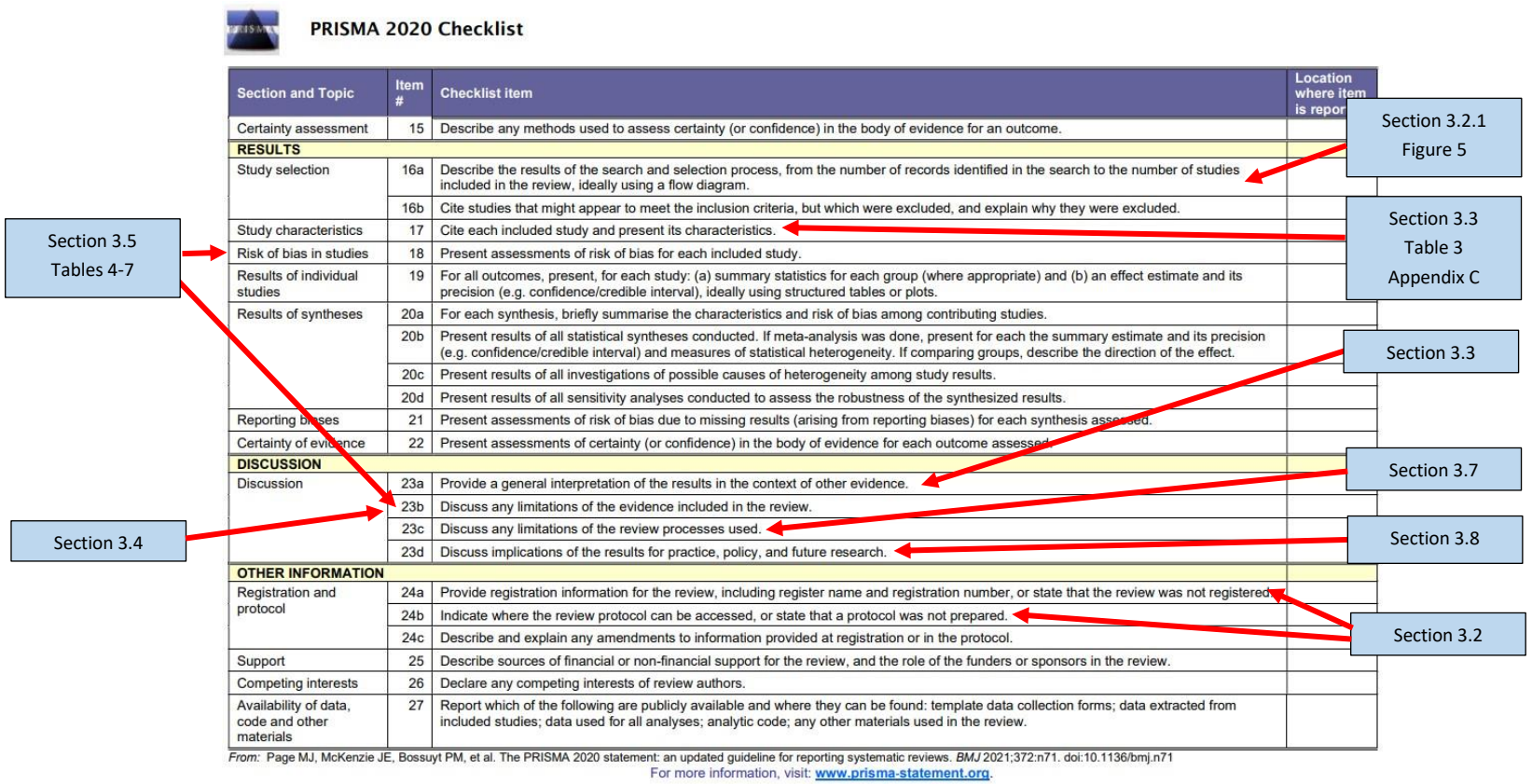


Figure 15: PRISMA 2020 Checklist(1031) with References to My Systematic Review. Public Domain, Available from PRISMA (prisma-statement.org)

This identifies how I have used the PRISMA 2020 checklist(1031) to structure my systematic review, with references to relevant sections of Literature Review in Chapter 3

Some points are not applicable, as my thesis abstract had scope wider than my systematic review; I was the sole reviewer, so agreement between reviewers was not possible and a meta-analysis was not appropriate due to the homogeneity of studies

Appendix B: Systematic Literature Review Search Terms

The following list details the search terms that were applied to all databases used within HDAS. The subsequent figures are taken from the HealthCare Databases Advanced Search (HDAS) provided in partnership with Health Education England (HEE) and the National Institute for Health and Care Excellence (NICE) via my NHS OpenAthens account. My searches were run from 19th-20th November 2021.

Table 15: Search Terms for Optic Nerve Disorders and Sleep Wake

OND	Glaucoma	Sleep
Optic atroph* (ADJ3) Congenital optic nerve* (ADJ3) Optic nerve hypoplas* (ADJ3) Septo-optic dysplas* De Morsier* syndrome Retinopathy of prematurity Congenital glaucoma* Buphthalm* Hereditary optic nerve* (ADJ3) Leber hereditary optic neuropath* LHON Dominant optic atroph* Kjer* Wolfram Syndrome DIDMOAD Autoimmune optic nerve* (ADJ3) Autoimmune optic neuropath* (ADJ3) Neuromyelitis optica NMOSD Devic* disease Demyelinat* optic nerve* (ADJ3) Demyelinat* optic neuropath* (ADJ3) Acute disseminated encephalomyeliti* Chronic relapsing inflammatory optic neuritis CRION Optic chiasm* compress* (ADJ3) Pituitary adenoma* optic chiasm* (ADJ3) Pituitary microadenoma* optic chiasm* (ADJ3) Pituitary macroadenoma* optic chiasm* (ADJ3)	Glaucoma* Primary open angle glaucoma* POAG Primary angle closure glaucoma* PACG Chronic open angle glaucoma* Chronic angle closure Infantile glaucoma* Juvenile glaucoma* Paediatric glaucoma* Pediatric glaucoma* Pseudoexfoliation glaucoma* Secondary glaucoma*	Sleep qualit* (ADJ3) Sleep tim* (ADJ3) Wake tim* (ADJ3) Time in bed Sleep onset Sleep offset Wake after sleep onset WASO Awakening* Sleep duration (ADJ3) Sleep disturb* (ADJ3) Sleep efficien* (ADJ3) Daytime sleep* (ADJ3) Daytime dysfunction* (ADJ3) Sleep laten* (ADJ3) Chronotype* Morningness Eveningness (ADJ3) Sleep disrupt* (ADJ3) Sleep* rhythm* (ADJ3) Sleep* pattern* (ADJ3) Sleep* disorder* (ADJ3) Insomnia* Somnolen* Hypersomnolen* Rapid Eye Movement* REM* Sleep* stage* (ADJ3) Bedtime* Bed-time* Bed time* (ADJ3)

Craniopharyngioma*optic chiasm* (ADJ3) Optic nerve* meningioma* (ADJ3) Optic nerve* glioma* (ADJ3) Infiltrat* optic neuropath*(ADJ3) Infiltrat* optic nerve* (ADJ3) Vascular optic neuropath* (ADJ3) Vascular optic nerve (ADJ3) Anterior ischemic optic neuropath* Anterior ischaemic optic neuropath* AION Non-arteritic ischaemic optic neuropath* Non-arteritic ischemic optic neuropath* NAION Posterior ischaemic optic neuropath* Posterior ischemic optic neuropath* Traumatic optic neuropath* Trauma* optic nerve* (ADJ3) Transect* optic nerve* (ADJ3) Compress* optic nerve* (ADJ3) Crush* optic nerve* (ADJ3) Degenerat* optic nerve* (ADJ3) Neurodegenerat* optic nerve* (ADJ3) Alzheimer* optic nerve* (ADJ3) Parkinson* optic nerve* (ADJ3) Nutrition* optic neuropath* (ADJ3) Nutrition* optic nerve* (ADJ3) Nutrition* optic atrophy* (ADJ3) Toxic* optic neuropath* (ADJ3) Toxic* optic nerve* (ADJ3) Toxic* optic atrophy* (ADJ3)		

Figure 16(a-e): EMBASE Optic Nerve Disorders and Sleep Wake Search Terms

Current search strategy: Combined Searches EMBASE 19.11.21

	Database(s)	Search Term		
1	EMBASE	(Optic ADJ3 atroph*).ti,ab	View Results (7,388)	Edit
2	EMBASE	"OPTIC NERVE DISEASE"/ OR "OPTIC NERVE DISEASES"/ OR "OPTIC NERVE DAMAGE"/ OR "OPTIC NERVE CANCER"/ OR "OPTIC NERVE ATROPHY, HEREDITARY"/ OR "OPTIC NERVE ATROPHY"/ OR "HEREDITARY OPTIC ATROPHY"/	View Results (25,306)	Edit
3	EMBASE	(Congenital ADJ3 optic nerve*).ti,ab	View Results (166)	Edit
4	EMBASE	(Optic nerve ADJ3 hypoplas*).ti,ab	View Results (1,006)	Edit
5	EMBASE	"OPTIC NERVE HYPOPLASIA"/	View Results (1,169)	Edit
6	EMBASE	(Septo-optic dysplas*).ti,ab	View Results (642)	Edit
7	EMBASE	"SEPTOOPTIC DYSPLASIA"/	View Results (711)	Edit
8	EMBASE	(De Morsier syndrome).ti,ab	View Results (62)	Edit
9	EMBASE	(Retinopathy of prematurity).ti,ab	View Results (9,327)	Edit
10	EMBASE	(Congenital glaucoma*).ti,ab	View Results (2,034)	Edit
11	EMBASE	"CONGENITAL GLAUCOMA"/	View Results (2,060)	Edit
12	EMBASE	(Buphthalm*).ti,ab	View Results (442)	Edit
13	EMBASE	(Hereditary ADJ3 optic nerve*).ti,ab	View Results (36)	Edit
14	EMBASE	"LEBER HEREDITARY OPTIC NEUROPATHY"/ OR "AUTOSOMAL DOMINANT OPTIC ATROPHY"/ OR "WOLFRAM SYNDROME"/ OR "HEREDITARY OPTIC ATROPHY"/	View Results (4,432)	Edit
15	EMBASE	(Leber hereditary optic neuropathy).ti,ab	View Results (774)	Edit
16	EMBASE	(LHON).ti,ab	View Results (1,544)	Edit
17	EMBASE	(Dominant optic atroph*).ti,ab	View Results (646)	Edit
18	EMBASE	(Kjer*).ti,ab	View Results (81)	Edit
19	EMBASE	(Wolfram syndrome).ti,ab	View Results (824)	Edit
20	EMBASE	(DIDMOAD).ti,ab	View Results (228)	Edit
21	EMBASE	(Autoimmune ADJ3 optic nerve*).ti,ab	View Results (32)	Edit
22	EMBASE	(Autoimmune ADJ3 optic neuropath*).ti,ab	View Results (40)	Edit
23	EMBASE	(Neuromyelitis optica).ti,ab	View Results (8,846)	Edit
24	EMBASE	"MYELOOPTIC NEUROPATHY"/ OR "MYELOOPTIC NEUROPATHY, SUBACUTE"/ OR MYELOOPTICONEUROPATHY/	View Results (10,566)	Edit

Figure 16a

☐ 25	EMBASE	(NMOSD).ti,ab	View Results (3,484)	Edit	
☐ 26	EMBASE	(Devic* disease).ti,ab	View Results (336)	Edit	
☐ 27	EMBASE	(Demyelinat* ADJ3 optic nerve*).ti,ab	View Results (352)	Edit	
☐ 28	EMBASE	"OPTIC NEURITIS, RETROBULBAR"/ OR "OPTIC NEURITIS"/	View Results (11,587)	Edit	
☐ 29	EMBASE	(Demyelinat* ADJ3 optic neuropath*).ti,ab	View Results (83)	Edit	
☐ 30	EMBASE	(Acute disseminated encephalomyeliti*).ti,ab	View Results (2,827)	Edit	
☐ 31	EMBASE	"ACUTE DISSEMINATED ENCEPHALOMYELITIS"/ OR "POSTINFECTIOUS ENCEPHALOPATHY"/	View Results (3,051)	Edit	
☐ 32	EMBASE	(Chronic relapsing inflammatory optic neuritis).ti,ab	View Results (20)	Edit	
☐ 33	EMBASE	(CRION).ti,ab	View Results (113)	Edit	
☐ 34	EMBASE	(Optic chiasm* ADJ3 compress*).ti,ab	View Results (547)	Edit	
☐ 35	EMBASE	(Pituitary adenoma* ADJ3 optic chiasm*).ti,ab	View Results (23)	Edit	
☐ 36	EMBASE	("HYPOPHYSIS ADENOMA"/ OR "HYPOPHYSIS TUMOR"/ OR "ACTH SECRETING ADENOMA"/ OR "CHROMOPHOBE ADENOMA"/ OR "GONADOTROPH ADENOMA"/ OR "GROWTH HORMONE SECRETING ADENOMA"/ OR "NONFUNCTIONING PITUITARY ADENOMA"/ OR "PLURIHORMONAL ADENOMA"/ OR PROLACTINOMA/ OR "THYROTROPIN SECRETING ADENOMA"/) ADJ3 optic chiasm*	View Results (1,339)	Edit	
☐ 37	EMBASE	(Pituitary microadenoma* ADJ3 optic chiasm*).ti,ab	View Results (0)	Edit	
☐ 38	EMBASE	(Pituitary macroadenoma* ADJ3 optic chiasm*).ti,ab	View Results (19)	Edit	
☐ 39	EMBASE	(Craniopharyngioma* ADJ3 optic chiasm*).ti,ab	View Results (14)	Edit	
☐ 40	EMBASE	(CRANIOPHARYNGIOMA/ OR "HYPOPHYSIS TUMOR"/) ADJ3 optic chiasm*	View Results (804)	Edit	
☐ 41	EMBASE	(Optic nerve* ADJ3 meningioma*).ti,ab	View Results (587)	Edit	
☐ 42	EMBASE	"OPTIC NERVE CANCER"/ OR "OPTIC NERVE TUMOR"/ OR "OPTIC NERVE TUMOUR"/	View Results (985)	Edit	
☐ 43	EMBASE	(Optic nerve* ADJ3 glioma*).ti,ab	View Results (633)	Edit	
☐ 44	EMBASE	"OPTIC NERVE GLIOMA"/	View Results (1,665)	Edit	
☐ 45	EMBASE	(Infiltrat* ADJ3 optic neuropath*).ti,ab	View Results (50)	Edit	
☐ 46	EMBASE	(Infiltrat* ADJ3 optic nerve*).ti,ab	View Results (329)	Edit	
☐ 47	EMBASE	(Vascular ADJ3 optic neuropath*).ti,ab	View Results (67)	Edit	
☐ 48	EMBASE	(Vascular ADJ3 optic nerve*).ti,ab	View Results (171)	Edit	
☐ 49	EMBASE	"ANTERIOR ISCHEMIC OPTIC NEUROPATHY"/ OR "ISCHEMIC OPTIC NEUROPATHY"/	View Results (3,444)	Edit	

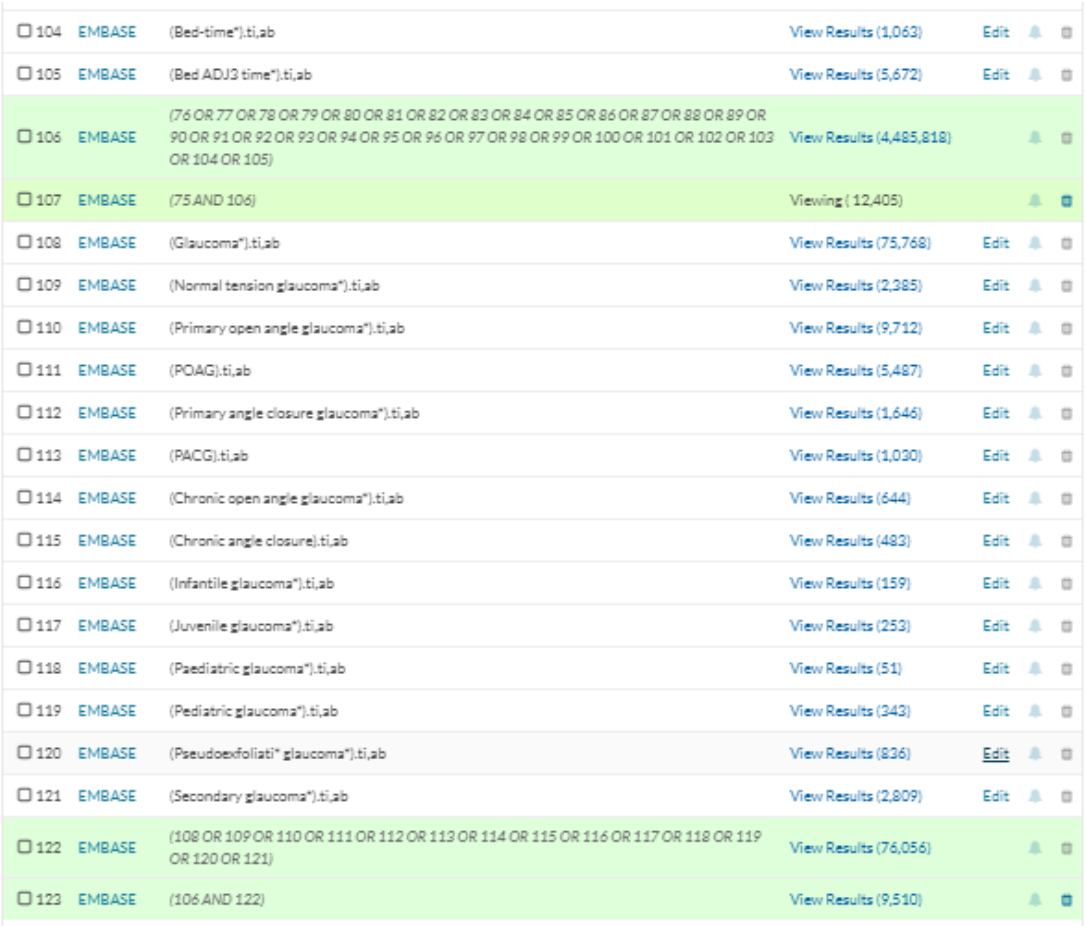
Figure 16b

☐ 50	EMBASE	(Anterior ischaemic optic neuropath*).ti,ab	View Results (412)	Edit	
☐ 51	EMBASE	(Anterior ischaemic optic neuropath*).ti,ab	View Results (412)	Edit	
☐ 52	EMBASE	(AION).ti,ab	View Results (568)	Edit	
☐ 53	EMBASE	(Non-arteritic ischaemic optic neuropath*).ti,ab	View Results (44)	Edit	
☐ 54	EMBASE	(Non-arteritic ischemic optic neuropath*).ti,ab	View Results (92)	Edit	
☐ 55	EMBASE	(NAION).ti,ab	View Results (750)	Edit	
☐ 56	EMBASE	(Posterior ischaemic optic neuropath*).ti,ab	View Results (40)	Edit	
☐ 57	EMBASE	(Posterior ischemic optic neuropath*).ti,ab	View Results (192)	Edit	
☐ 58	EMBASE	(Traumatic optic neuropath*).ti,ab	View Results (677)	Edit	
☐ 59	EMBASE	(Trauma* ADJ3 optic nerve*).ti,ab	View Results (392)	Edit	
☐ 60	EMBASE	'OPTIC NERVE INJURY'/ OR 'OPTIC NERVE LESION'/ OR 'OPTIC NERVE TRAUMA'/	View Results (5,197)	Edit	
☐ 61	EMBASE	(Transect* ADJ3 optic nerve*).ti,ab	View Results (742)	Edit	
☐ 62	EMBASE	(Compress* ADJ3 optic nerve*).ti,ab	View Results (953)	Edit	
☐ 63	EMBASE	(Crush* ADJ3 optic nerve*).ti,ab	View Results (1,325)	Edit	
☐ 64	EMBASE	(Degenerat* ADJ3 optic nerve*).ti,ab	View Results (891)	Edit	
☐ 65	EMBASE	(Neurodegenerat* ADJ3 optic nerve*).ti,ab	View Results (63)	Edit	
☐ 66	EMBASE	(Alzheimer* ADJ3 optic nerve*).ti,ab	View Results (11)	Edit	
☐ 67	EMBASE	(Parkinson* ADJ3 optic nerve*).ti,ab	View Results (6)	Edit	
☐ 68	EMBASE	(Nutrition* ADJ3 optic neuropath*).ti,ab	View Results (60)	Edit	
☐ 69	EMBASE	(Nutrition* ADJ3 optic nerve*).ti,ab	View Results (24)	Edit	
☐ 70	EMBASE	(Nutrition* ADJ3 optic atroph*).ti,ab	View Results (5)	Edit	
☐ 71	EMBASE	(Toxic* ADJ3 optic neuropath*).ti,ab	View Results (240)	Edit	
☐ 72	EMBASE	(Toxic* ADJ3 optic nerve*).ti,ab	View Results (89)	Edit	
☐ 73	EMBASE	(Toxic* ADJ3 optic atroph*).ti,ab	View Results (11)	Edit	
☐ 74	EMBASE	'TOXIC OPTIC NEUROPATHY'/	View Results (35)	Edit	
☐ 75	EMBASE	*(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74)*	View Results (77,143)		

Figure 16c

76	EMBASE	(Sleep ADJ3 qualit*).ti,ab	View Results (36,454)	Edit	
77	EMBASE	(Sleep ADJ3 tim*).ti,ab	View Results (22,666)	Edit	
78	EMBASE	(Wake ADJ3 tim*).ti,ab	View Results (3,969)	Edit	
79	EMBASE	(Time in bed).ti,ab	View Results (1,968)	Edit	
80	EMBASE	(Sleep onset).ti,ab	View Results (10,094)	Edit	
81	EMBASE	(Sleep offset).ti,ab	View Results (220)	Edit	
82	EMBASE	(Wake after sleep onset).ti,ab	View Results (2,254)	Edit	
83	EMBASE	(WASO).ti,ab	View Results (1,753)	Edit	
84	EMBASE	(Awakening*).ti,ab	View Results (17,645)	Edit	
85	EMBASE	(Sleep ADJ3 duration).ti,ab	View Results (18,383)	Edit	
86	EMBASE	(Sleep ADJ3 disturb*).ti,ab	View Results (35,344)	Edit	
87	EMBASE	(Sleep ADJ3 efficien*).ti,ab	View Results (9,414)	Edit	
88	EMBASE	(Daytime ADJ3 sleep*).ti,ab	View Results (18,973)	Edit	
89	EMBASE	(Daytime ADJ3 dysfunction*).ti,ab	View Results (1,108)	Edit	
90	EMBASE	(Sleep ADJ3 laten*).ti,ab	View Results (11,678)	Edit	
91	EMBASE	(Chronotype*).ti,ab	View Results (2,522)	Edit	
92	EMBASE	(Morningness ADJ3 Eveningness).ti,ab	View Results (1,498)	Edit	
93	EMBASE	(Sleep ADJ3 disrupt*).ti,ab	View Results (7,506)	Edit	
94	EMBASE	(Sleep* ADJ3 rhythm*).ti,ab	View Results (5,728)	Edit	
95	EMBASE	(Sleep* ADJ3 pattern*).ti,ab	View Results (12,874)	Edit	
96	EMBASE	(Sleep* ADJ3 disorder*).ti,ab	View Results (48,677)	Edit	
97	EMBASE	(Insomnia*).ti,ab	View Results (41,277)	Edit	
98	EMBASE	(Somnolen*).ti,ab	View Results (11,188)	Edit	
99	EMBASE	(Hypersomnolen*).ti,ab	View Results (1,215)	Edit	
100	EMBASE	(Rapid Eye Movement*).ti,ab	View Results (13,900)	Edit	
101	EMBASE	(REM*).ti,ab	View Results (4,327,809)	Edit	
102	EMBASE	(Sleep* ADJ3 stage*).ti,ab	View Results (10,673)	Edit	
103	EMBASE	(Bedtime*).ti,ab	View Results (9,941)	Edit	

Figure 16d



104	EMBASE	(Bed-time*).ti,ab	View Results (1,063)	Edit	
105	EMBASE	(Bed ADJ3 time*).ti,ab	View Results (5,672)	Edit	
106	EMBASE	*(76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105)*	View Results (4,485,818)		
107	EMBASE	*(75 AND 106)*	Viewing (12,405)		
108	EMBASE	(Glaucoma*).ti,ab	View Results (75,768)	Edit	
109	EMBASE	(Normal tension glaucoma*).ti,ab	View Results (2,385)	Edit	
110	EMBASE	(Primary open angle glaucoma*).ti,ab	View Results (9,712)	Edit	
111	EMBASE	(POAG).ti,ab	View Results (5,487)	Edit	
112	EMBASE	(Primary angle closure glaucoma*).ti,ab	View Results (1,646)	Edit	
113	EMBASE	(PACG).ti,ab	View Results (1,030)	Edit	
114	EMBASE	(Chronic open angle glaucoma*).ti,ab	View Results (644)	Edit	
115	EMBASE	(Chronic angle closure).ti,ab	View Results (483)	Edit	
116	EMBASE	(Infantile glaucoma*).ti,ab	View Results (159)	Edit	
117	EMBASE	(Juvenile glaucoma*).ti,ab	View Results (253)	Edit	
118	EMBASE	(Paediatric glaucoma*).ti,ab	View Results (51)	Edit	
119	EMBASE	(Pediatric glaucoma*).ti,ab	View Results (343)	Edit	
120	EMBASE	(Pseudoexfoliati* glaucoma*).ti,ab	View Results (836)	Edit	
121	EMBASE	(Secondary glaucoma*).ti,ab	View Results (2,809)	Edit	
122	EMBASE	*(108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118 OR 119 OR 120 OR 121)*	View Results (76,056)		
123	EMBASE	*(106 AND 122)*	View Results (9,510)		

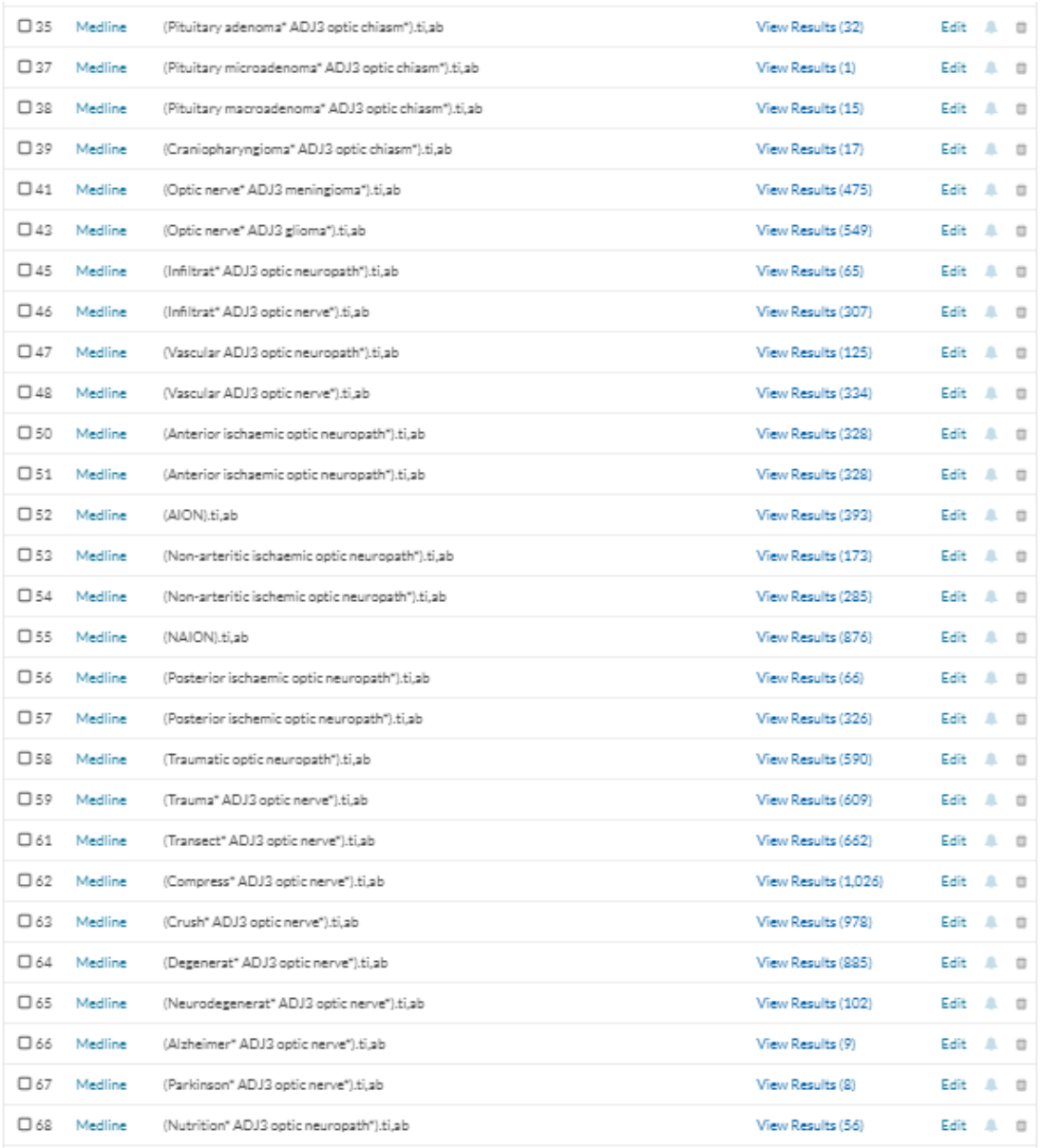
Figure 16e

Figure 17(a-e): Medline Optic Nerve Disorders and Sleep Wake Search Terms

Current search strategy: Combined Searched Medline 19.11.21

	Database(s)	Search Term		
1	Medline	(Optic ADJ3 atroph*).ti,ab	View Results (5,881)	Edit
3	Medline	(Congenital ADJ3 optic nerve*).ti,ab	View Results (261)	Edit
4	Medline	(Optic nerve ADJ3 hypoplas*).ti,ab	View Results (779)	Edit
6	Medline	(Septo-optic dysplas*).ti,ab	View Results (457)	Edit
8	Medline	(De Morsier syndrome).ti,ab	View Results (78)	Edit
9	Medline	(Retinopathy of prematurity).ti,ab	View Results (7,088)	Edit
10	Medline	(Congenital glaucoma*).ti,ab	View Results (2,809)	Edit
12	Medline	(Buphthalm*).ti,ab	View Results (429)	Edit
13	Medline	(Hereditary ADJ3 optic nerve*).ti,ab	View Results (452)	Edit
15	Medline	(Leber hereditary optic neuropathy).ti,ab	View Results (1,604)	Edit
16	Medline	(LHON).ti,ab	View Results (1,086)	Edit
17	Medline	(Dominant optic atroph*).ti,ab	View Results (747)	Edit
18	Medline	(Kjer*).ti,ab	View Results (53)	Edit
19	Medline	(Wolfram syndrome).ti,ab	View Results (655)	Edit
20	Medline	(DIDMOAD).ti,ab	View Results (172)	Edit
21	Medline	(Autoimmune ADJ3 optic nerve*).ti,ab	View Results (74)	Edit
22	Medline	(Autoimmune ADJ3 optic neuropath*).ti,ab	View Results (38)	Edit
23	Medline	(Neuromyelitis optica).ti,ab	View Results (4,601)	Edit
25	Medline	(NMOSD).ti,ab	View Results (1,595)	Edit
26	Medline	(Devic* disease).ti,ab	View Results (32,406)	Edit
27	Medline	(Demyelinat* ADJ3 optic nerve*).ti,ab	View Results (386)	Edit
29	Medline	(Demyelinat* ADJ3 optic neuropath*).ti,ab	View Results (116)	Edit
30	Medline	(Acute disseminated encephalomyeliti*).ti,ab	View Results (1,936)	Edit
32	Medline	(Chronic relapsing inflammatory optic neuritis).ti,ab	View Results (60)	Edit
33	Medline	(CRION).ti,ab	View Results (35)	Edit
34	Medline	(Optic chiasm* ADJ3 compress*).ti,ab	View Results (449)	Edit

Figure 17a



35	Medline	(Pituitary adenoma* ADJ3 optic chiasm*).ti,ab	View Results (32)	Edit	
37	Medline	(Pituitary microadenoma* ADJ3 optic chiasm*).ti,ab	View Results (1)	Edit	
38	Medline	(Pituitary macroadenoma* ADJ3 optic chiasm*).ti,ab	View Results (15)	Edit	
39	Medline	(Craniopharyngioma* ADJ3 optic chiasm*).ti,ab	View Results (17)	Edit	
41	Medline	(Optic nerve* ADJ3 meningioma*).ti,ab	View Results (475)	Edit	
43	Medline	(Optic nerve* ADJ3 glioma*).ti,ab	View Results (549)	Edit	
45	Medline	(Infiltrat* ADJ3 optic neuropath*).ti,ab	View Results (65)	Edit	
46	Medline	(Infiltrat* ADJ3 optic nerve*).ti,ab	View Results (307)	Edit	
47	Medline	(Vascular ADJ3 optic neuropath*).ti,ab	View Results (125)	Edit	
48	Medline	(Vascular ADJ3 optic nerve*).ti,ab	View Results (334)	Edit	
50	Medline	(Anterior ischaemic optic neuropath*).ti,ab	View Results (328)	Edit	
51	Medline	(Anterior ischaemic optic neuropath*).ti,ab	View Results (328)	Edit	
52	Medline	(AION).ti,ab	View Results (393)	Edit	
53	Medline	(Non-arteritic ischaemic optic neuropath*).ti,ab	View Results (173)	Edit	
54	Medline	(Non-arteritic ischemic optic neuropath*).ti,ab	View Results (285)	Edit	
55	Medline	(NAION).ti,ab	View Results (876)	Edit	
56	Medline	(Posterior ischaemic optic neuropath*).ti,ab	View Results (66)	Edit	
57	Medline	(Posterior ischemic optic neuropath*).ti,ab	View Results (326)	Edit	
58	Medline	(Traumatic optic neuropath*).ti,ab	View Results (590)	Edit	
59	Medline	(Trauma* ADJ3 optic nerve*).ti,ab	View Results (609)	Edit	
61	Medline	(Transect* ADJ3 optic nerve*).ti,ab	View Results (662)	Edit	
62	Medline	(Compress* ADJ3 optic nerve*).ti,ab	View Results (1,026)	Edit	
63	Medline	(Crush* ADJ3 optic nerve*).ti,ab	View Results (978)	Edit	
64	Medline	(Degenerat* ADJ3 optic nerve*).ti,ab	View Results (885)	Edit	
65	Medline	(Neurodegenerat* ADJ3 optic nerve*).ti,ab	View Results (102)	Edit	
66	Medline	(Alzheimer* ADJ3 optic nerve*).ti,ab	View Results (9)	Edit	
67	Medline	(Parkinson* ADJ3 optic nerve*).ti,ab	View Results (8)	Edit	
68	Medline	(Nutrition* ADJ3 optic neuropath*).ti,ab	View Results (56)	Edit	

Figure 17b

☐ 69	Medline	(Nutrition* ADJ3 optic nerve*).ti,ab	View Results (38)	Edit	
☐ 70	Medline	(Nutrition* ADJ3 optic atroph*).ti,ab	View Results (12)	Edit	
☐ 71	Medline	(Toxic* ADJ3 optic neuropath*).ti,ab	View Results (224)	Edit	
☐ 72	Medline	(Toxic* ADJ3 optic nerve*).ti,ab	View Results (162)	Edit	
☐ 73	Medline	(Toxic* ADJ3 optic atroph*).ti,ab	View Results (28)	Edit	
☐ 75	Medline	(Sleep ADJ3 qualit*).ti,ab	View Results (22,712)	Edit	
☐ 76	Medline	(Sleep ADJ3 tim*).ti,ab	View Results (15,041)	Edit	
☐ 77	Medline	(Wake ADJ3 tim*).ti,ab	View Results (2,468)	Edit	
☐ 78	Medline	(Time in bed).ti,ab	View Results (20,205)	Edit	
☐ 79	Medline	(Sleep onset).ti,ab	View Results (12,960)	Edit	
☐ 80	Medline	(Sleep offset).ti,ab	View Results (455)	Edit	
☐ 81	Medline	(Wake after sleep onset).ti,ab	View Results (2,022)	Edit	
☐ 82	Medline	(WASO).ti,ab	View Results (606)	Edit	
☐ 83	Medline	(Awakening*).ti,ab	View Results (11,151)	Edit	
☐ 84	Medline	(Sleep ADJ3 duration).ti,ab	View Results (12,182)	Edit	
☐ 85	Medline	(Sleep ADJ3 disturb*).ti,ab	View Results (21,892)	Edit	
☐ 86	Medline	(Sleep ADJ3 efficien*).ti,ab	View Results (5,297)	Edit	
☐ 87	Medline	(Daytime ADJ3 sleep*).ti,ab	View Results (11,218)	Edit	
☐ 88	Medline	(Daytime ADJ3 dysfunction*).ti,ab	View Results (655)	Edit	
☐ 89	Medline	(Sleep ADJ3 laten*).ti,ab	View Results (6,859)	Edit	
☐ 90	Medline	(Chronotype*).ti,ab	View Results (1,514)	Edit	
☐ 91	Medline	(Morningness ADJ3 Eveningness).ti,ab	View Results (856)	Edit	
☐ 92	Medline	(Sleep ADJ3 disrupt*).ti,ab	View Results (4,766)	Edit	
☐ 93	Medline	(Sleep* ADJ3 rhythm*).ti,ab	View Results (4,380)	Edit	
☐ 94	Medline	(Sleep* ADJ3 pattern*).ti,ab	View Results (8,900)	Edit	
☐ 95	Medline	(Sleep* ADJ3 disorder*).ti,ab	View Results (29,526)	Edit	
☐ 96	Medline	(Insomnia*).ti,ab	View Results (24,062)	Edit	
☐ 97	Medline	(Somnolen*).ti,ab	View Results (6,246)	Edit	

Figure 17c

98	Medline	(Hypersomnolen*).ti,ab	View Results (700)	Edit	
99	Medline	(Rapid Eye Movement*).ti,ab	View Results (12,105)	Edit	
100	Medline	(REM*).ti,ab	View Results (2,472,693)	Edit	
101	Medline	(Sleep* ADJ3 stage*).ti,ab	View Results (7,342)	Edit	
102	Medline	(Bedtime*).ti,ab	View Results (6,067)	Edit	
103	Medline	(Bed-time*).ti,ab	View Results (485)	Edit	
104	Medline	(Bed ADJ3 time*).ti,ab	View Results (3,597)	Edit	
105	Medline	(Glaucoma*).ti,ab	View Results (63,540)	Edit	
106	Medline	(Normal tension glaucoma*).ti,ab	View Results (2,117)	Edit	
107	Medline	(Primary open angle glaucoma*).ti,ab	View Results (8,717)	Edit	
108	Medline	(POAG).ti,ab	View Results (4,202)	Edit	
109	Medline	(Primary angle closure glaucoma*).ti,ab	View Results (1,834)	Edit	
110	Medline	(PACG).ti,ab	View Results (813)	Edit	
111	Medline	(Chronic open angle glaucoma*).ti,ab	View Results (1,141)	Edit	
112	Medline	(Chronic angle closure).ti,ab	View Results (650)	Edit	
113	Medline	(Infantile glaucoma*).ti,ab	View Results (273)	Edit	
114	Medline	(Juvenile glaucoma*).ti,ab	View Results (829)	Edit	
115	Medline	(Paediatric glaucoma*).ti,ab	View Results (137)	Edit	
116	Medline	(Pediatric glaucoma*).ti,ab	View Results (712)	Edit	
117	Medline	(Pseudoexfoliati* glaucoma*).ti,ab	View Results (1,348)	Edit	
118	Medline	(Secondary glaucoma*).ti,ab	View Results (5,423)	Edit	
120	Medline	*(105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118)*	View Results (63,653)		
121	Medline	*(75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104)*	View Results (2,596,850)		
122	Medline	*(120 AND 121)*	View Results (5,623)		

Figure 17d

123	Medline	*(1 OR 3 OR 4 OR 6 OR 8 OR 9 OR 10 OR 12 OR 13 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 25 OR 26 OR 27 OR 29 OR 30 OR 32 OR 33)*	View Results (57,799)		
125	Medline	*(121 AND 123)*	View Results (8,485)		
126	Medline	*(33 OR 34 OR 35 OR 37 OR 38 OR 39 OR 41 OR 43 OR 45 OR 46 OR 47 OR 48 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57)*	View Results (3,894)		
127	Medline	*(121 AND 126)*	View Results (512)		
128	Medline	*(58 OR 59 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73)*	View Results (4,541)		
129	Medline	*(121 AND 128)*	View Results (700)		

Figure 17e

Figure 18(a-e): PsychINFO Optic Nerve Disorders and Sleep Wake Search Terms

Current search strategy: Combined Searches PsychINFO 19.11.21

	Database(s)	Search Term		
1	PsycINFO	(Optic ADJ3 atroph*).ti,ab	View Results (411)	Edit
3	PsycINFO	(Congenital ADJ3 optic nerve*).ti,ab	View Results (8)	Edit
4	PsycINFO	(Optic nerve ADJ3 hypoplas*).ti,ab	View Results (60)	Edit
6	PsycINFO	(Septo-optic dysplas*).ti,ab	View Results (36)	Edit
8	PsycINFO	(De Morsier syndrome).ti,ab	View Results (7)	Edit
9	PsycINFO	(Retinopathy of prematurity).ti,ab	View Results (167)	Edit
10	PsycINFO	(Congenital glaucoma*).ti,ab	View Results (29)	Edit
12	PsycINFO	(Buphthalm*).ti,ab	View Results (4)	Edit
13	PsycINFO	(Hereditary ADJ3 optic nerve*).ti,ab	View Results (28)	Edit
15	PsycINFO	(Leber hereditary optic neuropathy).ti,ab	View Results (98)	Edit
16	PsycINFO	(LHON).ti,ab	View Results (73)	Edit
17	PsycINFO	(Dominant optic atroph*).ti,ab	View Results (91)	Edit
18	PsycINFO	(Kjer*).ti,ab	View Results (26)	Edit
19	PsycINFO	(Wolfram syndrome).ti,ab	View Results (44)	Edit
20	PsycINFO	(DIDMOAD).ti,ab	View Results (9)	Edit
21	PsycINFO	(Autoimmune ADJ3 optic nerve*).ti,ab	View Results (14)	Edit
22	PsycINFO	(Autoimmune ADJ3 optic neuropath*).ti,ab	View Results (0)	Edit
23	PsycINFO	(Neuromyelitis optica).ti,ab	View Results (976)	Edit
25	PsycINFO	(NMOSD).ti,ab	View Results (286)	Edit
26	PsycINFO	(Devic* disease).ti,ab	View Results (1,577)	Edit
27	PsycINFO	(Demyelinat* ADJ3 optic nerve*).ti,ab	View Results (43)	Edit
29	PsycINFO	(Demyelinat* ADJ3 optic neuropath*).ti,ab	View Results (12)	Edit
30	PsycINFO	(Acute disseminated encephalomyeliti*).ti,ab	View Results (318)	Edit
32	PsycINFO	(Chronic relapsing inflammatory optic neuritis).ti,ab	View Results (5)	Edit
33	PsycINFO	(CRION).ti,ab	View Results (5)	Edit
34	PsycINFO	(Optic chiasm* ADJ3 compress*).ti,ab	View Results (8)	Edit

Figure 18a

☐ 35	PsycINFO	(Pituitary adenoma* ADJ3 optic chiasm*).ti,ab	View Results (1)	Edit	
☐ 37	PsycINFO	(Pituitary microadenoma* ADJ3 optic chiasm*).ti,ab	View Results (0)	Edit	
☐ 38	PsycINFO	(Pituitary macroadenoma* ADJ3 optic chiasm*).ti,ab	View Results (0)	Edit	
☐ 39	PsycINFO	(Craniopharyngioma* ADJ3 optic chiasm*).ti,ab	View Results (0)	Edit	
☐ 41	PsycINFO	(Optic nerve* ADJ3 meningioma*).ti,ab	View Results (4)	Edit	
☐ 43	PsycINFO	(Optic nerve* ADJ3 glioma*).ti,ab	View Results (8)	Edit	
☐ 45	PsycINFO	(Infiltrat* ADJ3 optic neuropath*).ti,ab	View Results (2)	Edit	
☐ 46	PsycINFO	(Infiltrat* ADJ3 optic nerve*).ti,ab	View Results (9)	Edit	
☐ 47	PsycINFO	(Vascular ADJ3 optic neuropath*).ti,ab	View Results (1)	Edit	
☐ 48	PsycINFO	(Vascular ADJ3 optic nerve*).ti,ab	View Results (3)	Edit	
☐ 50	PsycINFO	(Anterior ischaemic optic neuropath*).ti,ab	View Results (1)	Edit	
☐ 51	PsycINFO	(Anterior ischaemic optic neuropath*).ti,ab	View Results (1)	Edit	
☐ 52	PsycINFO	(AION).ti,ab	View Results (35)	Edit	
☐ 53	PsycINFO	(Non-arteritic ischaemic optic neuropath*).ti,ab	View Results (3)	Edit	
☐ 54	PsycINFO	(Non-arteritic ischemic optic neuropath*).ti,ab	View Results (8)	Edit	
☐ 55	PsycINFO	(NAION).ti,ab	View Results (18)	Edit	
☐ 56	PsycINFO	(Posterior ischaemic optic neuropath*).ti,ab	View Results (0)	Edit	
☐ 57	PsycINFO	(Posterior ischemic optic neuropath*).ti,ab	View Results (8)	Edit	
☐ 58	PsycINFO	(Traumatic optic neuropath*).ti,ab	View Results (27)	Edit	
☐ 59	PsycINFO	(Trauma* ADJ3 optic nerve*).ti,ab	View Results (25)	Edit	
☐ 61	PsycINFO	(Transect* ADJ3 optic nerve*).ti,ab	View Results (73)	Edit	
☐ 62	PsycINFO	(Compress* ADJ3 optic nerve*).ti,ab	View Results (20)	Edit	
☐ 63	PsycINFO	(Crush* ADJ3 optic nerve*).ti,ab	View Results (148)	Edit	
☐ 64	PsycINFO	(Degenerat* ADJ3 optic nerve*).ti,ab	View Results (79)	Edit	
☐ 65	PsycINFO	(Neurodegenerat* ADJ3 optic nerve*).ti,ab	View Results (11)	Edit	
☐ 66	PsycINFO	(Alzheimer* ADJ3 optic nerve*).ti,ab	View Results (3)	Edit	
☐ 67	PsycINFO	(Parkinson* ADJ3 optic nerve*).ti,ab	View Results (2)	Edit	
☐ 68	PsycINFO	(Nutrition* ADJ3 optic neuropath*).ti,ab	View Results (5)	Edit	

Figure 18b

☐ 69	PsycINFO	(Nutrition* ADJ3 optic nerve*).ti,ab	View Results (2)	Edit	
☐ 70	PsycINFO	(Nutrition* ADJ3 optic atroph*).ti,ab	View Results (0)	Edit	
☐ 71	PsycINFO	(Toxic* ADJ3 optic neuropath*).ti,ab	View Results (12)	Edit	
☐ 72	PsycINFO	(Toxic* ADJ3 optic nerve*).ti,ab	View Results (8)	Edit	
☐ 73	PsycINFO	(Toxic* ADJ3 optic atroph*).ti,ab	View Results (2)	Edit	
☐ 75	PsycINFO	(Sleep ADJ3 qualit*).ti,ab	View Results (9,691)	Edit	
☐ 76	PsycINFO	(Sleep ADJ3 tim*).ti,ab	View Results (7,365)	Edit	
☐ 77	PsycINFO	(Wake ADJ3 tim*).ti,ab	View Results (1,300)	Edit	
☐ 78	PsycINFO	(Time in bed).ti,ab	View Results (2,615)	Edit	
☐ 79	PsycINFO	(Sleep onset).ti,ab	View Results (6,605)	Edit	
☐ 80	PsycINFO	(Sleep offset).ti,ab	View Results (231)	Edit	
☐ 81	PsycINFO	(Wake after sleep onset).ti,ab	View Results (1,110)	Edit	
☐ 82	PsycINFO	(WASO).ti,ab	View Results (310)	Edit	
☐ 83	PsycINFO	(Awakening*).ti,ab	View Results (6,456)	Edit	
☐ 84	PsycINFO	(Sleep ADJ3 duration).ti,ab	View Results (5,528)	Edit	
☐ 85	PsycINFO	(Sleep ADJ3 disturb*).ti,ab	View Results (10,924)	Edit	
☐ 86	PsycINFO	(Sleep ADJ3 efficien*).ti,ab	View Results (2,597)	Edit	
☐ 87	PsycINFO	(Daytime ADJ3 sleep*).ti,ab	View Results (4,840)	Edit	
☐ 88	PsycINFO	(Daytime ADJ3 dysfunction*).ti,ab	View Results (291)	Edit	
☐ 89	PsycINFO	(Sleep ADJ3 laten*).ti,ab	View Results (3,875)	Edit	
☐ 90	PsycINFO	(Chronotype*).ti,ab	View Results (1,087)	Edit	
☐ 91	PsycINFO	(Morningness ADJ3 Eveningness).ti,ab	View Results (853)	Edit	
☐ 92	PsycINFO	(Sleep ADJ3 disrupt*).ti,ab	View Results (2,484)	Edit	
☐ 93	PsycINFO	(Sleep* ADJ3 rhythm*).ti,ab	View Results (2,342)	Edit	
☐ 94	PsycINFO	(Sleep* ADJ3 pattern*).ti,ab	View Results (4,916)	Edit	
☐ 95	PsycINFO	(Sleep* ADJ3 disorder*).ti,ab	View Results (11,264)	Edit	
☐ 96	PsycINFO	(Insomnia*).ti,ab	View Results (13,305)	Edit	
☐ 97	PsycINFO	(Somnolen*).ti,ab	View Results (1,874)	Edit	

Figure 18c

98	PsycINFO	(Hypersomnolen*).ti,ab	View Results (248)	Edit	
99	PsycINFO	(Rapid Eye Movement*).ti,ab	View Results (4,982)	Edit	
100	PsycINFO	(REM*).ti,ab	View Results (332,424)	Edit	
101	PsycINFO	(Sleep* ADJ3 stage*).ti,ab	View Results (3,423)	Edit	
102	PsycINFO	(Bedtime*).ti,ab	View Results (2,816)	Edit	
103	PsycINFO	(Bed-time*).ti,ab	View Results (146)	Edit	
104	PsycINFO	(Bed ADJ3 time*).ti,ab	View Results (1,009)	Edit	
105	PsycINFO	(Glaucoma*).ti,ab	View Results (1,003)	Edit	
106	PsycINFO	(Normal tension glaucoma*).ti,ab	View Results (18)	Edit	
107	PsycINFO	(Primary open angle glaucoma*).ti,ab	View Results (84)	Edit	
108	PsycINFO	(POAG).ti,ab	View Results (45)	Edit	
109	PsycINFO	(Primary angle closure glaucoma*).ti,ab	View Results (16)	Edit	
110	PsycINFO	(PACG).ti,ab	View Results (10)	Edit	
111	PsycINFO	(Chronic open angle glaucoma*).ti,ab	View Results (17)	Edit	
112	PsycINFO	(Chronic angle closure).ti,ab	View Results (5)	Edit	
113	PsycINFO	(Infantile glaucoma*).ti,ab	View Results (5)	Edit	
114	PsycINFO	(Juvenile glaucoma*).ti,ab	View Results (1)	Edit	
115	PsycINFO	(Paediatric glaucoma*).ti,ab	View Results (3)	Edit	
116	PsycINFO	(Pediatric glaucoma*).ti,ab	View Results (3)	Edit	
117	PsycINFO	(Pseudoexfoliati* glaucoma*).ti,ab	View Results (3)	Edit	
118	PsycINFO	(Secondary glaucoma*).ti,ab	View Results (21)	Edit	
120	PsycINFO	*(105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118)*	View Results (1,005)		
121	PsycINFO	*(75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104)*	View Results (382,050)		
123	PsycINFO	*(120 AND 121)*	View Results (127)		

Figure 18d

124	PsycINFO	*(1 OR 3 OR 4 OR 6 OR 8 OR 9 OR 10 OR 12 OR 13 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 25 OR 26 OR 27 OR 29 OR 30 OR 32 OR 33)*	View Results (3,647)		
125	PsycINFO	*(34 OR 35 OR 37 OR 38 OR 39 OR 41 OR 43 OR 45 OR 46 OR 47 OR 48 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57)*	View Results (95)		
126	PsycINFO	*(58 OR 59 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73)*	View Results (353)		
127	PsycINFO	*(121 AND 124)*	View Results (504)		
128	PsycINFO	*(121 AND 125)*	View Results (13)		
129	PsycINFO	*(121 AND 126)*	View Results (61)		

Figure 18e

Figure 19(a-e): PubMed Optic Nerve Disorders and Sleep Wake Search Terms

Current search strategy: Combined Searches PubMed 20.11.21

	Database(s)	Search Term		
1	PubMed	(Optic ADJ3 atroph*).ti,ab	View Results (4,788)	Edit
3	PubMed	(Congenital ADJ3 optic nerve*).ti,ab	View Results (68)	Edit
4	PubMed	(Optic nerve ADJ3 hypoplas*).ti,ab	View Results (679)	Edit
6	PubMed	(Septo-optic dysplas*).ti,ab	View Results (463)	Edit
8	PubMed	(De Morsier syndrome).ti,ab	View Results (45)	Edit
9	PubMed	(Retinopathy of prematurity).ti,ab	View Results (7,116)	Edit
10	PubMed	(Congenital glaucoma*).ti,ab	View Results (1,845)	Edit
12	PubMed	(Buphthalm*).ti,ab	View Results (438)	Edit
13	PubMed	(Hereditary ADJ3 optic nerve*).ti,ab	View Results (12)	Edit
15	PubMed	(Leber hereditary optic neuropathy).ti,ab	View Results (617)	Edit
16	PubMed	(LHON).ti,ab	View Results (1,114)	Edit
17	PubMed	(Dominant optic atroph*).ti,ab	View Results (486)	Edit
18	PubMed	(Kjer*).ti,ab	View Results (54)	Edit
19	PubMed	(Wolfram syndrome).ti,ab	View Results (612)	Edit
20	PubMed	(DIDMOAD).ti,ab	View Results (184)	Edit
21	PubMed	(Autoimmune ADJ3 optic nerve*).ti,ab	View Results (785)	Edit
22	PubMed	(Autoimmune ADJ3 optic neuropath*).ti,ab	View Results (20)	Edit
23	PubMed	(Neuromyelitis optica).ti,ab	View Results (4,796)	Edit
25	PubMed	(NMOSD).ti,ab	View Results (1,650)	Edit
26	PubMed	(Devic* disease).ti,ab	View Results (42,320)	Edit
27	PubMed	(Demyelinat* ADJ3 optic nerve*).ti,ab	View Results (1,273)	Edit
29	PubMed	(Demyelinat* ADJ3 optic neuropath*).ti,ab	View Results (271)	Edit
30	PubMed	(Acute disseminated encephalomyeliti*).ti,ab	View Results (1,950)	Edit
32	PubMed	(Chronic relapsing inflammatory optic neuritis).ti,ab	View Results (10)	Edit
33	PubMed	(CRION).ti,ab	View Results (36)	Edit
34	PubMed	(Optic chiasm* ADJ3 compress*).ti,ab	View Results (633)	Edit

Figure 19a

35	PubMed	(Pituitary adenoma* ADJ3 optic chiasm*).ti,ab	View Results (304)	Edit	
37	PubMed	(Pituitary microadenoma* ADJ3 optic chiasm*).ti,ab	View Results (7)	Edit	
38	PubMed	(Pituitary macroadenoma* ADJ3 optic chiasm*).ti,ab	View Results (98)	Edit	
39	PubMed	(Craniopharyngioma* ADJ3 optic chiasm*).ti,ab	View Results (191)	Edit	
41	PubMed	(Optic nerve* ADJ3 meningioma*).ti,ab	View Results (1,022)	Edit	
43	PubMed	(Optic nerve* ADJ3 glioma*).ti,ab	View Results (1,340)	Edit	
45	PubMed	(Infiltrat* ADJ3 optic neuropath*).ti,ab	View Results (204)	Edit	
46	PubMed	(Infiltrat* ADJ3 optic nerve*).ti,ab	View Results (902)	Edit	
47	PubMed	(Vascular ADJ3 optic neuropath*).ti,ab	View Results (16)	Edit	
48	PubMed	(Vascular ADJ3 optic nerve*).ti,ab	View Results (6)	Edit	
50	PubMed	(Anterior ischaemic optic neuropath*).ti,ab	View Results (305)	Edit	
51	PubMed	(Anterior ischaemic optic neuropath*).ti,ab	View Results (305)	Edit	
52	PubMed	(AION).ti,ab	View Results (398)	Edit	
53	PubMed	(Non-arteritic ischaemic optic neuropath*).ti,ab	View Results (33)	Edit	
54	PubMed	(Non-arteritic ischemic optic neuropath*).ti,ab	View Results (65)	Edit	
55	PubMed	(NAION).ti,ab	View Results (571)	Edit	
56	PubMed	(Posterior ischaemic optic neuropath*).ti,ab	View Results (27)	Edit	
57	PubMed	(Posterior ischemic optic neuropath*).ti,ab	View Results (164)	Edit	
58	PubMed	(Traumatic optic neuropath*).ti,ab	View Results (515)	Edit	
59	PubMed	(Trauma* ADJ3 optic nerve*).ti,ab	View Results (1,734)	Edit	
61	PubMed	(Transect* ADJ3 optic nerve*).ti,ab	View Results (813)	Edit	
62	PubMed	(Compress* ADJ3 optic nerve*).ti,ab	View Results (1,537)	Edit	
63	PubMed	(Crush* ADJ3 optic nerve*).ti,ab	View Results (1,230)	Edit	
64	PubMed	(Degenerat* ADJ3 optic nerve*).ti,ab	View Results (3,238)	Edit	
65	PubMed	(Neurodegenerat* ADJ3 optic nerve*).ti,ab	View Results (1,093)	Edit	
66	PubMed	(Alzheimer* ADJ3 optic nerve*).ti,ab	View Results (211)	Edit	
67	PubMed	(Parkinson* ADJ3 optic nerve*).ti,ab	View Results (97)	Edit	
68	PubMed	(Nutrition* ADJ3 optic neuropath*).ti,ab	View Results (177)	Edit	

Figure 19b

69	PubMed	(Nutrition* ADJ3 optic nerve*).ti,ab	View Results (198)	Edit	
70	PubMed	(Nutrition* ADJ3 optic atroph*).ti,ab	View Results (71)	Edit	
71	PubMed	(Toxic* ADJ3 optic neuropath*).ti,ab	View Results (617)	Edit	
72	PubMed	(Toxic* ADJ3 optic nerve*).ti,ab	View Results (1,074)	Edit	
73	PubMed	(Toxic* ADJ3 optic atroph*).ti,ab	View Results (182)	Edit	
75	PubMed	(Sleep ADJ3 qualit*).ti,ab	View Results (18,578)	Edit	
76	PubMed	(Sleep ADJ3 tim*).ti,ab	View Results (8,313)	Edit	
77	PubMed	(Wake ADJ3 tim*).ti,ab	View Results (5,270)	Edit	
78	PubMed	(Time in bed).ti,ab	View Results (986)	Edit	
79	PubMed	(Sleep onset).ti,ab	View Results (5,715)	Edit	
80	PubMed	(Sleep offset).ti,ab	View Results (116)	Edit	
81	PubMed	(Wake after sleep onset).ti,ab	View Results (1,129)	Edit	
82	PubMed	(WASO).ti,ab	View Results (614)	Edit	
83	PubMed	(Awakening*).ti,ab	View Results (11,233)	Edit	
84	PubMed	(Sleep ADJ3 duration).ti,ab	View Results (9,669)	Edit	
85	PubMed	(Sleep ADJ3 disturb*).ti,ab	View Results (17,946)	Edit	
86	PubMed	(Sleep ADJ3 efficien*).ti,ab	View Results (4,839)	Edit	
87	PubMed	(Daytime ADJ3 sleep*).ti,ab	View Results (8,790)	Edit	
88	PubMed	(Daytime ADJ3 dysfunction*).ti,ab	View Results (551)	Edit	
89	PubMed	(Sleep ADJ3 laten*).ti,ab	View Results (4,589)	Edit	
90	PubMed	(Chronotype*).ti,ab	View Results (1,642)	Edit	
91	PubMed	(Morningness ADJ3 Eveningness).ti,ab	View Results (836)	Edit	
92	PubMed	(Sleep ADJ3 disrupt*).ti,ab	View Results (2,301)	Edit	
93	PubMed	(Sleep* ADJ3 rhythm*).ti,ab	View Results (13,411)	Edit	
94	PubMed	(Sleep* ADJ3 pattern*).ti,ab	View Results (22,749)	Edit	
95	PubMed	(Sleep* ADJ3 disorder*).ti,ab	View Results (54,505)	Edit	
96	PubMed	(Insomnia*).ti,ab	View Results (24,982)	Edit	
97	PubMed	(Somnolen*).ti,ab	View Results (6,322)	Edit	

Figure 19c

98	PubMed	(Hypersomnolen*).ti,ab	View Results (748)	Edit	
99	PubMed	(Rapid Eye Movement*).ti,ab	View Results (11,207)	Edit	
100	PubMed	(REM*).ti,ab	View Results (2,270,683)	Edit	
101	PubMed	(Sleep* ADJ3 stage*).ti,ab	View Results (15,204)	Edit	
102	PubMed	(Bedtime*).ti,ab	View Results (6,112)	Edit	
103	PubMed	(Bed-time*).ti,ab	View Results (454)	Edit	
104	PubMed	(Bed ADJ3 time*).ti,ab	View Results (454)	Edit	
105	PubMed	(Glaucoma*).ti,ab	View Results (65,656)	Edit	
106	PubMed	(Normal tension glaucoma*).ti,ab	View Results (1,917)	Edit	
107	PubMed	(Primary open angle glaucoma*).ti,ab	View Results (7,886)	Edit	
108	PubMed	(POAG).ti,ab	View Results (4,229)	Edit	
109	PubMed	(Primary angle closure glaucoma*).ti,ab	View Results (1,305)	Edit	
110	PubMed	(PACG).ti,ab	View Results (815)	Edit	
111	PubMed	(Chronic open angle glaucoma*).ti,ab	View Results (599)	Edit	
112	PubMed	(Chronic angle closure).ti,ab	View Results (365)	Edit	
113	PubMed	(Infantile glaucoma*).ti,ab	View Results (164)	Edit	
114	PubMed	(Juvenile glaucoma*).ti,ab	View Results (267)	Edit	
115	PubMed	(Paediatric glaucoma*).ti,ab	View Results (51)	Edit	
116	PubMed	(Pediatric glaucoma*).ti,ab	View Results (264)	Edit	
117	PubMed	(Pseudoexfoliati* glaucoma*).ti,ab	View Results (1,378)	Edit	
118	PubMed	(Secondary glaucoma*).ti,ab	View Results (2,378)	Edit	
119	PubMed	*(105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113 OR 114 OR 115 OR 116 OR 117 OR 118)*	View Results (65,706)		
120	PubMed	*(75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104)*	View Results (2,396,134)		
121	PubMed	*(119 AND 120)*	View Results (5,207)		

Figure 19d

122	PubMed	*(1 OR 3 OR 4 OR 6 OR 8 OR 9 OR 10 OR 12 OR 13 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20)*	View Results (16,543)		
123	PubMed	*(120 AND 122)*	View Results (1,618)		
124	PubMed	*(21 OR 22 OR 23 OR 25 OR 26 OR 27 OR 29 OR 30 OR 32 OR 33)*	View Results (49,953)		
125	PubMed	*(120 AND 124)*	View Results (7,028)		
126	PubMed	*(34 OR 35 OR 37 OR 38 OR 39 OR 41 OR 43 OR 45 OR 46)*	View Results (4,025)		
127	PubMed	*(120 AND 126)*	View Results (513)		
128	PubMed	*(47 OR 48 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57)*	View Results (1,329)		
129	PubMed	*(120 AND 128)*	View Results (158)		
130	PubMed	*(58 OR 59 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73)*	View Results (9,615)		
131	PubMed	*(120 AND 130)*	View Results (1,235)		

Figure 19e

Appendix C: Full Results of Systematic Literature Search

Table 16: Systematic Literature Search Results in Detail

Author(s)	Pathology Type	Subjects	Study Design	Findings	Comments
1. Prihodova et al (2021)(1028)	LHON and DOA	n=36 with genetically confirmed LHON or DOA of whom n=13 with unilateral or bilateral VI (n=10 LHON, n=3 DOA), and n=23 asymptomatic (non-VI)	Cross-sectional study	PSQI: No difference in scores between VI group (7.2±3,6) and non-VI group (8.2±6.5) (p>0.05) ESS: No difference in scores between VI group (3.5±2.6) and non-VI group (8.1±3.9) (p>0.05) PSG: No correlation with subjective sleep data (p>0.05). Sleep structure, AHI (OSA) and PLM similar to published values for general population (p>0.05)	Non-VI subjects were relatives of those with VI which may have contaminated results if they lived in the same house or were carers for VI subjects No true control group Non-VI group included children (n=6) who did not complete PSQI or ESS Large age distribution of sample
2. La Morgia et al (2010)(1034)	LHON and DOA	n=9 with HON (n=5 with LHON, n=4 with Kjer DOA). Controls: n=9 with normal vision Immunostaining of postmortem subjects' retinae (2 with LHON, 1 with DOA, 3 controls)	Cross-sectional study	PSQI: Positive correlation with absolute % difference of melatonin suppression in subjects with HON and controls (p=0.019) ESS, MEQ, Berlin Questionnaire, Zung depression and anxiety scale: No differences found between subjects with HON and controls (p>0.05) SF-36: Physical functioning and pain components worse in HON (P<0.05) MNST: Melatonin levels higher in HON (p=0.05). Suppression of melatonin with blue light in HON and controls (p<0.005, p<0.0001 respectively). Magnitude of melatonin suppression comparable between groups (p>0.05) Post-mortem subjects demonstrated sparing of pRGCs in DOA and LHON	Extensive ophthalmological examination including VA, VF, PLR, OCT RNFL carried out on subjects with HON Small sample size

				similar to that of controls, despite dramatic loss of total RGCs in DOA and LHON	
3.Munch et al (2015)(280)	HON and OAG	n=11 with HON, n=11 with chronic OAG Controls: n=11 age-matched to HON subjects; n=11 age-matched to OAG subjects	Cross-sectional study	Subjective sleepiness: OAG subjects became sleepier during light exposure than controls (p=0.016); comparable in HON and controls (p=0.7) PSQI: Worse scores in HON and OAG than controls (p<0.041) MNST: Similar in HON and OAG compared to controls (p=0.70, p=0.72 respectively) PLR: Post red light larger MPS and SPS in OAG compared to controls (both p<0.009), other findings comparable (p>0.08) Post-blue light OAG had larger MPS (p<0.03), SPS (p=0.002) and PSPS (0.007) than controls. MPS larger in HON than controls (p=0.041). Other findings between HON and controls comparable (p>0.2) Association of smaller blue light PSPS with melatonin suppression (p=0.002)	Extensive ophthalmological examination including VA, VF, pupil responses, OCT RNFL VA worse in HON compared to OAG (p=0.005) OAG group older than HON (p<0.009) Small numbers
4.Flynn-Evans et al (2014)(1035)	Sample included OA and glaucoma	n=127 blind female subjects, of whom n=6 had OA and n=8 had glaucoma	Cross-sectional study	Sleep diaries and urinary aMT6s: 57% of OA and glaucoma subjects normally entrained Of OA and glaucoma subjects with NPL vision, 50% normally entrained and 50%	No NS control group Small numbers of subjects with OA and glaucoma Descriptive statistics of entrainment only

				either abnormally entrained or non-entrained	
5.Lockley et al (1997)(1036)	Sample contains congenital glaucoma (buphthalmos, TON and congenital OA)	n=15 registered blind subjects, of whom n=1 had buphthalmos, with VA of NPL and one eye absent; n=1 had TON with both eyes present and NPL vision; and n=1 had congenital optic atrophy with VA≥3/60	Cross-sectional study	PSQI: Score of 5 in subject with buphthalmos; 14 in subject with TON; 7 in subject with congenital OA Melatonin (aMT6s) rhythms: Abnormally entrained in subjects with congenital OA and TON; FR in subject with buphthalmos	No control group Small number of subjects with OND/glaucoma
6.Adeoti (2010)(1037)	Sample includes glaucoma and OA	n=170 with BCVA poorer than 3/60 in better eye, of which, n=56 had glaucoma and n=10 had OA	Cross-sectional study	PSQI: Mean score 8.6±3.1 in subjects with glaucoma, and 9.9±3.4 in subjects with OA Daytime napping found in 62.5% with glaucoma and 50% with OA. Short sleep duration found in 50% with glaucoma and 60% with OA. Interrupted sleep found in 30.35% with glaucoma and 20% with OA subjects. Increased SL found in 21.43% of glaucoma and 0% of OA subjects. Cause of blindness associated with prevalence of sleep wake disorder (p=0.007)	No control group Non-validated questionnaire used to collect data on daytime napping, sleep duration, sleep interruption and SL, reduced generalisability Type of glaucoma not stated

7.Tabandeh et al (1998)(15)	Sample includes OND/glaucoma as a combined group	n=403 blind subjects VA<20/200 or VF<5°, of whom n=45 had optic nerve disease including glaucoma n=44 normally sighted controls	Cross-sectional study	PSQI: Mean score 6.6±4.3 in subjects with optic nerve/glaucoma compared to 2.9±0.5 in control subjects. Correlation of sleep quality with extent of visual loss (NPL vision vs PL or better vision vs controls (p<0.001))	Subjects as young as 9y recruited, sleep patterns can differ between children and adults No group demographics published No statistical analysis between ocular pathologies published
8.Wee & Van Gelder (2004)(114)	OND (questionable classification)	n=11 with VI due to OND/glaucoma (n=4 ROP, n=2 ONH, n=1 TON, n=4 glaucoma) and n=14 with VI due to other causes Controls: n=12 NS	Cross-sectional study	Sleep quality questionnaire: Comparable scores between groups Actigraphy: Higher total nap time, wake-up time instability, and SL in OND compared to non-OND and NS controls (p<0.01, p=0.02, p=0.02 respectively)	Sleep quality questionnaire not validated Subjects with VI lived in residential school with a campus morning alarm vs control subjects who lived in a residential school but set own alarm
9.Bischoff et al (2015)(305)	WS	n=19 with WS, of whom n=18 had OA Controls: n=25 with T1DM, n=25 healthy controls	Cross-sectional study	PSQ (in n=4 with WS <18y): More symptoms reported for WS (p=0.001). Increased sleepiness in WS (p=0.01). Subjects with WS more at risk of sleep problems (p<0.01) Behavioural interview: n=6 with WS diagnosed with hypersomnolence disorder	No ophthalmological examination reported PSQI performed in n=5 subjects with WS over 18, but this data was not reported Small sample
10.Webb et al (2010)(1038)	SOD	n=6 children with SOD; n=10 age- and sex-matched healthy children	Cross-sectional study	Sleep diary and actigraphy: Reduced SE in SOD compared to controls (p<0.001) 24-h plasma melatonin profiles: Lack of circadian rhythmicity and no melatonin	Small numbers Assessment of VA but not VF

				production in 2 children with SOD (both of whom had VA≥2.5mm object at 30cm)	Pituitary dysfunction and maldevelopment of SCN in SOD can cause sleep wake disturbances
11.Rech et al (2020)(1039)	BBSOAS	54 subjects with BBSOAS, mean age 12.4 years	Collection of case reports	Parent-reported sleep difficulties in 61% of sample (longer SL, disturbed sleep, early morning waking)	BBSOAS is a multi-system disorder, so many other factors could influence sleep No control group No standardised sleep questionnaires Mean age of sample 12.4 years – children have different sleep patterns to adults
12.Pickering et al (2014)(974)	CP	n=15 with treated CP Controls: n=15 matched subjects	Cross-sectional study	PSQI: Increased SL and daytime dysfunction in CP (p=0.04, p=0.05 respectively) ESS: Trend towards increased daytime sleepiness in CP (p=0.06) SF-36: Lower general health scores in CP (p=0.01). Mental and physical component scores comparable between groups (p>0.05) Actigraphy: Earlier morning wake times in CP (p=0.01). Serum melatonin: Low midnight levels associated with reduced TST, night sleep, SE and low activity counts in CP (p=0.03, p=0.03, p=0.02, p=0.04 respectively)	Subjects with NPL vision excluded No visual assessment recorded Endocrine dysfunction and hypothalamic injury can also affect sleep in CP
13.Joustra et al (2014)(1040)	NFMA and CP	17 with NFMA, 17 healthy controls, 8 CP	Exploratory study (cross-sectional)	VFD present in 82% of NFMA and 88% of CP subjects	Presence of VFD stated, but no detailed information on visual function

				Berlin Questionnaire: Impaired sleep quality in NFMA and CP ($p<0.05$; $p=0.004$ respectively) CSS: Impaired sleep quality in NFMA and CP ($p<0.05$; $p=0.01$) ESS: Increased daytime sleep propensity in CP ($p=0.02$) MFI: Increased general fatigue, physical fatigue, physical activity and motivational activity in CP ($p=0.008$; $p=0.001$; $p=0.015$; $p=0.007$ respectively) SF-36: Poorer physical function in NFMA and CP ($p<0.05$; $p=0.001$). Poorer social function and health perception in CP ($p=0.017$; $p=0.034$)	
14.Sagan et al (2021)(1041)	PA	29 subjects with PA, of whom 15 had OCC	Interventional study pre- and several months post transsphenoidal resection	PSQI: Improved sleep quality, sleep duration and SE post resection in subjects with OCC ($p<0.05$ for all. Comparable scores for SL, sleep disturbances, use of sleeping medications and daytime dysfunction post-resection in subjects with OCC ($p>0.05$ for all) ESS: Comparable scores pre- and post-resection in subjects with OCC ($p>0.05$) SF-36: In OCC: Correlation of ESS with bodily pain and mental health scores ($p<0.05$ for both), but no correlation with PSQI ($p>0.05$). Correlation of PSQI with general health, physical function	No visual assessment recorded Small sample Other causes for sleep disturbance in PA, including hormonal, psychiatric and compression of SCN No healthy control group with no history of PA or CP

				and social function in subjects without OCC (P<0.05 for all)	
15.Romeijn et al (2012)(1042)	Tumour with suprasellar extension and pituitary insufficiency with or without OCC	n=33 with OCC (associated VFD or progressive loss of VA); n=17 without OCC	Cross-sectional study	PSQI: Later bedtimes in OCC compared to those without OCC (p=0.03). Comparable get up time, SL, sleep duration, SE and daytime dysfunction between groups (p>0.05) ESS: Comparable between groups (p=0.71) 24-hour skin temperature: Daytime proximal temperature and bedtime proximal to distal temperature gradient lower in OCC (p=0.03, p=0.04)	No ophthalmological assessment recorded No healthy control group without pituitary insufficiency
16.Borgers et al (2011)(1043)	(Para)sellar tumour with pituitary insufficiency with or without OCC	n=38 with OCC (associated VFD or progressive loss of VA); n=18 without OCC	Cross-sectional study	PSQI: Comparable global PSQI scores (p=0.238). Later habitual bedtime in OCC (p=0.044) ESS: Comparable scores (p=0.879) AIS comparable scores (p=0.279) Actigraphy: Shorter TST and later sleep onset in OCC (p=0.034, p=0.020 respectively). History of radiotherapy and surgery associated with longer TST (p=0.010, p=0.007 respectively). History of OCC associated with shorter TST (p=0.006). Age associated with TST (p=0.003)	No ophthalmological assessment recorded More males and higher BMI in OCC group (p=0.021, p=0.023 respectively) Lower proportion of subjects had undergone radiotherapy in OCC group (p=0.012) No healthy control group without pituitary insufficiency
17.DelRosso et al (2014)(468)	TON	38-year-old female with bilateral optic nerve and optic chiasm damage	Case report	Modified ESS: Score 10/18 PSG: TST 325 min, SL 48 min, WASO 143 min, SE 52%	Single subject Pupils dilated and unreactive but no confirmation of VA

				Hypnogram: Multiple nocturnal awakenings	
18.Tian et al (2014)(1044)	TON: IOFB touching optic nerve	n=5 subjects with IOFB who underwent lateral orbitotomy for removal	Case series	Sleep difficulties in n=2 subjects with IOFB, which improved following removal Anxiety in n=3 subjects with IOFB which resolved following removal VA improved in n=3 subjects following IOFB removal	Method of evaluating sleep not reported Small numbers No control group Timing of postoperative follow up not stated – unable to ascertain whether reported sleep and anxiety improvements were short or long term
19.Tsika et al (2015)(1045)	AION	n=8 with bilateral AION (n=7 with ODD, n=1 with NAION); n=10 with unilateral AION (all 10 NAION) n=29 age-matched NS controls	Cross-sectional study	PSQI: No difference between unilateral AION, bilateral AION and control groups (p=0.27) MEQ: Unilateral AION and control subjects generally morning types. Bilateral AION generally intermediate type RNFL: Reduced in affected vs unaffected eyes in unilateral AION (p=0.0001) PLR: At high light intensities of 2.0log cd/m^2, difference in PSPS found between groups (p=0.001) but not at lower light intensities of 1.0log cd/m^2 or 1.5 log cd/m^2 (p=0.2, p=0.3 respectively). Larger median PSPS in affected vs unaffected eyes in unilateral AION group (p=0.005) and in affected vs control eyes (p=0.003)	Detailed ophthalmological data collected: VA, VF MD, RAPD, OCT RNFL Small numbers No statistical analysis of MEQ
20.Hishikawa et al (2019)(1046)	SMON	106 with SMON, 110 age- and sex-matched controls	Cross-sectional study	PSQI: 75.6% SMON vs 39.6% controls poor sleep quality. All subscale components worse in SMON (sleep	Mean age of sample for SMON 80.8y and controls 81.4y. Generalised sleep disturbance more common in elderly

				quality (p<0.01), SL (p<0.05), sleep duration (p<0.05), (p<0.01), SE (p<0.01), sleep disturbance (p<0.01), sleep medication use (p<0.01), daytime dysfunction (p<0.01) AIS: 89.6% SMON vs 54.4% controls experience insomnia. All subscale components worse in SMON (sleep induction, awakening during the night, final awakening, total sleep duration, sleep quality, wellbeing during the day, functioning capacity during the day, sleepiness during the day (all p<0.01)) ESS: Excessive daytime sleepiness in 34.0% SMON vs 9.0% controls. All subscale components worse in SMON (sleepiness when talking (p<0.05), watching TV (p<0.01), sitting quietly after lunch (p<0.01), lying down to rest in the afternoon (p<0.01), passenger in a car (p<0.01)) Frequent sleep medication use in 29.8% SMON vs 11.7% controls RBD global score similar between SMON and controls (p>0.05). RBD subscales of "dreams matching nocturnal behaviour" and "limb movements" (p<0.05 for both) worse in SMON	No assessment of vision included SMON affects the optic nerves but is a whole body disorder including bladder and bowel dysfunction and pain Nocturia and dyspnoea higher in SMON – these may have affected non-circadian components of sleep
21.Turkoglu et al (2020)(1047)	MS with or without ON	Initial sample of 218 consecutive MS patients	Cross-sectional study	PSQI: Comparable between MON and SMS (p=0.326). Comparable between combined MON/SON vs rest of SMS group (p=0.467)	Small sample

		admitted to outpatient clinic 10 with ON as first MS event (MON); 16 age and gender matched MS subjects where ON was not first MS event (SMS), (including 8 who had later episodes of ON (SON))		ESS: Higher in MON compared to SMS (p=0.07). Higher in MON/SON vs rest of SMS group (p=0.027) PSG: Reduced SL, REML, TWT in MON compared to SMS (p=0.026, p=0.038, p<0.001 respectively). Increased SE and NREM duration in MON (p=0.023, p=0.022 respectively). Increased SE and NREM duration, reduced TWT in MON/SON vs rest of SMS group (p=0.030, p=0.014, p=0.004 respectively) Serum melatonin lower in MON (p=0.042), but not in MON/SON vs rest of SMS group (p=0.314) Serum orexin A lower in MON (p=0.042) but not in MON/SON vs rest of SMS group (p=0.427)	Longer MS duration in subjects with MON or SON compared to those without (p=0.027) Large number of original sample were excluded as they did not meet inclusion or exclusion criteria may have introduced bias No data on visual function No healthy control group
22.Barzegar et al (2018)(812)	NMOSD and MS	41 subjects with NMOSD, 136 age- and sex-matched subjects with MS	Cross-sectional study	History of ON in 30.1% of NMOSD and 59.4% of MS PSQI: No difference between groups (p>0.05). Sleep quality not affected by gender (p>0.05). Males with MS had poorer sleep quality than females with MS (P<0.05) Worse total depression, somatic depression and cognitive depression in NMOSD (p=0.004, p=0.011, p=0.001 respectively)	No visual assessment recorded No healthy control group; comparison between NMOSD and MS only Frequency of comorbidities higher in NMOSD

				Worse cognitive fatigue in NMOSD (p=0.006)	
23.Shi et al (2016)(1048)	NMOSD	n=73 with NMOSD	Cross-sectional study	PSQI: Mean score 7.74±4.4. 68% defined as poor sleepers (score >5) MSQOL-54: Correlation of PSQI with physical component score (p<0.01)	No visual assessment recorded No control group
24.Miao et al (2017)(1049)	NMOSD	42 subjects with stable NMOSD recruited from outpatient department	Cross-sectional study	PSQI: 64% prevalence of poor sleep in sample. Mean PSQI of sample 7.5±4.9. Correlation of PSQI score with depression (p=0.001), pain-affective descriptors (p=0.006) and EDSS (p=0.024).	No assessment of ocular involvement recorded No control group Several other features of NMOSD pathology (depression, anxiety, pain, level of disability) show association with sleep quality
25.Pan et al (2015)(1050)	NMOSD	n=33 with NMOSD (n=21 with fatigue and n=12 without fatigue) Controls: n=20 healthy subjects	Cross-sectional study	Fatigue score higher in NMOSD than controls (p=0.002). PSQI: Higher in NMOSD subjects (mean 9.2±1.2) with fatigue compared to those without fatigue (mean 5.8±1.0) (p=0.046) ESS: Higher in NMOSD subjects with fatigue (mean 7.3±1.3) compared to those without fatigue (mean 3.8±0.7) PSG: Association of NREM stage 3 with fatigue (p=0.033)	No ophthalmological assessment recorded
26.Seok et al (2017)(1026)	NMOSD with/without fatigue	n=25 NMOSD with fatigue, n=10 NMOSD without fatigue	Cross-sectional study	PSQI: Poorer sleep quality in NMOSD with fatigue (p=0.009). Higher proportion of PSQI>5 in NMOSD with fatigue (p=0.004)	No visual assessment recorded No healthy control comparison

				History of ON comparable between groups (p=0.829) BDI-II: Depression worse in NMOSD with fatigue (p=0.001) SF-36: Physical and mental component scores worse in NMOSD with fatigue (p=0.033, p=0.04 respectively)	
27.La Morgia et al (2016)(115)	AD	n= 16 with AD, n=10 age-matched controls Postmortem analysis: 17 with AD, 13 age-matched controls	Cross-sectional study	ESS/PSQI: Comparable subjective sleepiness/sleep quality between groups (p>0.05) OCT: RNFL thickness reduced in AD (p=0.04). Actigraphy: Reduced SE in AD (p=0.001), with lower variability in rest-activity between sleep and wake periods (p=0.041) Postmortem analysis: Reduced pRGC density in AD (p=0.003) and abnormal pRGC morphology. Correlation of pRGC number with age in controls, but not in AD (p=0.04, p=0.3 respectively). Dendrites smaller diameter in AD (p=0.003)	No assessment of VA or VF recorded Small numbers Details of control recruitment not stated
28.Leger et al (2002)(1051)	Sample included subjects with glaucoma (congenital or other)	n=26 blind subjects with NPL vision, negative pupillary reflexes and negative ERG, and FR rhythm, of whom	Cross-sectional study	PSQI: All subjects with glaucoma (n=8) had PSQI>5, of whom n=6 subjects had PSQI>10 PSG: Blind subjects (n=26) had lower TST and SE than controls (p=0.0001 for both)	Control group did not complete PSQI, participated in PSG only Blind subjects selected on basis of FR rhythm Small number of subjects with glaucoma

		n=8 had glaucoma n=24 age- and sex-matched controls			
29.Gubin et al (2021)(1052)	POAG	n=65 with S-POAG; n=50 with A-POAG	Interventional cross-sectional study (pre-and post-90 days of 2mg slow-release melatonin	Sleep diaries at baseline: Mean sleep duration shorter in A-POAG ($p<0.01$); Mean sleep phase longer in A-POAG ($p=0.02$) PSQI post intervention scores better for all components (duration, quality, efficiency, latency) in S-POAG and A-POAG ($p<0.01$ for all scores)	Detailed visual assessment – VF MD, IOP, PERG, OCT GCC No healthy control group Analysis of PSQI scores between S-POAG and A-POAG not discussed Sleep wake in a 90 day interventional study may also be affected by seasonal changes
30.Gubin et al (2019)(1053)	POAG	Same sample as Gubin et al (2021) 115 subjects, 65 with S-POAG, 50 with A-POAG	Cross-sectional study	MEQ: A-POAG group more prone to morningness ($p<0.05$) RCG loss associated with disrupted (delayed phase) body temperature circadian rhythm ($P<0.00001$)	Ophthalmological assessment: IOP, OCT GCC (VA and VF not recorded) No healthy control group
31.Gracitelli et al (2016)(1054)	POAG	n=30 with POAG Controls: n=10 NS	Cross-sectional study	ESS: Mean ESS higher in glaucoma ($p=0.029$) Correlation between ESS and glaucoma severity ($p<0.001$) PSG: ESS associated with higher number of night-time arousals and arousal duration after falling asleep ($p=0.039$, $p<0.001$ respectively). Inverse correlation between ESS score and SE ($p=0.002$).	Detailed ophthalmological examination including VA, HVF, LogMAR, IOP, c:d ratio, central corneal thickness Subjective sleep quality not assessed (e.g. PSQI), daytime sleepiness (ESS) only

				PLR: Inverse correlation between ESS and peak and sustained responses to blue flash and sustained response to red flash (p=0.017, p=0.009, p=0.01)	
32.Lanzani et al (2012)(1055)	Bilateral advanced POAG	n=9 with bilateral advanced POAG (c:d ratio ≥0.8; MD<-12dB). Controls: n=9 normal subjects	Cross-sectional study	Sleep log and questionnaire: More glaucoma subjects (n=6) had poor subjective sleep quality compared to controls (n=1) Actigraphy: Longer wake times, less night time sleep and lower SE in subjects with glaucoma (p<0.05, p<0.05, p<0.01 respectively)	Detailed ophthalmological examination including VA, HVF, IOP and optic disc assessment Small numbers Controls included spouses and relatives Sleep questionnaire used not validated No statistical analysis of subjective sleep data
33.Ma et al (2018)(1056)	PACG, POAG	n=80 with PACG, n=120 with POAG Controls: n=120 normal subjects	Cross-sectional study	PSQI: Prevalence of sleep disorder higher in PACG than in POAG and controls (p=0.000 for both). Sleep disturbance associated with sex and worse eye IOP in glaucoma (p=0.02, p=0.03 respectively) Morning serum melatonin: Higher in PACG and POAG than in controls (p<0.001). No difference between PACG and POAG (p=0.216). Elevated levels associated with depression, anxiety and sleep disturbance in glaucoma (p=0.00 for all)	Ophthalmological examination of subjects with glaucoma, but only IOP details recorded. No VF or optic disc assessment performed PSQI>7 taken to indicate poor sleep quality (standard cutoff is >6) Large sample
34.Wang et al (2013)(641)	POAG, PACG	n=92 with POAG; n=48 with PACG; n=210 healthy controls	Cross-sectional study	PSQI: Higher prevalence of sleep disorder in POAG than in controls (p<0.05)	Large numbers VF and IOP recorded, but not VA PSQI subgroups not discussed

				Higher prevalence of sleep disturbance in subjects with PACG aged 41-80y than in controls (p<0.001) Higher prevalence of sleep disturbance in subjects with PACG aged 61-80y than in controls (p<0.05) Decreased sleep quality with age in POAG and controls (p<0.05)	
35.Chin et al (2020)(1057)	POAG/PACG	79 with POAG, 27 with PACG, 89 healthy controls POAG/PACG subjects divided into mild (better eye VF MD>-6), moderate (better eye VF MD>-12) and severe (better eye VF MD<-12)	Cross-sectional study	PSQI: Median score higher in PACG than in POAG or controls (p=0.004) Higher proportion of PACG but not POAG with PSQI>5 (p=0.013, p=0.511 respectively) Subjects with PACG but not POAG had poorer sleep when VA≤6/15 (p=0.092, p=0.074 respectively) Adjusted for age, gender and possible depression, worse sleep quality in PACG but not POAG (p=0.016, p=0.819 respectively) and higher proportion with PSQI>5 in PACG (P>0.001) ESS: Comparable between PACG, POAG and controls (p=0.959) PHQ-2: Presence of depression associated with poorer sleep quality (p=0.015)	Assessment of VA and VF Underpowered study at 75% power
36.Bierings et al (2019)(1029)	OAG (POAG, PXF or	MCTQ sent to 221 with OAG, of whom 178 (81%)	Cross-sectional study	MCTQ: No major differences in measurements of mean sleep times	Primary control group were partners, friends and neighbours – data not clean as

	pigment dispersion)	replied and 19 did not meet study criteria. Remaining 159 with OAG stratified into 63% early glaucoma (better eye HVF MD >-6); 16% moderate glaucoma (better eye HVF MD >-12); 21% severe glaucoma (better eye HVF MD <-12); 163 primary controls; 17073 secondary controls		between OAG and primary control groups Larger variability in bedtimes, time to fall asleep, SL, minutes to get up after waking and hours spent outside in OAG group compared to primary controls, but did not reach significance (p>0.05) Mean distribution of MSF_{sc} comparable in OAG and primary controls (p>0.05) Mean MSF_{sc} earlier in OAG compared to secondary controls (p-0.024)	their sleep may be affected by sleep of subject with OAG Primary control group were younger (p<0.001), higher percentage females (p=0.005) and worked more days per week (p=0.004) than OAG group Visual field data used to stratify OAG subjects Bias due to unreturned questionnaires (19% of original sample)
37.Lee et al (2016)(1058)	OAG	368 subjects with OAG (3.91% prevalence) and 9042 control subjects who took part in KNHANES. Sample also divided into those with BMI≥25kg/m^2 and those with BMI<25kg/m^2; those with abdominal obesity and those without	Epidemiological study	Subjects who slept <5h/night had highest prevalence of glaucoma, followed by those who slept ≥9h/night (p=0.072 for trend) In subjects with BMI≥25kg/m^2, prevalence of glaucoma was highest in those who slept <5h/night, followed by those who slept ≥9h/night (U-shaped pattern) (p=0.056) In subjects with abdominal obesity, prevalence of glaucoma was highest in subjects who slept≥9h/night followed by those who slept <5h/night (U-shaped pattern) (p=0.022)	Ophthalmological exam including IOP, autorefraction, HVF, fundus photos Sleep-disordered breathing (associated with high BMI/abdominal obesity) may have influenced sleep quality and duration Sleep questionnaire not validated

		abdominal obesity			
38.Ahmadi et al (2020)(1030)	NTG	18 with NTG (3 excluded); 19 healthy controls (2 excluded)	Cross-sectional study	PSQI: Global score similar between groups (p=0.63); SE and sleep quality similar between groups (p=0.515, p=0.983 respectively) Pupillometry: Baseline consensual response to red and blue light smaller in NTG (p=0.024, p=0.006 respectively) Early and late blue light PIPR reduced in NTG (P<0.001 for both). Early red light PIPR reduced in NTG (p=0.009), but late red light PIPR similar (p-0.602). Pupillary constriction amplitude reduced for blue but not red light in NTG (p=0.02, p=0.06 respectively) Correlation between VF MD and RNFLT (p=0.01) but not between late PIPR and RNFLT or VF MD in NTG (p=0.02, p>0.05 respectively)	Detailed ophthalmological assessment including VA, VF MD, IOP, OCT RNFL, PLR, dilated fundus photography, documentation of refraction NTG group older than control group (p=0.031) 6 with NTG had history of cataract surgery which may have altered pupil responses VF MD of NTG group 9.05 (95% CI 5.75-12.35) indicating few subjects with severe glaucoma and pRGC loss Small sample size Details of 2 out of 3 control subjects excluded not given
39.Ayaki et al (2016)(1059)	Glaucoma	n=69 with glaucoma (cataract, dry eye, retinal pathology excluded) Controls: n=71 without VI	Cross-sectional study	PSQI: Global score and SL worse in advanced glaucoma (MD < -12dB) than in controls (p=0.02 and p=0.01 respectively) Global PSQI correlated with worse eye MD(p<0.05), number and frequency of medications (p<0.05), and HADS-D (p<0.001) but not RNFL thickness or c:d ratio (p>0.05) Earlier bedtime in advanced glaucoma than in controls (p=0.007)	Detailed ophthalmological examination including VA, HVF, IOP, OCT RNFL, biomicroscopy Type of glaucoma not specified Large number of exclusions from original sample of 200 subjects with glaucoma – possible bias

				HADS-D correlated with MD of worse and better eye and RNFL thickness in worst hemisphere ($p<0.01$, $p<0.05$, $P<0.05$ respectively)	
40.Agorastos et al (2013)(1060)	Glaucoma	n=49 with glaucoma with mild to severe VFD; n=37 with glaucoma and no VFD	Cross-sectional study	PSQI: Higher global score and sleep disturbance in VFD group ($p=0.046$, $p=0.022$ respectively); higher proportion of subjects with VFD with PSQI>5 ($p=0.005$). Higher time in minutes in bed before falling asleep in subjects with VFD ($p=0.011$) BDI-II: Higher proportion of subjects with VFD at least moderately depressed ($p=0.026$) STAI: Higher prevalence of trait anxiety in VFD ($p=0.046$)	Detailed ophthalmological examination, including VF and VA Glaucoma diagnoses not described No healthy control group
41.Ayaki et al (2015)(1027)	Sample includes glaucoma	n=109 with glaucoma as part of a wider survey of eye conditions (n=730)	Cross-sectional study	PSQI: >5 in 34.9% glaucoma subjects HADS: HADS ≥10 in 38.8% of glaucoma subjects. Age ($p<0.001$, $p=0.04$) and dry eye ($p=0.03$, $p=0.03$) correlated with worse PSQI and HADS scores respectively Presence of dry eye 32.9% in glaucoma subjects Mean LogMAR of better and worse eyes in subjects with glaucoma 0.08±0.20 and 0.00±0.11 respectively	No normally sighted control subjects Type of glaucoma not stated Good mean VA in subjects with glaucoma. No VF/pupil responses recorded Dry eye not excluded from glaucoma group
42.Qiu et al (2019)(1061)	Glaucoma (DDG and VFD-defined)	n=6784 with glaucoma from NHANES, of	Cross-sectional study	Outcome measure: NHANES sleep questionnaire	NHANES sleep questionnaire is not validated – poor generalisability

		whom n=3361 were excluded due to unknown DDG or VFD status (total after exclusions = 3423) Control group: 3742 healthy subjects		Odds of DDG higher in subjects who slept ≥10h/night (p=0.01) and those with SL of ≤9min or ≥30min (p<0.01) Odds of VFD higher in subjects who slept ≤3h/night or ≥10h/night (p=0.03, p<0.01 respectively) FOSQ: Worse daytime dysfunction in VFD (remembering things p<0.01; working on a hobby p<0.01)	Large numbers excluded Glaucoma defined by non-stereoscopic disc photographs or VFD rather than a full clinical assessment Self-report is likely to over-estimate sleep duration and SL
43.Jung & Park (2016)(1062)	Undiagnosed glaucoma	n=12079 >40 years, of whom 570 (4.27%) had undiagnosed glaucoma and 11,509 did not have glaucoma	Epidemiological survey	Glaucoma related to short (≤5h) or long (≥9h) sleep duration (p=0.041) Glaucoma associated with depressive mood (p=0.037) Symptoms of anxiety and depression higher in glaucoma (p<0.001) Worse BCVA associated with poorer QOL (p=0.021)	Detailed ophthalmological examination including VA, BCVA, fundus photo, disc assessment Sleep questionnaire not validated Subjects with glaucoma were older, more likely to be male, had higher BMI, were more likely to have chronic disease and had lower income and level of education than those without (p<0.05 for all)

Key: AION=Anterior ischaemic optic neuropathy; AIS=Athens Insomnia Scale; A-POAG=Advanced POAG; BCVA: Best-corrected visual acuity; BDI-II: Beck Depression Inventory Score-II; BBSOAS=Bosch-Boonstra-Schaaf optic atrophy syndrome; CI=Confidence interval; CP=Craniopharyngioma; CSS=Clinical Symptom Score for Sleep Disorders; DOA=Dominant optic atrophy; DDG=Disc-defined glaucoma; ERG=Electroretinography; ESS=Epworth Sleepiness Scale; FOSQ=Functional Outcomes of Sleep Questionnaire; FR=Free running; GCC=Ganglion cell complex; HADS=Hospital Anxiety and Depression Scale; HADS-A=HADS anxiety subscore; HADS-D=HADS depression subscore; HC=Healthy controls; HD-OCT=High definition optical coherence tomography; HON=Hereditary optic neuropathy; HVF=Humphrey visual field; IOFB=Intraorbital foreign body; KNHANES=Korean National Health and Nutrition Examination Survey; LE=Light exposure; LHON=Leber hereditary optic neuropathy; MCTQ=Munich ChronoType Questionnaire; MD=Mean deviation; MFI=Multiple Fatigue Index; MNST=Melatonin suppression test; MON=Optic neuritis as first MPS=Minimum pupil size; MS event; MSF_{sc}=Corrected mid sleep to account for shorter sleep duration during working week; NAION=Nonarteritic anterior ischaemic optic neuropathy; NFMA=Nonfunctioning pituitary macroadenoma; NHANES=National Health and Nutrition Examination Survey; NMOSD=Neuromyelitis optica spectrum disorder; NS=Normally sighted; NTG=Normal tension glaucoma; OA=Optic atrophy; OAG=Open angle glaucoma; OCC=Optic chiasm compression; ODD=Optic disc drusen; ON=Optic neuritis; OND=Optic nerve disorder; PA=Pituitary adenoma; PHQ-2=Patient Health Questionnaire-2; PIPR=Post-illumination pupil response; PLR=Pupillary light response; POAG=Primary open angle glaucoma; PSG=Polysomnography; PSQI=Pittsburgh Sleep Quality Index; PXF=Pseudoexfoliation; RBDSQ=REM Sleep Behaviour Disorder Screening Questionnaire; RNFL=Retinal nerve fibre layer; RNFLT=RNFL thickness; SE=Sleep efficiency; SF-36: Medical Outcomes Study Short-Form 36 Item Questionnaire; SL=Sleep latency; SMON=Subacute myelo-optic neuropathy; SMS=MS where first event was not optic neuritis; SON=Optic neuritis during course of MS rather than initial event; S-POAG=Stable POAG; SOD=Septo-optic dysplasia; SPS=Sustained pupil size; STAI=State Trait Anxiety Inventory; TON=Traumatic optic neuropathy; VA=Visual acuity; VF=Visual fields; VFD=Visual field defects; VI=Visual impairment; WASO=Wake after sleep onset

Appendix D: Front Sheet for Raw Data, Questionnaires, Patient Information Sheet and Consent Form

Effect of ocular disease on sleep and body clocks.

Site:…….

Study Number:……..

Diabetic Retinopathy:

R ☐ M ☐ P ☐ R ☐ M ☐ P ☐ ETDRS ☐ ☐

AMD:

Early ☐ Dry ☐ Wet ☐ Fovea involving: Yes ☐ No ☐

Glaucoma:

Primary Open Angle Glaucoma ☐ HVF MD: ☐ ☐

Inherited Eye Disease:

Diagnosis (based on EDTS i.e. “cone-rod dystrophy”) ……

Diagnosis (Clinical i.e.”Stargardt”) …… Electrophysiology report attached ☐

Goldmanns visual field area (natural log of V4e in cm2)…….

Optic Nerve Disease:

Diagnosis ……

Visual Field done Yes ☐ No ☐ HVF MD: ☐ ☐

Visual Acuity (preferred logMAR):

Right ☐

Left ☐

Comments, including medications/ cataract/ previous laser/other:

……
……
……
……
……
……

Appendix-1

Patient no: ☐ Questionnaire no: ☐

The Pittsburgh Sleep Quality Index

Instructions:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions on **both sides** of the paper.

During the past month,

1. What time have you usually gone to bed? _____

2. How long (in minutes) has it taken you to fall asleep each night? _____

3. What time have you usually gotten up in the morning? _____

4. How many hours of **actual sleep** do you get at night? (This may be different than the number of hours you spend in bed) _____

5. Please tick the appropriate box for each of the following questions:

During the past month, how often have you had trouble sleeping because you.....	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				

h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

Appendix-2

Patient No: ☐ **Questionnaire no:** ☐

JUPITER MEDICAL CENTER – Sleep Questionnaire

Date completed……

Please complete all questions. All questions are about your sleep over the last four weeks unless otherwise stated.

Falling asleep

1. What time do you usually fall asleep on a week night?

……..am/pm weekend night? ……am/pm

2. How much does this time vary during a typical month?

(earliest)……am/pm to ……..am/pm (latest)

3. How long does it usually take to fall asleep? …….minutes

4. How many nights a week does it take longer than 30 minutes to fall asleep?

☐ ☐ ☐ ☐

None 1-2 3-4 5 or more

5. How many nights a week does it take longer than 60 minutes

to fall asleep?

☐ ☐ ☐ ☐

None 1-2 3-4 5 or more

6. When falling asleep, or trying to sleep, are you frequently bothered by:

( ) Thoughts racing through your mind?

( ) Feel muscular tension?

( ) Feel afraid of not being able to sleep?

( ) Have any kind of pain or discomfort?

( ) Suddenly become awake or alert?

( ) Feeling sad or depressed?

( ) Have anxiety or worry about things?

( ) Feel unable to move?

( ) Have vivid, dream-like images or scenes?

( ) Feel afraid of the dark or anything else?

7. Have you ever had 'growing pains'?

☐ ☐

Occasionally Sometimes

(less than 1 time a month) (1-2 times a month)

☐ ☐ ☐

Frequently Only in the past Never

(1-2 times a week to daily)

8. Do you have uncomfortable or funny feelings (creeping, crawling, tingling) in your legs?

☐ Occasionally (less than 1 time a month)

☐ Sometimes (1-2 times a month)

☐ Frequently (1-2 times a week to daily)

☐ Only in the past

☐ Never

9. Do you ever:

	Yes	No	Don't Know
a. Notice funny feelings in your legs (or do they seem worse) when lying down or sitting?	☐	☐	☐
b. Have partial relief with movement (wiggling feet, toes, or walking)?	☐	☐	☐
c. Notice that the feeling is worse at night?	☐	☐	☐
d. Have a lot of fidgeting or wiggling of your feet or toes when sitting or lying down?	☐	☐	☐

e. Have repeated jerking movements in toes or legs or the whole body while sleeping? ☐ ☐ ☐

About your sleep

10. How many hours of sleep do you usually get each night?

.....hours

11. Does your nightly amount of sleep vary?

From…….to……..hours

12. How many times do you awaken each night? …….

13. On a usual night, what is your longest period of wakefulness? ……..

14. Adding all of your usual periods of wake together, how many hours of WAKE do you have each night?

……

15. If you are awake during the night, is it usually during the:

☐ 1st half of the night? ☐ 2nd half? ☐ No pattern

16. Do you snore on most nights (more than 3 times per week)?

☐ ☐

Yes No

17. Is your snoring loud (can it be heard through a door or wall)?

☐ ☐

Yes No

18. Do you ever stop breathing or gasp during sleep?

☐ ☐

Yes No

19. Do you occasionally doze or fall asleep during the day when you are not busy or active?

☐ ☐

Yes No

20. Are you frequently bothered by any of the following? (Please tick all that apply)

( ) Feeling afraid you won't fall back asleep after awakening?

( ) Have restless, disturbed sleep?

( ) Do you snore, snort, or gasp loudly?

( ) Feel your heart pounding during the night?

( ) Walk in your sleep?

( ) Wake up screaming, violent, or confused?

( ) Wet the bed?

( ) Grind teeth during the night?

( ) Wake up to urinate?

( ) Wake up with chest pain?

( ) Wake up due to hunger, or thirst?

( ) Wake up from bad dreams?

( ) Wake up due to noise or movement of bed partner?

( ) Sleep with someone else in your bed?

( ) Get up at night due to children, pets, family member?

( ) Do you stop breathing?

( ) Sweat a lot during the night?

( ) Fall out of bed while asleep?

( ) Have unusual movements while asleep?

( ) Have dreams?

( ) Wake because of heartburn or reflux (GERD)?

( ) Wake with restless, creepy, crawly legs or leg cramps?

( ) Wake up with shortness of breath, asthma, or choking?

( ) Wake up due to heat, cold, or noise?

( ) Wake up from too much light in the bedroom?

About waking up

21. What time do you usually awaken?.....am/pm

22. How long do you stay in bed, after awakening, before getting up? ……..minutes

23. Does your final awakening vary over a 30 day period?

Earliest:…….am/pm Latest:……am/pm

24. When waking up, do you often?

( ) Depend on an alarm to wake up?
( ) Sleep in more than 1 hour past usual wake time?
( ) Have vivid, dream like images when waking?
( ) Wake up with a headache?
( ) Wake up with a dry mouth?
( ) Have a hard time waking up?
( ) Feel unable to move (paralysed)?
( ) Wake up disoriented or confused?
( ) Wake up sick to your stomach?
( ) Wake up 1-2 hours earlier than you want to?

About daytime activities & alertness

25. How many naps do you take in a typical week? …….

If you do take naps, how long are your naps? ……

26. Are the naps refreshing and do they restore alertness?

☐ Yes ☐ No

Appendix-3

Patient no: ☐ **Questionnaire no:** ☐

General Health Questionnaire

Date completed:……..

General Part

Please complete all questions about yourself

1. Weight ……
2. Height:……

3. Current status: Please circle which describes you best.

Single (never married) Married Partnership

In a relationship Divorced Widowed

Separated

Children: Yes/No

4. Current living situation: Please circle which best describes your living situation:

Alone With Partner With Friends

With Family With Parents Other ……..

5. What type of accommodation do you live in:

House Nursing Home Supported Housing

Flat Shared Accommodation Hospital

6. What is the highest level of education you have ever completed? Please circle one.

Secondary school Polytechnic

Apprenticeship Bachelor degree (BSc/BA)

Grammar school Masters degree

Doctoral degree

Other, please describe:……..

Medical Part

7. Have you ever been told that you have high blood pressure?

Yes No

If Yes, please give details

.....
……..

8. Have you had any history of heart trouble?

Yes No

If Yes, please give details

……..
.....

9. Have you a family history of heart disease/stroke?

Yes No

If Yes, please give details

……
……..

10. Have you ever been told by a doctor that you have asthma?

Yes No

11. Do you suffer from a wheezy chest?

Yes No

12. Do you ever have pains in your heart and chest?

Yes No

13. Do you ever feel faint or have spells of dizziness?

Yes No

14. Has a doctor ever told you that you have a bone or joint problem which could be made worse by exercise?

Yes No

15. Have you been in hospital at all in the last two years?

Yes No

If Yes, please give reason and outcome

……
……..

16. Have you had any operations or major illness in the last 6 months?

Yes No

If Yes, please give details

……
…...

17. Are you undergoing treatment or having any regular medication at the moment?

Yes No

If Yes, please give details

……
……
……

18. Are you taking any pills or any other medicines, including inhalers, for any of the following:

Heart trouble/angina?……Yes/No

Chest pains or blood pressure?……..Yes/No

Asthma or other chest diseases?..... Yes/No

Contraceptives?..... Yes/No

Or for anything else?..... Yes/No

If Yes, please give full details:

……
……

19. Do you have any physical disabilities of any kind?

Yes No

If Yes, please give details

……
……

20. Have you ever suffered any complications from previous trials or treatments?

Yes No

If Yes, please give details

……
……

21. Do you suffer from any allergies?

Yes No

If Yes, please give details

……
……

22. Have you ever had an adverse reaction to a medicine or food?

Yes No

If Yes, please give details

……
……

23. What is your average weekly intake of alcohol?

……..units per week

(One unit is half a pint of beer/one glass of wine/one measure of spirits)

24. Has there been a time when you regularly consumed more than 14 units of alcohol per week?

Yes No

If Yes, please give details

……
……

25. How many cigarettes, cigars and/or tobacco do you smoke?

☐ ☐ ☐

None 1-5 a day 5-10 a day

☐ ☐

10-20 a day more than 20 per day

☐

Less than 10 a month

☐ Other (please specify)

……

26. Have you, or a member of your family, ever been told by a doctor that you had epilepsy problems?

Yes No

If Yes, please give details

……
……

27. Have you ever been diagnosed with a mental problem such as depression?

Yes No

If Yes, please specify

……
……

28. Have you done any shift work in the last year?

Yes No

29. Have you travelled across more than one time zone in the past 3 months?

Yes No

30. *(Women only)* Do you have regular menstrual cycles? (ranging in length from 26-35 days with a maximum of three days variation month to month).

Yes No

31. How often, on average, do you consume caffeine containing beverages or food? (coffee, tea, cola beverages, chocolate etc.)

Never ☐

Rarely (less than 10 times a month) ☐

Occasionally (less than 1 time per day) ☐

Sometimes (1-3 times per day) ☐

Frequently (3-7 times per day) ☐

Often (more than 7 times per day) ☐

Appendix-4

Patient no : **Questionnaire no :**

SF-36 QUESTIONNAIRE

Please answer the questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

◯ Excellent ◯ Very good ◯ Good ◯ Fair ◯ Poor

Compared to one year ago, how would you rate your health in general now?

◯ Much better now than one year ago

◯ Somewhat better now than one year ago

◯ About the same as one year ago

◯ Somewhat worse now than one year ago

◯ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Lifting or carrying groceries

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Climbing several flights of stairs

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Climbing one flight of stairs

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Bending, kneeling, or stooping

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Walking more than a mile

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Walking half a mile

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Walking one hundred yards

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

Bathing or dressing yourself

◯ Yes, limited a lot ◯ Yes, limited a little ◯ No, not limited at all

PHYSICAL HEALTH PROBLEMS:

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

Cut down the amount of time you spent on work or other activities

◯ Yes ◯ No

Accomplished less than you would like

◯ Yes ◯ No

Were limited in the kind of work or other activities

◯ Yes ◯ No

Had difficulty performing the work or other activities (for example, it took extra effort)

◯ Yes ◯ No

EMOTIONAL HEALTH PROBLEMS:

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

◯ Yes ◯ No

Accomplished less than you would like

◯ Yes ◯ No

Didn't do work or other activities as carefully as usual

◯ Yes ◯ No

SOCIAL ACTIVITIES:

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

◯ Not at all ◯ Slightly ◯ Moderately ◯ Quite a bit ◯ Extremely

PAIN:

How much bodily pain have you had during the <u>past 4 weeks</u>?

◯ None ◯ Very Mild ◯ Mild ◯ Moderate ◯ Severe ◯ Very Severe

During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

◯ Not at all ◯ A little bit ◯ Moderately ◯ Quite a bit ◯ Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the <u>last 4 weeks</u>. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of life?

◯ All of the time

◯ Most of the time

◯ A good bit of the time

◯ Some of the time

◯ A little bit of the time

◯ None of the time

Have you been a very nervous person?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

Have you felt so down in the dumps that nothing could cheer you up?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

Have you felt calm and peaceful?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

Did you have a lot of energy?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

Have you felt downhearted and blue?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

Did you feel worn out?

- ◯ All of the time
- ◯ Most of the time
- ◯ A good bit of the time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the time

Have you been a happy person?

◯ All of the time

◯ Most of the time

◯ A good bit of the time

◯ Some of the time

◯ A little bit of the time

◯ None of the time

Did you feel tired?

◯ All of the time

◯ Most of the time

◯ A good bit of the time

◯ Some of the time

◯ A little bit of the time

◯ None of the time

SOCIAL ACTIVITIES:

During the <u>past 4 weeks</u>, how much of the time has <u>your physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

◯ All of the time

◯ Most of the time

◯ Some of the time

◯ A little bit of the time

◯ None of the time

GENERAL HEALTH:

How TRUE or FALSE is each of the following statements for you?

I seem to get ill a little easier than other people

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

I am as healthy as anybody I know

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

I expect my health to get worse

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

My health is excellent

◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

Date ……..

Appendix-5

Patient no: ☐ **Questionnaire no:** ☐

MORNINGNESS-EVENINGNESS (LARK/OWL) QUESTIONNAIRE

Date completed: _____

INSTRUCTIONS

a) Please read each question very carefully before answering.
b) Answer all questions.
c) Answer questions in numerical order.
d) Each question should be answered independently of others. Do **NOT** go back and check your answers.
e) For some questions, you are required to respond by placing a cross alongside your answer. In such cases, select **ONE** answer only.

Question 1

Considering your feelings, at what time would you get up if you were entirely free to plan your day?

or earlier	**05:00 – 06:30**	**…..**
	06:31 – 07:45	**…..**
Time:	**07:46 – 09:45**	**…..**
	09:46 – 11:00	**…..**
	11:01 – 12:00 or later	**…..**

Question 2

Considering only your feelings, at what time would you go to bed if you were entirely free to plan your day?

	20:00 – 21:00	**…..**
	21:01 – 22:15	**…..**
	22:16 – 00:30	**…..**
Time:	**00:31 – 01:45**	**…..**
	01:46 – 03:00 or later	**…..**

Question 3

If there is a specific time for you at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?

a. Not at all dependent [ ]

b. Slightly dependent [ ]

c. Fairly dependent [ ]

d. Very dependent [ ]

Question 4

Assuming adequate environmental conditions, how easy do you find getting up in the morning?

a. Not at all easy [ ]

b. Slightly easy [ ]

c. Fairly easy [ ]

d. Very easy [ ]

Question 5

How alert do you feel during the first half hour after having woken in the morning?

a. Not at all alert [ ]

b. Slightly alert [ ]

c. Fairly alert [ ]

d. Very alert [ ]

Question 6

How is your appetite during the first half hour after having woken in the morning?

a. Not at all good [ ]

b. Slightly good [ ]

c. Fairly good [ ]

d. Very good [ ]

Question 7

During the first half hour after having woken in the morning, how tired do you feel?

a. Very tired [ ]

b. Slightly tired [ ]

c. Fairly refreshed [ ]

d. Very refreshed [ ]

Question 8

When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?

a. Seldom or never later [ ]

b. Less than one hour later [ ]

c. 1-2 hours later [ ]

d. More than 2 hours later [ ]

Question 9

You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him is between 07:00 and 08:00h. Bearing in mind nothing else but your own inclinations, how do you think you would perform?

a. Would be on good form [ ]

b. Would be on reasonable form [ ]

c. Would find it difficult [ ]

d. Would find it very difficult [ ]

Question 10

At what time in the evening do you feel tired and as a result in need of sleep?

Time: …….

Question 11

You wish to be at your peak for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day, and considering only your own "feeling best" - which ONE of the four testing times would you choose?

a. 08:00 – 10:00 [ ]

b. 11:00 – 13:00 [ ]

c. 15:00 – 17:00 [ ]

d. 19:00 – 21:00 [ ]

Question 12

If you went to bed at 23:00h at what level of tiredness would you be?

a. Not at all tired [ ]

b. A little tired [ ]

c. Fairly tired [ ]

d. Very tired [ ]

Question 13

For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?

a. Will wake up at the usual time and will NOT fall asleep again [ ]

b. Will wake up at the usual time and will doze thereafter [ ]

c. Will wake up at the usual time but will fall asleep again [ ]

d. Will NOT wake up until later than usual [ ]

Question 14

One night you have to remain awake between 04:00 and 06:00h in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?

a. Will NOT go to bed until watch was over [ ]

b. Would take a nap before the watch and sleep after [ ]

c. Would take a good sleep before the watch and nap after [ ]

d. Would take ALL sleep before the night watch [ ]

Question 15

You have to do two hours of hard physical work. You are entirely free to plan your day and considering only your own "feeling best" not your physical abilities, which ONE of the following times would you choose?

a. 08:00 – 10:00 [ ]

b. 11:00 – 13:00 [ ]

c. 15:00 – 17:00 [ ]

d. 19:00 – 21:00 [ ]

Question 16

You have decided to engage in some physical exercise. A friend suggests that you do this for one hour twice a week and the best time for him is between 22:00 and 23:00h. Bearing in mind nothing else but your own "feeling best" not your physical abilities - how well do you think you would perform:

a. Would be on good form [ ]

b. Would be on reasonable form [ ]

c. Would find it difficult [ ]

d. Would find it very difficult [ ]

Question 17

Suppose that you can choose your own work hours. Assume that you had to work a FIVE-hour day (including breaks) and that your job was interesting and paid by results. Which FIVE CONSECUTIVE HOURS would you choose:

Note hours here: ……

Question 18

At what time of day do you think that you reach your "feeling best" peak?

Note time here: ……

Question 19

One hears of "morning" and "evening" types. Which ONE of these types do you consider yourself to be?

a. Definitely a "morning type" [ ]

b. Rather more a "morning" than an "evening" type [ ]

c. Rather more an "evening" than a "morning" type [ ]

d. Definitely an "evening" type [ ]

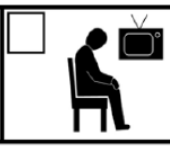
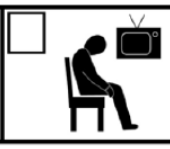
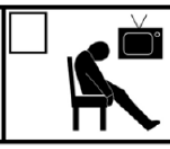
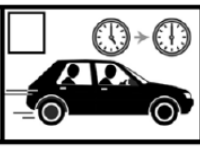
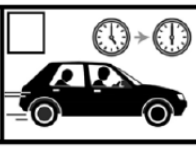
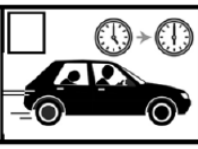
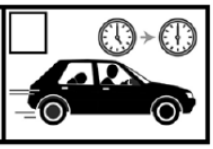
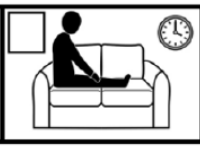
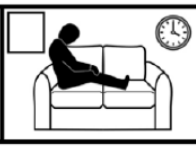
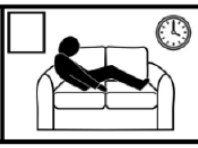
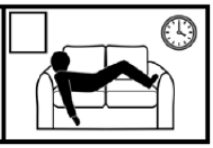
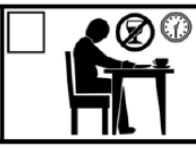
Appendix-6

Patient No: ☐ **Questionnaire No:** ☐

Date completed: _____

Pictorial Epworth Sleepiness Scale

In contrast to just feeling tired, how likely are you to doze off or fall asleep in the following situations? Even if you have not done some of these things recently, try to work out how they would affect you.
Use the following scale to choose the most appropriate number for each situation.

Situation ☑ *Please tick box*	0 No chance of dozing	1 Slight chance	2 Moderate chance	3 Definitely would doze
Sitting and reading	☐ 	☐ 	☐ 	☐ 
Watching TV	☐ 	☐ 	☐ 	☐ 
Sitting inactive in a public place (e.g. Theatre or a meeting)	☐ 	☐ 	☐ 	☐ 
As a passenger in a car for an hour without a break	☐ 	☐ 	☐ 	☐ 
Lying down to rest in the afternoon when circumstances permit	☐ 	☐ 	☐ 	☐ 
Sitting and talking to someone	☐ 	☐ 	☐ 	☐ 
Sitting quietly after lunch without alcohol	☐ 	☐ 	☐ 	☐ 
In a car, while stopped for a few minutes in traffic	☐ 	☐ 	☐ 	☐ 

total sleepiness score / 24

Appendix-7

Hospital Anxiety and Depression (HAD) Scale

Patient no: ☐ **Questionnaire no:** ☐

(Please tick the box that applies to you).

I feel tense or 'wound up':

Most of the time	
A lot of the time	
Time to time, occasionally	
Not at all	

I still enjoy the things I used to enjoy:

Definitely as much	
Not quite so much	
Only a little	
Hardly at all	

I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly -	
Yes, but not too badly	
A little, but it doesn't worry me -	
Not at all	

I can laugh and see the funny side of things:

As much as I always could	
Not quite so much now	
Definitely not so much now	
Not at all	

Worrying thoughts go through my mind:

A great deal of the time	
A lot of the time	
From time to time but not too often	
Only occasionally	

I feel cheerful:

Not at all	
Not often	
Sometimes	
Most of the time	

I can sit at ease and feel relaxed:

Definitely	
Usually	
Not often	
Not at all	

I feel as if I am slowed down:

Nearly all the time	
Very often	
Sometimes	
Not at all	

I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all	
Occasionally	
Quite often	
Very often	

I have lost interest in my appearance:

Definitely	
I don't take so much care as I should	
I may not take quite as much care	
I take just as much care as ever	

I feel restless as if I have to be on the move:

Very much indeed	
Quite a lot	
Not very much	
Not at all	

I look forward with enjoyment to things:

As much as ever I did	
Rather less than I used to	
Definitely less than I used to----	
Hardly at all	

I get sudden feelings of panic:

Very often indeed	
Quite often	
Not very often	
Not at all	

I can enjoy a good book or radio or TV programme:

Often	
Sometimes	
Not often	
Very seldom	

Date completed: _____

University of Oxford

Nuffield Laboratory of Ophthalmology

Levels 5&6, West Wing,

John Radcliffe Hospital

Participant Information Sheet – PATIENT GROUP

Version 8, 24/01/2019

Effect of Ocular Diseases on Sleep and 'Body-Clocks' (Circadian Rhythms).
REC Reference: South Central - Oxford B 11/SC/0093
Professor S Downes, Principal Investigator

Part 1

We would like to invite you to take part in a research study. The doctors working on this study will be carrying out research degrees (MSc, MD) undertaken at the University of Oxford. Before you decide whether or not to take part you need to understand why the research is being done and what it would involve for you. **Please take the time to read the following information carefully. You may talk to others about the study if you wish.**

Part 1 of this form tells you the purpose of this study and what will happen to you if you take part. Part 2 gives more detailed information about the conduct of the study. Please ask us if there is anything that is not clear or if you would like more information. **Take your time to decide whether or not you wish to take part. Your participation is completely voluntary.** Thank you for reading this.

What is the purpose of the study?

Our sleep/wake cycles are controlled by a receptor situated at the back of the eye. These receptors are sensitive to blue light and are known as the photosensitive retinal ganglion cells (pRGC). Depending on whether it is day or night, different amounts of light pass into the eye. As light enters the eye, this receptor detects how much blue light is present, and

sends a signal to a certain part of the brain. This part of the brain controls the sleep/wake cycle that ensures a person sleeps at night and is awake during the day.

The light input can be upset for a number of reasons. For example, certain eye diseases like glaucoma, inherited retinal degenerations or macular degeneration may cause reduced light perception due to the changes at the back of the eye where the pRGC system is situated. This in turn may have an impact on the sleep/wake cycle. Indeed a significant proportion of patients with progressive degenerative eye disease such as inherited retinal degeneration, glaucoma or with other visual impairment have been shown to suffer from sleep disturbances. Cataract is a common condition where the lens gets cloudy and stops as much light entering the eye. As well as affecting the vision, cataract also reduces the amount of the blue light transmission reaching the back of the eye and thereby may affect sleep. Removal of cataract has shown to improve the sleep patterns in some patients in the preliminary results of one of our ongoing studies. By assessing the impact of different eye conditions on sleep patterns and sleep/wake cycle we plan to develop an informed approach in the overall management of the various eye problems.

There are two groups participating in this study:

1) Patient group (patients with various ocular diseases)
2) Control group (healthy volunteers or patients attending the eye hospital with conditions that won't affect the clarity of their vision or the extent of their visual field (peripheral vision), such as lid problems.)

Why have I been invited to take part?

You have been invited to take part in this research study because you have been diagnosed with an eye condition that is of interest to us with regard to the effect of ocular diseases and sleep / circadian rhythms.

You are already attending the outpatient clinic for your own eye problem so we will use words "clinic visit" for this visit and "study visit" for any other future visit that is a part of the research study. You may have also contacted the research team to express your interest in participating, without having previously visited the Oxford Eye Hospital.
In total, we are planning to recruit approximately 3400 participants in this study.

Do I have to take part?

No. It is up to you to decide whether you wish to participate in any parts of the study or not. If you wish to take some more time to think about the study and discuss it with friends or family, please take the information leaflet with you today. If you wish to take part, and decide to do later then you can inform the researcher later about your decision by either calling the contact number provided or asking them to call you. If you decide that you do not wish to take part, your care will not be affected in any way.

What will happen to me if I take part?

As mentioned before, the study has four parts. Please read carefully the information about all the parts and what is involved in each of them. A study flow chart is attached at the end of this information sheet for your convenience.

There is one visit required (day 0) for Part A, or this may be carried out over the phone if appropriate. **Most participants will only be required to take part in Part A**, but a selection will be invited to take part in Parts B and C +/- Part D.

Parts B and C will be home based and no study visits are required. However, for Part D, we will require you to come to clinic, or be available over the telephone if we already have a sample in storage from you from previous diagnostic or research testing, so that we can explain the genetic testing part of the study to you. Your blood sample or, if you don't like needles, a buccal (cheek) swab can be collected in the same visit or we are happy for you to come down again for it.

Part A:

This is a general part and all willing participants will be entered into the study through this part. Once you've consented to take part in this research study, at the time of the clinic visit (either as a patient or a friend/relative) we will ask you to fill in a set of questionnaires about your sleep and general health. Help can be provided by the researcher in filling in the questionnaires, if needed. Alternatively, the researcher will ask you the questions over the phone or send them to you via email/ in the post. If you send back your questionnaire and study documents by email then these will be printed and electronic copies deleted.

Participants are under no obligation to take part in any further part(s) of the study and can withdraw at any time without consequence. However, we may ask you if you would consider taking part in the next part(s) of the study.

Once we have analysed your questionnaire responses in Part A, we may invite you to take part in Parts B, C and / or D.

Parts B and C:

Parts B and C are completed over a three-week period. During this time we will ask you to wear an Actiwatch (a small watch that senses movement and the amount of light in your environment throughout the day and night) and complete a '3 week sleep diary' (detailing bedtime, get up time, daytime naps, etc.) and a mood questionnaire. You can fill these at home and return them to us by post along with the Actiwatch at the end of the three-week period. Stamped addressed envelopes will be provided.

In order to interpret the results from the sleep diaries and Actiwatch we will need to analyse urine samples over three 48 hour periods (i.e. two days of each week when you are wearing the watch). Urine collection involves collecting urine each time you use the toilet for a 48-hour period: we will ask you to measure and record the volume of urine on each occasion and then to take two small samples, to be returned to us, before discarding the majority of the urine. At the end of each 48 hours urine collection, the researcher will collect the bottles from your home or provide packaging and paid postage for their return. The Actiwatch and diaries can be posted back to us at the end of the three week period. Again, stamped addressed envelopes will be provided. The above methods can be adapted if you are sight impaired and the research team will provide support as necessary.

Part D:

You may also be given the option of participation in Part D. We will collect a single blood sample or buccal swab for genetic testing in this part. Prior to any genetic testing, participants will have a detailed discussion with an appropriately-trained healthcare professional to ensure they are fully aware of the potential consequences of the results of genetic testing, e.g. discovery of a disorder or risk factor for a disorder, that the

participant was previously unaware of. This will involve one extra visit, or a phone call if we already have an existing sample from you, for the discussion and, if appropriate and the participant is in agreement, a blood sample or buccal swab will be taken for testing and analysis to look for any genetic correlation in the 'body-clocks' genes.

As part of this study we may want to analyse many different genes with unknown functions (whole genome analysis). During this analysis, there is a small possibility that we could identify additional findings that in some cases can predispose people to other conditions. Often it is unclear what an incidental finding might mean for the patient concerned and, consequently, these results won't be passed back to you or your healthcare provider**. It is important that you understand this before proceeding with the test.**

	Part A	Parts B and C	Part D
Sleep/General Health questionnaire	√		
Sleep diary (3 weeks)		√	
Mood questionnaire		√	
Actiwatch (wearing on wrist)		√	
Urine collection (48 hours x 3)		√	
Blood sample or buccal swab (genetic testing)			√

Schedule of procedures

Expenses and payments

Unfortunately we are not able to pay you for taking part in the study. However, we will be able to reimburse any reasonable travel expenses you or a person accompanying you might incur for any extra visits to the eye hospital.

What will I have to do?

If you decide to take part in the study you should let us know after reading this leaflet. We will then ask you to sign a consent form before you can participate in any parts of the study. You may be consented to the study over the telephone if it is not necessary for you

to come into clinic or you live a long distance away. You will receive the study information and consent form in the post or by email so that you will have the relevant information to review prior to receiving a telephone call. This will be discussed in detail with you to ensure that you are happy that you are fully briefed regarding the study.
With your consent, we may need to contact your GP to confirm that you are eligible for the study.

What are the possible disadvantages and risks of taking part?
The main 'disadvantage' of taking part in the study in Part A is filling out the questionnaires. Help and advice will be provided in filling them if necessary.

For taking part in Parts B and C, the 'disadvantage' is that you will need to fill in sleep diary at home and wear a wrist Actiwatch (a watch-like device) for three weeks. You will also be asked to do a 48 hour urine collection at home (i.e. on two days of each of the three weeks).

For Part D (genetic testing), an extra visit may be necessary for a blood sample or buccal swab to be taken.

What are the side effects of any treatment received when taking part?
This is not a drug testing trial and you will not receive any treatment as a part of this research study. However, if you have an eye condition, you should continue with your routine treatment. Your routine care or legal rights will not be affected by your participation in this research study.

What are the possible benefits of taking part?
It is unlikely that you will notice a direct benefit yourself from taking part in the study. We hope that the results of this study will help us to answer whether sleep patterns are affected by the various eye conditions. Knowing the answers will give us an improved understanding of the eye diseases and help doctors in advising patients with various eye conditions in the future.

What happens when the research study stops?

We would not anticipate that control group participants will need to attend any follow-up visits relating to this study after the study finishes. However, if you have any existing eye condition, you will be followed up for your eye condition as appropriate in the outpatient clinic as for anybody else with similar condition.

Participating in future research

You also have an opportunity to be informed of any future research projects you may be eligible for. To be a part of future research projects your details will be added to an outstanding secure database and you will be sent information regarding relevant research projects. You would then need to contact the research team if you choose to be involved.

As part of advertising this study we are using a number of recruitment methods. These include interviews or case studies with current participants, which may be published in the media. If you are interested in helping us with this then please let us know, although this is only an optional extra for the study and will not affect your current participation.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time without giving any reason. This will not affect your care in any way. The information already obtained from your tests will be kept and may still be used.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact [redacted] on [redacted]; email: [redacted] in the first instance or [redacted] on [redacted]. You may also wish to contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on [redacted] or the head of CTRG, email [redacted].

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Relevant data collected during the study may be looked at by individuals from the University of Oxford, Sponsor of this study, for the purpose of audit and monitoring.

We will follow ethical and legal practice and all information about you will be handled in strictest confidence.

What will happen to any samples I give?

You will not give any samples for testing in Part A or Part B of the study.

In Part C, the urine samples taken from you will be sent to a lab in the University of Surrey. The samples will be analysed for the hormone melatonin to correlate this with the actigraphy data. In Part D, the blood sample or buccal swab taken will be analysed in Oxford. At the end of the analysis, all urine and blood samples will be destroyed as per Human Tissue Act.

Will any genetic tests be done?

Yes, only in Part D, once we have received your consent. Not in Parts A, B or C of the study. Selected patients (depending on their sleep wake profile/pattern) will be asked if they would be prepared to have an additional blood test or buccal swab for genetic testing. If we already have a leftover DNA sample in storage from you, after previous testing that was undertaken, we may contact you for your consent to use this instead of asking for a new sample. Prior to any genetic testing, participants will have a detailed discussion with

an appropriately-trained healthcare professional to ensure they are fully aware of the potential consequences of the results of genetic testing, e.g. discovery of a disorder or risk factor for a disorder, that the participant was previously unaware of.

What will happen to the results of the research study?

The results of the study will be published in scientific journals and presented at scientific meetings. No participant will be identifiable in any report or publication.

Who is organising, funding and monitoring the research?

The research is organised by the Nuffield Laboratory of Ophthalmology, University of Oxford and sponsored by the University of Oxford. A Wellcome Trust Grant has provided funding for this research.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed by the Research Ethics Committee: South Central - Oxford B.

Further information and contact details

If you wish to be given any further information about this study or have any specific questions, please contact the study coordinator, [redacted], on [redacted] (leave a message if necessary and they will call you back). Alternatively you can contact [redacted] on [redacted]. If you are unhappy about any aspect of the study then you can contact the above number/email addresses.

Effect of Ocular Diseases on Sleep and 'Body-Clocks' (Circadian Rhythms)

Reference: South Central - Oxford B 11/SC/0093

Version 6, 24/01/2019

Patient Identification Number:

CONSENT FORM Part A

Name of Principal Investigator: Professor Susan Downes Please initial box

1. I confirm that I have read and understand the information sheet dated 24/01/2019 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Oxford, or from the Oxford University Hospitals NHS Trust or local NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my General Practitioner being contacted to confirm my eligibility for the study. ☐

5. I agree to take part in the above study. ☐

6. I wish to be told the results of the study once available Y ☐ N ☐

7. I agree that I can be approached in regard to relevant research studies in the future (optional) Y ☐ N ☐

8. I agree that I can be approached in regard to potential media opportunities, including filming and voice recording (optional) Y ☐ N ☐

_____ _____ _____

Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix E: Link to SOMNUS Study Information

1) Nuffield Department of Clinical Neurosciences, Laboratory of Ophthalmology Clinical Trials

https://www.ndcn.ox.ac.uk/divisions/nlo/nlo-clinical-trials

(Accessed on 18th November 2020)

2) Eye Research Group Oxford

https://eyeresearchoxford.org.uk/?page_id=113

(Accessed on 18th November 2020)

3) EU Clinical Trials Register

This gives details of SANDMAN, an interventional trial of melatonin in patients with circadian rhythm disorders. Recruitment is via the SOMNUS study "Effect of Ocular Diseases on Sleep and "Body-Clocks" (Circadian Rhythms) study (REC References: B 11/SC/0093

https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002189-39/GB#A

(Accessed on 18th November 2020)

Appendix F: Snellen to LogMAR Conversion

Figure 20: Snellen to LogMAR Conversion Chart

	4m			2m			1m		
	LogMAR	Snellen	Letters	LogMAR	Snellen	Letters	LogMAR	Snellen	Letters
D S R K N	1	6/60	35	1.3	6/120	20	1.6	6/240	5
C K Z O H	0.9	6/48	40	1.2	6/96	25	1.5	6/192	10
O N R K D	0.8	6/38	45	1.1	6/76	30	1.4	6/152	15
K Z V D C	0.7	6/30	50	1	6/60	35	1.3	6/120	20
V S H Z O	0.6	6/24	55	0.9	6/48	40	1.2	6/96	25
H D K C R	0.5	6/19	60	0.8	6/38	45	1.1	6/76	30
C S R H N	0.4	6/15	65	0.7	6/30	50	1	6/60	35
S V Z D K	0.3	6/12	70	0.6	6/24	55	0.9	6/48	40
N C V O Z	0.2	6/10	75	0.5	6/19	60	0.8	6/38	45
R H S D V	0.1	6/7.5	80	0.4	6/15	65	0.7	6/30	50
S N R O H	0	6/6	85	0.3	6/12	70	0.6	6/24	55
O D H K R	-0.1	6/4.8	90	0.2	6/10	75	0.5	6/19	60
Z K C S N	-0.2	6/3.8	95	0.1	6/7.5	80	0.4	6/15	65
C R H D V	-0.3	6/3	100	0	6/6	85	0.3	6/12	70

Appendix G: R Package Statistical Code

1.1 Prospective Study Analysis

```
wilcox.test(age~group)

        Wilcoxon rank sum test with continuity correction

data:  age by group
W = 19640, p-value = 0.4279
alternative hypothesis: true location shift is not equal to 0

 wilcox.test(bmi~group)

        Wilcoxon rank sum test with continuity correction

data:  bmi by group
W = 13906, p-value = 0.005039
alternative hypothesis: true location shift is not equal to 0

> wilcox.test(meq1~group)

        Wilcoxon rank sum test with continuity correction

data:  meq1 by group
W = 19724, p-value = 0.3866
alternative hypothesis: true location shift is not equal to 0

season
> chisq.test(testor1)

        Pearson's Chi-squared test
```

data: testor1

X-squared = 2.4718, df = 3, p-value = 0.4804

sex

> chisq.test(testor2)

	Pearson's Chi-squared test with Yates' continuity correction

data: testor2

X-squared = 18.783, df = 1, p-value = 1.464e-05

 wilcox.test(anx1~group)

	Wilcoxon rank sum test with continuity correction

data: anx1 by group

W = 19287, p-value = 0.6248

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(dep1~group)

	Wilcoxon rank sum test with continuity correction

data: dep1 by group

W = 14162, p-value = 6.501e-05

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(ess1~group)

	Wilcoxon rank sum test with continuity correction

data: ess1 by group

W = 17409, p-value = 0.3095

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(phfunc1~group)

Wilcoxon rank sum test with continuity correction

data: phfunc1 by group

W = 25033, p-value = 1.148e-08

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(limph1~group)

Wilcoxon rank sum test with continuity correction

data: limph1 by group

W = 25555, p-value = 6.636e-14

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(limemo1~group)

Wilcoxon rank sum test with continuity correction

data: limemo1 by group

W = 20743, p-value = 0.008408

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(enfat1~group)

Wilcoxon rank sum test with continuity correction

data: enfat1 by group

W = 24377, p-value = 2.803e-07

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(emwb1~group)

Wilcoxon rank sum test with continuity correction

data: emwb1 by group

W = 19370, p-value = 0.4518

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(socfun1~group)

Wilcoxon rank sum test with continuity correction

data: socfun1 by group

W = 23236, p-value = 1.91e-06

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(pain1~group)

Wilcoxon rank sum test with continuity correction

data: pain1 by group

W = 21524, p-value = 0.003063

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(genh1~group)

Wilcoxon rank sum test with continuity correction

data: genh1 by group

W = 26531, p-value = 7.196e-12

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(caff~group)

Wilcoxon rank sum test with continuity correction

data: caff by group

W = 18588, p-value = 0.901

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(alc~group)

Wilcoxon rank sum test with continuity correction

data: alc by group

W = 20360, p-value = 0.145

alternative hypothesis: true location shift is not equal to 0

> wilcox.test(smo~group)

Wilcoxon rank sum test with continuity correction

data: smo by group

W = 17682, p-value = 0.06813

alternative hypothesis: true location shift is not equal to 0

> mod1<-glm(gpsqicat~group+age+sex+caff+alc+bmi+anx1+dep1+season1, family="binomial")

> summary(mod1)

Call:

glm(formula = gpsqicat ~ group + age + sex + caff + alc + bmi +

```
   anx1 + dep1 + season1, family = "binomial")

Deviance Residuals:
   Min      1Q  Median      3Q     Max
-2.1684  -0.8705  -0.4795   0.8641   2.0469

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.442794   0.787175  -5.644 1.66e-08 ***
group        1.325810   0.286651   4.625 3.74e-06 ***
age          0.029094   0.007844   3.709 0.000208 ***
sex          0.568277   0.271498   2.093 0.036338 *
caff        -0.190835   0.105286  -1.813 0.069903 .
alc         -0.012193   0.017527  -0.696 0.486647
bmi          0.041571   0.019795   2.100 0.035719 *
anx1         0.220744   0.043149   5.116 3.12e-07 ***
dep1         0.100939   0.048687   2.073 0.038150 *
season1      0.091013   0.108178   0.841 0.400168
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 557.12  on 402  degrees of freedom
Residual deviance: 435.99  on 393  degrees of freedom
  (23 observations deleted due to missingness)
AIC: 455.99

Number of Fisher Scoring iterations: 4

> mod1<-glm(gpsqicat~group+age+sex+caff+alc+bmi+anx1+dep1, family="binomial")
> summary(mod1)
```

```
Call:
glm(formula = gpsqicat ~ group + age + sex + caff + alc + bmi +
    anx1 + dep1, family = "binomial")

Deviance Residuals:
   Min      1Q  Median      3Q     Max
-2.1704  -0.8671  -0.4846   0.8863   2.0457

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.330161   0.774186  -5.593 2.23e-08 ***
group        1.316219   0.286184   4.599 4.24e-06 ***
age          0.028867   0.007832   3.686 0.000228 ***
sex          0.560056   0.270897   2.067 0.038695 *
caff        -0.188603   0.105122  -1.794 0.072791 .
alc         -0.012352   0.017464  -0.707 0.479413
bmi          0.043772   0.019706   2.221 0.026333 *
anx1         0.220577   0.043080   5.120 3.05e-07 ***
dep1         0.102532   0.048561   2.111 0.034739 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 557.12  on 402  degrees of freedom
Residual deviance: 436.70  on 394  degrees of freedom
  (23 observations deleted due to missingness)
AIC: 454.7

Number of Fisher Scoring iterations: 4
```

```
> nullmod <- glm(gpsqicat~1, family="binomial")
> 1-logLik(mod1)/logLik(nullmod)
'log Lik.' 0.25854 (df=9)

plot(density(sqrt(gpsqi1),na.rm=TRUE))

 mod1<-lm(sqrt(gpsqi1)~group+sex+age+caff+alc+smo+bmi+anx1+dep1)
> summary(mod1)

Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
   smo + bmi + anx1 + dep1)

Residuals:
    Min      1Q  Median      3Q     Max
-2.64446 -0.37160  0.03222  0.38387  1.92476

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.006948   0.187887   5.359 1.43e-07 ***
group        0.382603   0.074101   5.163 3.86e-07 ***
sex          0.171578   0.071055   2.415 0.016203 *
age          0.004923   0.002047   2.405 0.016640 *
caff        -0.033588   0.027366  -1.227 0.220427
alc         -0.003166   0.004711  -0.672 0.501990
smo         -0.009622   0.031795  -0.303 0.762333
bmi          0.016974   0.004849   3.500 0.000518 ***
anx1         0.070549   0.010571   6.674 8.52e-11 ***
dep1         0.041545   0.012429   3.343 0.000910 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

```
Residual standard error: 0.6297 on 393 degrees of freedom
  (23 observations deleted due to missingness)
Multiple R-squared:  0.3442,      Adjusted R-squared:  0.3292
F-statistic: 22.92 on 9 and 393 DF,  p-value: < 2.2e-16

#ordinal regression
library(ordinal)
squal1<-factor(squal1)
slat1<-factor(slat1)
sdur1<-factor(sdur1)
seff1<-factor(seff1)
sdist1<-factor(sdist1)
smed1<-factor(smed1)
dtdys1<-factor(dtdys1)

 summary(mod1)
formula: squal1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1

 link  threshold nobs logLik  AIC    niter max.grad cond.H
 logit flexible  403  -418.41 860.82 6(0)  5.01e-12 4.1e+05

Coefficients:
      Estimate Std. Error z value Pr(>|z|)
group  0.513633   0.229841   2.235   0.0254 *
age    0.007879   0.006313   1.248   0.2120
sex    0.487069   0.218484   2.229   0.0258 *
caff  -0.110106   0.084825  -1.298   0.1943
alc    0.016574   0.014079   1.177   0.2391
smo    0.023258   0.094585   0.246   0.8058
bmi    0.036441   0.015104   2.413   0.0158 *
anx1   0.145258   0.033343   4.356 1.32e-05 ***
dep1   0.094080   0.037991   2.476   0.0133 *
```

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:

	Estimate	Std. Error	z value
0|1	1.1114	0.5865	1.895
1|2	3.8210	0.6175	6.188
2|3	6.2003	0.6881	9.011

(23 observations deleted due to missingness)

> summary(mod2)

formula: slat1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1

link	threshold	nobs	logLik	AIC	niter	max.grad	cond.H
logit	flexible	403	-400.71	825.41	8(0)	2.07e-07	5.9e+05

Coefficients:

	Estimate	Std. Error	z value	Pr(>|z|)	
group	0.828542	0.228178	3.631	0.000282	***
age	0.002075	0.006243	0.332	0.739573	
sex	0.266504	0.214541	1.242	0.214160	
caff	-0.145271	0.086098	-1.687	0.091550	.
alc	-0.006849	0.014256	-0.480	0.630913	
smo	0.100731	0.094703	1.064	0.287491	
bmi	0.015490	0.015025	1.031	0.302568	
anx1	0.170553	0.033789	5.048	4.47e-07	***
dep1	-0.005508	0.038336	-0.144	0.885761	

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:

	Estimate	Std. Error	z value
0|1	0.6783	0.5804	1.169

```
1|2   2.8543     0.5992   4.764
2|3   7.8127     1.1733   6.659
(23 observations deleted due to missingness)
> summary(mod3)
formula: sdur1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1

 link  threshold nobs logLik  AIC    niter max.grad cond.H
 logit flexible  403  -437.86 899.72 5(0)  2.41e-11 4.0e+05

Coefficients:
      Estimate Std. Error z value Pr(>|z|)
group  0.546413   0.228940   2.387  0.01700 *
age    0.009577   0.006329   1.513  0.13022
sex    0.393325   0.222097   1.771  0.07657 .
caff  -0.073175   0.085830  -0.853  0.39390
alc   -0.009345   0.014568  -0.641  0.52122
smo   -0.205401   0.107748  -1.906  0.05661 .
bmi    0.041077   0.014184   2.896  0.00378 **
anx1   0.146757   0.031984   4.588 4.47e-06 ***
dep1   0.031414   0.037067   0.847  0.39672
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:
   Estimate Std. Error z value
0|1   2.5163     0.5870   4.287
1|2   4.0611     0.6107   6.650
2|3   5.4116     0.6437   8.407
(23 observations deleted due to missingness)
> summary(mod4)
formula: seff1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1
```

```
 link  threshold nobs logLik  AIC    niter max.grad cond.H
 logit flexible  403  -429.91 883.81 5(0)  8.06e-13 4.3e+05

Coefficients:
      Estimate Std. Error z value Pr(>|z|)
group  0.898841   0.233599   3.848 0.000119 ***
age    0.026335   0.006684   3.940 8.15e-05 ***
sex    0.893239   0.232292   3.845 0.000120 ***
caff  -0.060208   0.086313  -0.698 0.485459
alc    0.001318   0.014677   0.090 0.928464
smo   -0.148337   0.100268  -1.479 0.139034
bmi    0.036850   0.013995   2.633 0.008464 **
anx1   0.153675   0.033161   4.634 3.58e-06 ***
dep1   0.024832   0.037581   0.661 0.508761
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:
   Estimate Std. Error z value
0|1   3.8709     0.6093   6.353
1|2   5.2467     0.6377   8.227
2|3   6.1003     0.6589   9.258
(23 observations deleted due to missingness)
> summary(mod5)
formula: sdist1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1

 link  threshold nobs logLik  AIC    niter max.grad cond.H
 logit flexible  403  -285.07 594.13 8(0)  3.78e-13 4.9e+05

Coefficients:
      Estimate Std. Error z value Pr(>|z|)
group  0.533618   0.257186   2.075 0.038002 *
```

```
age    0.026756   0.007596   3.523 0.000427 ***
sex    0.366737   0.255480   1.435 0.151149
caff  -0.028270   0.095486  -0.296 0.767181
alc   -0.006335   0.016447  -0.385 0.700106
smo    0.125027   0.106648   1.172 0.241064
bmi    0.066906   0.017326   3.862 0.000113 ***
anx1   0.147950   0.037878   3.906 9.39e-05 ***
dep1   0.106873   0.042343   2.524 0.011604 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Threshold coefficients:
   Estimate Std. Error z value
0|1   0.4458     0.7230   0.617
1|2   5.3464     0.7392   7.232
2|3   9.1780     0.9027  10.167
(23 observations deleted due to missingness)
> summary(mod6)
formula: smed1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1

 link  threshold nobs logLik  AIC    niter max.grad cond.H
 logit flexible  403  -197.69 419.37 7(1)  9.24e-14 3.8e+05

Coefficients:
      Estimate Std. Error z value Pr(>|z|)
group  1.373448   0.336034   4.087 4.37e-05 ***
age    0.009327   0.010257   0.909   0.3632
sex    0.100738   0.347030   0.290   0.7716
caff  -0.054244   0.126102  -0.430   0.6671
alc   -0.024952   0.024764  -1.008   0.3137
smo    0.085750   0.131293   0.653   0.5137
bmi   -0.029139   0.025518  -1.142   0.2535
```

anx1 0.106548 0.046363 2.298 0.0216 *

dep1 0.066872 0.051168 1.307 0.1912

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:

Estimate Std. Error z value

0|1 2.7967 0.9317 3.002

1|2 3.4790 0.9453 3.680

2|3 3.9237 0.9565 4.102

(23 observations deleted due to missingness)

> summary(mod7)

formula: dtdys1 ~ group + age + sex + caff + alc + smo + bmi + anx1 + dep1

link threshold nobs logLik AIC niter max.grad cond.H

logit flexible 403 -391.55 807.10 6(0) 7.79e-14 4.0e+05

Coefficients:

Estimate Std. Error z value Pr(>|z|)

group 0.455756 0.230648 1.976 0.04816 *

age -0.012070 0.006435 -1.876 0.06069 .

sex -0.207235 0.222501 -0.931 0.35165

caff 0.112564 0.087523 1.286 0.19841

alc -0.016548 0.014709 -1.125 0.26055

smo -0.102971 0.101381 -1.016 0.30978

bmi 0.031079 0.014835 2.095 0.03617 *

anx1 0.107660 0.033178 3.245 0.00117 **

dep1 0.296559 0.041845 7.087 1.37e-12 ***

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Threshold coefficients:

```
   Estimate Std. Error z value
0|1   1.4419     0.5880   2.452
1|2   3.8048     0.6203   6.134
2|3   6.0640     0.6963   8.709
(23 observations deleted due to missingness)

 summary(mod1)

Call:
glm(formula = gpsqicat ~ NMO + age + sex + caff + alc + bmi +
   anx1 + dep1, family = "binomial")

Deviance Residuals:
   Min      1Q  Median      3Q     Max
-2.2651  -0.8691   0.4265   0.7945   1.6824

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.35694    1.35999  -2.468   0.0136 *
NMO         -0.61024    0.57200  -1.067   0.2860
age          0.04081    0.01588   2.571   0.0102 *
sex          0.05656    0.50383   0.112   0.9106
caff        -0.11273    0.18681  -0.603   0.5462
alc         -0.01541    0.03071  -0.502   0.6158
bmi          0.05775    0.03617   1.597   0.1104
anx1         0.16930    0.07589   2.231   0.0257 *
dep1         0.13181    0.08061   1.635   0.1020
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)
```

```
    Null deviance: 153.27  on 118  degrees of freedom
Residual deviance: 118.17  on 110  degrees of freedom
  (5 observations deleted due to missingness)
AIC: 136.17

Number of Fisher Scoring iterations: 5
 mod1<-glm(gpsqicat~bva+age+sex+caff+alc+bmi+anx1+dep1, family="binomial")
>  summary(mod1)

Call:
glm(formula = gpsqicat ~ bva + age + sex + caff + alc + bmi +
    anx1 + dep1, family = "binomial")

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.1006  -0.8900   0.4640   0.7677   1.7864

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.88748    1.33384  -2.915  0.00356 **
bva          0.07446    0.34846   0.214  0.83080
age          0.04119    0.01595   2.582  0.00983 **
sex          0.10737    0.50450   0.213  0.83147
caff        -0.08910    0.18531  -0.481  0.63064
alc         -0.02142    0.03026  -0.708  0.47902
bmi          0.05637    0.03626   1.555  0.11999
anx1         0.15757    0.07507   2.099  0.03583 *
dep1         0.14601    0.08057   1.812  0.06997 .
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)
```

```
    Null deviance: 153.27  on 118  degrees of freedom
Residual deviance: 119.29  on 110  degrees of freedom
  (5 observations deleted due to missingness)
AIC: 137.29

Number of Fisher Scoring iterations: 5

> qqnorm(mod1)
Error in min(x, na.rm = na.rm) : invalid 'type' (list) of argument
> mod1<-glm(gpsqicat~bemd+age+sex+caff+alc+bmi+anx1+dep1, family="binomial")
>  summary(mod1)

Call:
glm(formula = gpsqicat ~ bemd + age + sex + caff + alc + bmi +
    anx1 + dep1, family = "binomial")

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.2260  -0.7629   0.4187   0.7326   1.6964

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.48004    2.15859  -2.075   0.0379 *
bemd        -0.03134    0.09197  -0.341   0.7333
age          0.07049    0.03547   1.987   0.0469 *
sex          0.70673    0.94568   0.747   0.4549
caff        -0.34494    0.30238  -1.141   0.2540
alc         -0.05220    0.05325  -0.980   0.3269
bmi          0.04197    0.05428   0.773   0.4394
anx1         0.08002    0.11103   0.721   0.4711
dep1         0.19004    0.12966   1.466   0.1427
```

```
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 63.422  on 46  degrees of freedom
Residual deviance: 47.215  on 38  degrees of freedom
  (77 observations deleted due to missingness)
AIC: 65.215

Number of Fisher Scoring iterations: 4

  mod1<-lm(sqrt(gpsqi1)~bva+sex+age+caff+alc+smo+bmi+anx1+dep1)
>  summary(mod1)

Call:
lm(formula = sqrt(gpsqi1) ~ bva + sex + age + caff + alc + smo +
    bmi + anx1 + dep1)

Residuals:
    Min      1Q  Median      3Q     Max
-1.6525 -0.3870  0.0235  0.3635  1.9364

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.275220   0.350770   3.635 0.000425 ***
bva          0.116161   0.092405   1.257 0.211407
sex          0.074248   0.140683   0.528 0.598734
age          0.007729   0.004235   1.825 0.070721 .
caff        -0.050428   0.050690  -0.995 0.322025
alc         -0.005116   0.008065  -0.634 0.527128
smo         -0.068937   0.055230  -1.248 0.214639
```

```
bmi         0.018510   0.009636   1.921 0.057344 .
anx1        0.059157   0.018382   3.218 0.001700 **
dep1        0.062006   0.019192   3.231 0.001633 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6758 on 109 degrees of freedom
  (5 observations deleted due to missingness)
Multiple R-squared:  0.3717,      Adjusted R-squared:  0.3199
F-statistic: 7.166 on 9 and 109 DF,  p-value: 4.117e-08

> qqnorm(resid(mod1))
>  mod2<-lm(sqrt(gpsqi1)~NMO+sex+age+caff+alc+smo+bmi+anx1+dep1)
>  summary(mod2)

Call:
lm(formula = sqrt(gpsqi1) ~ NMO + sex + age + caff + alc + smo +
    bmi + anx1 + dep1)

Residuals:
     Min       1Q   Median       3Q      Max
-1.69612 -0.38074  0.01158  0.39519  1.73414

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.498465   0.365314   4.102 7.93e-05 ***
NMO         -0.166764   0.151891  -1.098 0.274659
sex          0.040265   0.141419   0.285 0.776395
age          0.007591   0.004242   1.789 0.076347 .
caff        -0.055336   0.050974  -1.086 0.280058
alc         -0.003578   0.008224  -0.435 0.664370
smo         -0.067481   0.055285  -1.221 0.224866
```

```
bmi         0.017359   0.009570   1.814 0.072423 .
anx1        0.064632   0.018445   3.504 0.000666 ***
dep1        0.056303   0.019687   2.860 0.005081 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6769 on 109 degrees of freedom
  (5 observations deleted due to missingness)
Multiple R-squared:  0.3696,      Adjusted R-squared:  0.3176
F-statistic: 7.101 on 9 and 109 DF,  p-value: 4.86e-08

> mod3<-lm(sqrt(gpsqi1)~bemd+sex+age+caff+alc+smo+bmi+anx1+dep1)
> summary(mod3)

Call:
lm(formula = sqrt(gpsqi1) ~ bemd + sex + age + caff + alc + smo +
    bmi + anx1 + dep1)

Residuals:
    Min      1Q  Median      3Q     Max
-1.2568 -0.3120  0.0696  0.3040  1.1026

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.3079836  0.5246350   2.493   0.0173 *
bemd        -0.0008943  0.0217800  -0.041   0.9675
sex          0.1676684  0.2453981   0.683   0.4987
age          0.0069555  0.0081821   0.850   0.4007
caff        -0.0765137  0.0729838  -1.048   0.3013
alc         -0.0079395  0.0135423  -0.586   0.5613
smo         -0.0326688  0.1093608  -0.299   0.7668
bmi          0.0171014  0.0142268   1.202   0.2370
```

anx1 0.0530943 0.0297184 1.787 0.0822 .

dep1 0.0622253 0.0281033 2.214 0.0331 *

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6321 on 37 degrees of freedom

(77 observations deleted due to missingness)

Multiple R-squared: 0.4292, Adjusted R-squared: 0.2904

F-statistic: 3.091 on 9 and 37 DF, p-value: 0.007226

>

1.2 Retrospective Sensitivity Analysis

1.2.1 Linear Model

```
full model


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = input)

Residuals:
     Min       1Q   Median       3Q      Max
-2.63807 -0.37111  0.03146  0.37492  1.92388

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.006214   0.187768   5.359 1.43e-07 ***
group        0.383088   0.074564   5.138 4.40e-07 ***
sex          0.175437   0.071083   2.468  0.01401 *
age          0.004812   0.002048   2.350  0.01928 *
caff        -0.031996   0.027380  -1.169  0.24329
alc         -0.003912   0.004732  -0.827  0.40896
smo         -0.008577   0.031790  -0.270  0.78745
bmi          0.017138   0.004851   3.533  0.00046 ***
anx1         0.070888   0.010569   6.707 6.98e-11 ***
dep1         0.039952   0.012464   3.205  0.00146 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6293 on 391 degrees of freedom
  (23 observations deleted due to missingness)
Multiple R-squared:  0.3438, Adjusted R-squared:  0.3287
F-statistic: 22.77 on 9 and 391 DF,  p-value: < 2.2e-16
```

```
------------------------------------------------------------

osa model


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = osa_comb)

Residuals:
     Min       1Q   Median       3Q      Max
-2.61136 -0.38740  0.02273  0.37929  1.84672

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.086308   0.191115   5.684 2.68e-08 ***
group        0.401806   0.081111   4.954 1.11e-06 ***
sex          0.143439   0.073235   1.959 0.050912 .
age          0.003867   0.002125   1.820 0.069521 .
caff        -0.031589   0.028161  -1.122 0.262706
alc         -0.003263   0.004968  -0.657 0.511734
smo         -0.020337   0.033020  -0.616 0.538338
bmi          0.017292   0.004919   3.516 0.000494 ***
anx1         0.071215   0.010974   6.489 2.78e-10 ***
dep1         0.033141   0.013061   2.537 0.011582 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6261 on 369 degrees of freedom
  (22 observations deleted due to missingness)
Multiple R-squared:  0.3284, Adjusted R-squared:  0.3121
F-statistic: 20.05 on 9 and 369 DF,  p-value: < 2.2e-16


------------------------------------------------------------

Exclude shift work


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = osa_noshift_comb)

Residuals:
     Min       1Q   Median       3Q      Max
-2.62624 -0.38914  0.02033  0.36699  1.80458

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.103197   0.195360   5.647 3.32e-08 ***
group        0.425944   0.084385   5.048 7.12e-07 ***
sex          0.129711   0.074763   1.735 0.083605 .
age          0.003723   0.002166   1.719 0.086438 .
caff        -0.036558   0.029254  -1.250 0.212232
alc         -0.003801   0.005110  -0.744 0.457546
smo         -0.016304   0.033604  -0.485 0.627837
```

```
bmi          0.017491   0.005042   3.469 0.000585 ***
anx1         0.073078   0.011241   6.501 2.67e-10 ***
dep1         0.033654   0.013406   2.510 0.012502 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6295 on 359 degrees of freedom
  (22 observations deleted due to missingness)
Multiple R-squared:  0.3317, Adjusted R-squared:  0.315
F-statistic:  19.8 on 9 and 359 DF,  p-value: < 2.2e-16


------------------------------------------------------------

Exclude travel


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = osa_notravel_comb)

Residuals:
     Min       1Q   Median       3Q      Max
-2.63171 -0.39496  0.04616  0.39795  1.60089

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.973901   0.195368   4.985 9.69e-07 ***
group        0.361471   0.084972   4.254 2.69e-05 ***
sex          0.152266   0.073906   2.060 0.040097 *
age          0.004650   0.002160   2.153 0.031989 *
caff        -0.018345   0.028577  -0.642 0.521318
alc         -0.002053   0.005353  -0.383 0.701595
smo         -0.018000   0.033121  -0.543 0.587149
bmi          0.017544   0.004979   3.524 0.000481 ***
anx1         0.072636   0.011086   6.552 1.99e-10 ***
dep1         0.035121   0.013290   2.643 0.008590 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6227 on 357 degrees of freedom
  (21 observations deleted due to missingness)
Multiple R-squared:  0.3305, Adjusted R-squared:  0.3136
F-statistic: 19.58 on 9 and 357 DF,  p-value: < 2.2e-16


------------------------------------------------------------

Exclude travel and shift


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = osa_notravelorshift_comb)

Residuals:
     Min       1Q   Median       3Q      Max
-2.64480 -0.38756  0.04773  0.39038  1.58469
```

```
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.987752   0.199383   4.954 1.14e-06 ***
group        0.383581   0.088267   4.346 1.82e-05 ***
sex          0.139519   0.075134   1.857 0.064163 .
age          0.004543   0.002190   2.074 0.038823 *
caff        -0.022618   0.029688  -0.762 0.446669
alc         -0.002165   0.005437  -0.398 0.690800
smo         -0.014498   0.033650  -0.431 0.666847
bmi          0.017610   0.005093   3.458 0.000612 ***
anx1         0.074346   0.011300   6.579 1.73e-10 ***
dep1         0.035914   0.013569   2.647 0.008496 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6251 on 349 degrees of freedom
  (21 observations deleted due to missingness)
Multiple R-squared:  0.3334, Adjusted R-squared:  0.3162
F-statistic: 19.39 on 9 and 349 DF,  p-value: < 2.2e-16


------------------------------------------------------------

Exclude Systemic Glucocorticoids


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = osa_nosteroids_comb)

Residuals:
     Min       1Q   Median       3Q      Max
-2.60708 -0.38617  0.01337  0.36171  1.65646

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.060675   0.205495   5.162 4.27e-07 ***
group        0.323776   0.099832   3.243  0.00130 **
sex          0.143349   0.078605   1.824  0.06912 .
age          0.003522   0.002236   1.575  0.11623
caff        -0.028124   0.030132  -0.933  0.35133
alc         -0.004046   0.005215  -0.776  0.43845
smo         -0.003431   0.034185  -0.100  0.92012
bmi          0.018367   0.005094   3.606  0.00036 ***
anx1         0.071639   0.011711   6.117 2.73e-09 ***
dep1         0.033294   0.014517   2.293  0.02246 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.6228 on 325 degrees of freedom
  (21 observations deleted due to missingness)
Multiple R-squared:  0.2933, Adjusted R-squared:  0.2737
F-statistic: 14.99 on 9 and 325 DF,  p-value: < 2.2e-16


------------------------------------------------------------
```

```
Exclude travel, shift and Systemic Glucocorticoids


Call:
lm(formula = sqrt(gpsqi1) ~ group + sex + age + caff + alc +
    smo + bmi + anx1 + dep1, data = osa_notravelorshiftorsteroids_comb)

Residuals:
     Min       1Q   Median       3Q      Max
-2.62015 -0.38802  0.02666  0.36564  1.66629

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  1.053337   0.209866   5.019 8.70e-07 ***
group        0.302819   0.110200   2.748  0.00634 **
sex          0.136345   0.080097   1.702  0.08970 .
age          0.003847   0.002298   1.674  0.09512 .
caff        -0.025192   0.031532  -0.799  0.42494
alc         -0.003406   0.005652  -0.603  0.54722
smo         -0.001763   0.034861  -0.051  0.95969
bmi          0.017561   0.005300   3.313  0.00103 **
anx1         0.071598   0.012117   5.909 8.94e-09 ***
dep1         0.035254   0.015005   2.350  0.01942 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.628 on 315 degrees of freedom
  (20 observations deleted due to missingness)
Multiple R-squared:  0.2866, Adjusted R-squared:  0.2663
F-statistic: 14.06 on 9 and 315 DF,  p-value: < 2.2e-16
```

1.2.2 Generalised Linear Model

```
full model


Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data = input)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.1772  -0.8637  -0.4855   0.8877   2.0453

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.336185   0.774413  -5.599 2.15e-08 ***
group        1.341303   0.289097   4.640 3.49e-06 ***
sex          0.569009   0.271116   2.099 0.035837 *
age          0.028467   0.007843   3.630 0.000284 ***
caff        -0.179420   0.105429  -1.702 0.088790 .
alc         -0.012875   0.017636  -0.730 0.465367
smo         -0.066766   0.117275  -0.569 0.569147
```

```
bmi          0.043929   0.019774   2.222 0.026313 *
anx1         0.223238   0.043356   5.149 2.62e-07 ***
dep1         0.099285   0.048687   2.039 0.041425 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 554.34  on 400  degrees of freedom
Residual deviance: 434.64  on 391  degrees of freedom
  (23 observations deleted due to missingness)
AIC: 454.64

Number of Fisher Scoring iterations: 4


------------------------------------------------------------

osa model


Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data = osa_comb)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.1248  -0.8847  -0.5232   0.9047   2.0098

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.141360   0.779771  -5.311 1.09e-07 ***
group        1.218082   0.311040   3.916 9.00e-05 ***
sex          0.542577   0.278861   1.946  0.05169 .
age          0.026467   0.008071   3.279  0.00104 **
caff        -0.174004   0.108008  -1.611  0.10717
alc         -0.011916   0.018140  -0.657  0.51125
smo         -0.075511   0.121168  -0.623  0.53316
bmi          0.042077   0.019769   2.128  0.03330 *
anx1         0.212879   0.044749   4.757 1.96e-06 ***
dep1         0.103372   0.050103   2.063  0.03909 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 522.53  on 378  degrees of freedom
Residual deviance: 417.35  on 369  degrees of freedom
  (22 observations deleted due to missingness)
AIC: 437.35

Number of Fisher Scoring iterations: 4


------------------------------------------------------------

Exclude shift work
```

```
Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data = osa_noshift_comb)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.1270  -0.8869  -0.5427   0.9258   1.9747

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.965077   0.783762  -5.059 4.21e-07 ***
group        1.171399   0.319472   3.667 0.000246 ***
sex          0.512643   0.281445   1.821 0.068535 .
age          0.024863   0.008129   3.059 0.002223 **
caff        -0.190570   0.110854  -1.719 0.085595 .
alc         -0.014389   0.018515  -0.777 0.437066
smo         -0.064483   0.122149  -0.528 0.597565
bmi          0.041877   0.020143   2.079 0.037614 *
anx1         0.210500   0.045298   4.647 3.37e-06 ***
dep1         0.105244   0.050789   2.072 0.038248 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 507.41  on 368  degrees of freedom
Residual deviance: 409.42  on 359  degrees of freedom
  (22 observations deleted due to missingness)
AIC: 429.42

Number of Fisher Scoring iterations: 4


------------------------------------------------------------

Exclude travel


Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data = osa_notravel_comb)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.0528  -0.8817  -0.5309   0.8993   2.0454

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.337429   0.807551  -5.371 7.83e-08 ***
group        1.065402   0.325719   3.271  0.00107 **
sex          0.533259   0.282957   1.885  0.05948 .
age          0.026907   0.008278   3.250  0.00115 **
caff        -0.126827   0.109419  -1.159  0.24642
alc         -0.010743   0.019756  -0.544  0.58659
smo         -0.072324   0.121366  -0.596  0.55123
bmi          0.042116   0.020038   2.102  0.03557 *
anx1         0.217573   0.045347   4.798 1.60e-06 ***
```

```
dep1         0.102403   0.050599   2.024  0.04299 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 504.62  on 366  degrees of freedom
Residual deviance: 405.21  on 357  degrees of freedom
  (21 observations deleted due to missingness)
AIC: 425.21

Number of Fisher Scoring iterations: 4


------------------------------------------------------------

Exclude travel and shift


Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data =
osa_notravelorshift_comb)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.0651  -0.8929  -0.5492   0.9210   2.0223

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.186340   0.811691  -5.158 2.50e-07 ***
group        1.024994   0.334902   3.061  0.00221 **
sex          0.514982   0.285309   1.805  0.07108 .
age          0.025919   0.008332   3.111  0.00187 **
caff        -0.139866   0.112976  -1.238  0.21571
alc         -0.011932   0.019919  -0.599  0.54916
smo         -0.065209   0.122527  -0.532  0.59459
bmi          0.040679   0.020358   1.998  0.04570 *
anx1         0.213408   0.045862   4.653 3.27e-06 ***
dep1         0.108790   0.051227   2.124  0.03370 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 492.52  on 358  degrees of freedom
Residual deviance: 398.37  on 349  degrees of freedom
  (21 observations deleted due to missingness)
AIC: 418.37

Number of Fisher Scoring iterations: 4


------------------------------------------------------------

Exclude Systemic Glucocorticoids
```

```
Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data = osa_nosteroids_comb)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.0733  -0.8897  -0.5681   0.9408   1.9604

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.965420   0.836393  -4.741 2.13e-06 ***
group        1.087692   0.375674   2.895  0.00379 **
sex          0.463753   0.298000   1.556  0.11966
age          0.023660   0.008454   2.799  0.00513 **
caff        -0.187636   0.114872  -1.633  0.10238
alc         -0.013620   0.019115  -0.713  0.47615
smo         -0.060038   0.124901  -0.481  0.63074
bmi          0.045503   0.020684   2.200  0.02781 *
anx1         0.212154   0.046551   4.557 5.18e-06 ***
dep1         0.096743   0.053842   1.797  0.07237 .
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 457.22  on 334  degrees of freedom
Residual deviance: 376.15  on 325  degrees of freedom
  (21 observations deleted due to missingness)
AIC: 396.15

Number of Fisher Scoring iterations: 4


------------------------------------------------------------

Exclude travel, shift and Systemic Glucocorticoids


Call:
glm(formula = gpsqicat ~ group + sex + age + caff + alc + smo +
    bmi + anx1 + dep1, family = "binomial", data =
osa_notravelorshiftorsteroids_comb)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-2.0373  -0.9035  -0.5968   0.9549   1.9443

Coefficients:
             Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.795901   0.834060  -4.551 5.34e-06 ***
group        0.839651   0.405851   2.069  0.03856 *
sex          0.444863   0.298617   1.490  0.13629
age          0.022578   0.008556   2.639  0.00832 **
caff        -0.164861   0.117594  -1.402  0.16093
alc         -0.014157   0.020448  -0.692  0.48873
smo         -0.052689   0.124969  -0.422  0.67330
bmi          0.040381   0.020845   1.937  0.05271 .
anx1         0.201540   0.046936   4.294 1.76e-05 ***
```

```
dep1         0.104658   0.054381   1.925  0.05429 .
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 441.19  on 324  degrees of freedom
Residual deviance: 369.18  on 315  degrees of freedom
  (20 observations deleted due to missingness)
AIC: 389.18

Number of Fisher Scoring iterations: 4
```

Glossary

Acetylcholine A neurotransmitter of the central, sympathetic and parasympathetic nervous systems

Achromatopsia Total colour blindness

Acromegaly Signs and symptoms of excess growth hormone secretion after puberty is complete: growth of the hands and feet, coarse facial features, thickened skin, low voice, headaches and visual dysfunction

Actigraph A graphical representation of rest-activity patterns that correspond to sleep and wake

Actigraphy Objective measurement of sleep wake using a calibrated movement sensor on the non-dominant wrist, which records of rest-activity patterns. It is usually worn for a set period of days or weeks. An actigraph can be produced from the stored data.

Acute disseminated encephalomyelitis (ADEM) A demyelinating disease of the central nervous system that usually occurs following a viral or bacterial illness or vaccination

Adipsia No thirst drive leading to no fluid intake

Advance phase sleep disorder (APSD) Forward shifting of the internal circadian clock, so that an individual is more likely to wake earlier in the morning and sleep earlier in the evening than is normal

Affective disorder A condition that changes the affect or mood (also known as mood disorder). Examples include depression and bipolar disorders

Allele A gene locus on a chromosome. One allele of each gene is inherited from each parent

Alpha-wave sleep Corresponding to light sleep, as in NREM stage 1

Alzheimer disease A degenerative neurological condition which is characterised by progressive memory loss and dementia

Amaurosis fugax Temporary loss of vision in one or both eyes, which is usually painless

Amblyopia A condition of visual development in which neural pathways from one eye to the visual processing centres of the brain do not become established to the same extent as they do from the contralateral eye. The eye may be structurally normal, but the presence of myopia, hyperopia or astigmatism, or a turn (strabismus) in the eye may cause its visual input to be out of focus or alignment

Amenorrhoea The absence of menstruation

Amygdala An assembly of nuclei located deep within each temporal lobe of the brain. Its predominant functions are emotional, memory and decision-making processes. It forms part of the limbic system

Aniridia Complete or partial absence of the iris. This can be associated with mutations or deletions in the *PAX6* gene

Anophthalmia Absence of eye(s), or the absence of any ocular structures that are sensitive to light. This is either congenital or the result of trauma or surgery (such as evisceration, enucleation or exenteration)

Anterior cingulate cortex A structure in the midline of the brain, anterior to the corpus callosum. It is associated with high-level cognition and emotional interpretation including self-awareness, verification of error, interpretation of social situations, learning, memory, pain experience and sleep

Anxiety disorder A category of mental health disorder with fear and anxiety as prominent features

Anterior ischaemic optic neuropathy (AION) Damage to the optic nerve as a result of ischaemia (reduced blood supply). This can be arteritic (AAION), due to inflammation of the arteries supplying the optic nerve (branches of the temporal artery, hence its association with temporal arteritis), or non-arteritic (NAION) in which the ischaemic damage is not due to inflammatory changes of these vessels

Arteritic anterior ischaemic optic neuropathy (AAION) Inflammation of the arteries supplying the optic nerve (branches of the temporal artery, hence its association with temporal arteritis) causing ischaemic damage to the optic nerve

Astrocyte (Pleural astroglia) a star-shaped cell present in the brain and spinal cord which provides structural and metabolic support to the central nervous system and has a role in maintaining the blood-brain barrier. It is also thought to have a role in circadian function

Astrocytoma A tumour of the central nervous system formed from astroglia

Ataxia A disorder of muscle control, with characteristic coordination difficulties of movement, gait and speech and ocular movements

Autoimmune disease A disorder in which the immune system forms antibodies against its own (self) cells in a particular tissue or tissues. Examples include neuromyelitis optica spectrum disorder, type 1 diabetes, myasthenia gravis, vitiligo, ulcerative colitis and Crohns disease

Autoimmune optic neuropathy A disorder of the optic nerve caused by an autoimmune condition such as neuromyelitis optica spectrum disorder

Best corrected visual acuity (BCVA) The best vision an individual can achieve using glasses or contact lenses

Best visual acuity (BVA) In this study, the best visual acuity of the better seeing eye was used as an outcome measure

Biogenic amine Refers to a monoamine neurotransmitter of the central nervous system, i.e. serotonin, dopamine or noradrenaline

Bitemporal hemianopia loss of the outer half of the visual field in both eyes

Blood-brain barrier (BBB) A cellular barrier with tight junctions between the circulating blood and the extracellular fluid within the brain and spinal cord. It affords a high level of discrimination in allowing solutes to pass through and is protective against infection

Buphthalmos Meaning “ox-eye” this is a phenomenon associated with congenital glaucoma, in which high intraocular pressure exerted on the elastic infantile globe leads to enlargement of the eye, which is usually accompanied by other signs of high intraocular pressure, including corneal haze and Haab striae

Café-au-lait spots Flat, pigmented spots which are light brown in colour and characteristic of certain disorders, including the neurofibromatoses

Caudate nucleus This forms part of the striatum, which is itself part of the basal ganglia. As such, it has a high density of dopaminergic neurones and is involved in spatial memory and initiation of movement. It also has roles in inhibitory regulation, emotional function, sleep, memory, goal-orientated activity and concomitant learning

Cerebrospinal fluid (CSF) The fluid that surrounds the brain and spinal cord. Its function is protection, homeostasis and clearance of waste products. It is produced by the choroid plexus and absorbed by the arachnoid villi of the meninges

Chronotype The circadian tendency of an individual either towards morningness (early bird), eveningness (night owl) or intermediate type

Ciliary body This comprises the ciliary muscle, which controls the lens shape for focusing, and the ciliary epithelium which produces aqueous humour

Clock genes Genes that regulate the internal circadian rhythm

Combined hamartomas of the retina and retinal pigment epithelium (CHRRPE) An oval-shaped benign pigmentation of the retina which may be an isolated finding, but may be associated with inherited disorders such as neurofibromatosis, particularly when found bilaterally or in clusters

Compressive optic neuropathy A deficiency of optic nerve function caused by compression of the optic nerve pathway anywhere between the optic chiasm and the eye. For example, a craniopharyngioma or pituitary adenoma could cause a compressive optic neuropathy

Confusional arousals A NREM sleep parasomnia in which the sleeping person appears to be awake as the sensorimotor system is active, but is dissociated from other brain systems, which are in slow wave sleep. Movement and vocalisations, slow mental processing and lack of recall after the event are common

Congenital optic neuropathy A disorder of the optic nerve that is present at or prior to birth, for example septo-optic dysplasia

Corpus callosum A structure in the midline of the brain that contains millions of nerve axons connecting the right and left cerebral hemispheres

Corticotrophic tumour A tumour of the pituitary gland arising from cells that secrete adrenocorticotrophic hormone (corticotrophs)

Counting Fingers (CF) A measure of visual acuity. At this measurement, the vision is too poor to visualise the letter chart.

Craniopharyngeal duct A channel that forms in the sphenoid bone anterior to the sella turcica. It is thought to be a remnant of embryologic development

Craniopharyngioma An embryogenic tumour that develops in the region of the sella turcica, which can produce deficits in pituitary and hypothalamic function due to its proximity to these structures, in addition to visual defects due to its propinquity to the optic chiasm

Cushing disease A constellation of symptoms due to increased secretion of cortisol. These include central obesity, insulin resistance, high blood pressure, fragile skin, moon-like facial features, proximal muscle weakness, sweating, mood changes, sexual dysfunction and sleep disturbances

Delayed phase sleep disorder (DPSD) Backward shifting of the circadian clock so that an individual is more likely to wake later in the day and sleep later at night than is normal

Delta-wave sleep This corresponds to deep sleep (NREM stages 3 and 4)

Demyelinating optic neuropathy An optic nerve disorder caused by a demyelinating condition, for example multiple sclerosis

Descemet membrane The basement membrane of the corneal epithelium, which serves as a barrier to maintain corneal desiccation and transparency

Diabetes insipidus A condition of excessive dilute urine production and markedly increased thirst. This can be due to dysfunction of the hypothalamus, pituitary gland, kidneys or genetic causes

Diplopia Double vision

Dominant optic atrophy (DOA) Also known as Kjer optic neuropathy, this is a dominantly inherited optic nerve disorder, most frequently caused by mutations of the *OPA1* gene

Dopamine A monoamine neurotransmitter of the central nervous system which plays an important role in reward circuitry, motor control and sleep wake

Dorsal raphe nucleus One of the raphe nuclei, which lies in the midline of the midbrain with a role in circadian regulation. It contains serotonergic neurones and pain mediation and is thought to have a role in narcolepsy and depression

Dysaesthesiae Abnormal sensory experiences such as pins and needles, shooting pains or numbness

Early Treatment Diabetic Retinopathy Study (ETDRS) The gold standard of evaluating best corrected visual acuity, in which the patient typically stands 4m from the chart and scoring is by letter count

Electroencephalogram (EEG) A measurement of brain activity used in polysomnography.

Electromyogram (EMG) A measurement of muscle activity used in polysomnography.

Electrooculogram (EOG) A measurement of eye movement which is used in polysomnography to determine when REM sleep is occurring

Electrophysiology A measurement of alterations in electrical current across cells. In this study, electrophysiology refers to visual evoked potentials (VEP) and electroretinography (ERG)

Electroretinogram (ERG) A measurement of the activity of rods, cones and ganglion cells of the retina. A flash of light is used to stimulate the retinal tissues and difference in electrical current is recorded

Enucleation Removal of the whole of the eyeball (globe) and its contents

Entrained circadian rhythm An internal circadian rhythm that is aligned to the light and dark cycle

Ependymoma A tumour that originates from the lining of the brain or central spinal canal

Epworth Sleepiness Scale (ESS) A measure of subjective daytime sleepiness

Evisceration Removal of the contents of the eyeball (globe), including all light sensitive structures, but leaving the outer layers of the eyeball in place

Exenteration Removal of the whole of the eyeball (globe) and its contents, in addition to the whole contents of the eye socket

Free-running circadian rhythm An internal circadian rhythm that is regular, but that is unrelated to the external light and dark cycle. The internal circadian clock usually runs at 24.5 hours per day, so this misalignment can accumulate over time.

Fundoscopy Examination of the back of the eye (posterior pole). This is usually with an ophthalmoscope or slit lamp

GABA Gamma aminobutyric acid, a neurotransmitter of the central nervous system

Galactorrhoea Milk secretion from the breast tissue

General Health Questionnaire (GHQ) A subjective measure of general health. The version used in this study was adapted from the Patient Health Questionnaire and collected demographic, socioeconomic and general health information

Glaucoma This is a group of eye conditions in which there is characteristic damage to the optic nerve. It is often associated with high intraocular pressure

Glioblastoma A malignant aggressive brain tumour originating from the central nervous system, of unknown cellular origin

Glioneural hamartoma A tumour formed from a combination of glial cells (myelin cells) and neural cells

Glutamate An excitatory neurotransmitter of the central nervous system. It forms the basic chemical structure of GABA

Goldmann visual field A formal assessment of visual fields, often the gold standard in optic nerve disorders

Gonadotrophin A hormone produced by the anterior pituitary gland to direct growth, sexual development and procreation. Examples are luteinising hormone and follicle stimulating hormone

Gonadotrophic tumour A tumour of the pituitary gland arising from cells that secrete luteinising hormone or follicle stimulating hormone (gonadotrophs)

Growth hormone (GH) A hormone produced by the anterior pituitary gland that stimulates growth, and cellular repair and replication

Gynaecomastia Development of breast tissue in males

Haab striae These are breaks in the Descemet membrane seen in congenital glaucoma due to the effects of high intraocular pressure

Hamartoma A cellular malformation that results in a benign tumour. It may be symptomatic due to its location, for example pituitary hamartomas can cause seizures

Hand movements (HM) A notation of poor visual acuity when an individual is unable to see the vision chart or count fingers, but is able to see movement of a hand in front of the eye

Hemianopia Loss of half of the visual field. This may be a homonymous hemianopia in which the same side of the visual field is lost in both eyes, or bitemporal, in which the outer half of the visual field is lost in each eye

Hereditary optic neuropathy (HON) An optic nerve disorder which is inherited as a result of the genetic information (either from inherited genes and chromosomes or from maternal mitochondrial DNA) passed from parent to child

Hippocampus This forms part of the limbic system and has a major role in storage of long-term memory and declarative memory. It is located in the inner temporal lobe of the brain

Hospital Anxiety and Depression Scale (HADS) A subjective assessment of mood, which particularly measures traits of depression and anxiety

Humphrey visual field (HVF) An objective measure of the visual field of each eye. A graphical plot is generated. A 24-2 HVF is a standard assessment of visual fields in glaucoma.

Hydrocephalus A build-up of fluid within the brain. This can cause an increase in intracranial pressure

Hyperpituitarism Oversecretion of hormones by the pituitary gland, most commonly resulting from a pituitary adenoma. Hormones that may be secreted in excess include prolactin, adrenocorticotrophic hormone, thyroid stimulating hormone, growth hormone, follicle stimulating hormone and luteinising hormone

Hypersomnolence Higher than normal sleep propensity, either in the day or at night. This is characterised by a reduced sleep latency (time taken to fall asleep) of less than eight minutes and elevated sleep times of nine hours or more

Hyperthyroidism Excessive secretion of thyroid hormones resulting in raised heart rate and blood pressure, palpitations, sweating, anxiety, diarrhoea and weight loss

Hypnagogic During the transition from wakefulness to sleep

Hypnagogic hallucinations A parasomnia of REM sleep, in which vivid visual, auditory and tactile hallucinations occur at the onset of sleep

Hypnopompic During the transition from sleep to wakefulness

Hypocretin Also known as orexin, a neuropeptide neurotransmitter that is produced by the hypothalamus and governs arousal, appetite and mood. Low levels are associated with narcolepsy

Hypogonadism Reduced function of the reproductive organs. This may be associated with diminished secretion of sex hormones, and underdevelopment or shrinkage of the organs

Hypopituitarism Deficiency of secretion of one or more of the eight hormones produced by the pituitary gland (prolactin, adrenocorticotrophic hormone, growth hormone, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone, antidiuretic hormone, oxytocin)

Hypothalamo-pituitary-adrenal (HPA) axis A set of interrelated glands with a major role in endocrine functioning with regulatory feedback governing hormonal secretion. This axis coordinates the stress response and immune, digestive and sexual activities in addition to mood, emotion and sleep

Hypothalamus A small midline structure at the base of the brain with several collections of nuclei which control secretion of hormones, regulate circadian cycles, control body temperature, blood pressure, heart rate, arousal, appetite, emotions and sexual activity

Hypothyroidism The consequence of insufficient production of thyroxine by the thyroid gland. This presents with reduced heart rate and blood pressure, low mood, tiredness, intolerance of cold, constipation and weight gain

Idiopathic intracranial hypertension (IIH) A disorder of increased pressure within the cerebrospinal fluid and increased intracranial pressure. The cause is unknown, although it is most prevalent in young women with a high body mass index

Infiltrative optic neuropathy An optic nerve disorder in which the optic nerve is infiltrated by growth of another tissue, for example an optic nerve glioma

Inflammatory optic neuropathy An optic nerve disorder caused by an inflammatory disorder, for example sarcoidosis

Intergeniculate leaflet A nucleus of the lateral thalamus that is involved in entrainment of circadian rhythms to a basic framework

Intraocular pressure The pressure exerted by the contents of the eye on the globe. This is measured with a tonometer, usually in mmHg

Iridocorneal angle Also known as the anterior chamber angle, this is the angle between the iris and the base of the cornea. The openness of this angle can be graded. A narrow angle has implications for drainage of aqueous humour and intraocular pressure

Jupiter Medical Centre Questionnaire (JMCQ) A subjective measure of sleep that evaluates features of sleep-disordered breathing and restless leg syndrome

Kjer optic neuropathy Also known as Dominant Optic Atrophy, this is a dominantly inherited optic nerve disorder which is most frequently caused by mutations in the *OPA1* gene

Leber hereditary optic neuropathy (LHON) A mitochondrially inherited optic neuropathy characterised by rapid loss of optic nerve axons and corresponding loss of vision over days or weeks. It is most common in young adult males

Lisch nodule A pigmented (melanocytic) hamartoma of the iris

Medial prefrontal cortex (MPFC) An area near to the midline of the frontal lobe of the brain that is involved in complex social interactions and self-referential memory

Medial raphe nucleus This lies in the midline of the midbrain and contains serotonergic neurones. It is thought to have a role in depressive mood and modulation of anxiety

Medulla oblongata Also known as the medulla, this forms part of the brainstem and carries out vital functions such as control of heart rate, blood pressure, breathing, swallowing, tongue movements, muscle tone and sensation, cough, gag and sneeze reflexes, balance and sleep

Meninges The membranous layers that surround the brain and spinal cord, which comprise the dura mater (outer layer) arachnoid mater (middle layer) and pia mater (inner layer)

Meningioma A slow-growing tumour of the central nervous system that arises from the meninges

Melanopsin A light-sensitive pigment found in photosensitive retinal ganglion cells (pRGCs) in the retina

Melatonin A hormone produced principally by the pineal gland. It is secreted in dim light conditions and regulates sleep wake

Melatonin suppression test (MNST) An assessment of melatonin levels (and by extrapolation, circadian entrainment) following exposure to bright light

Microglia These are macrophages located within the central nervous system, and form part of its immune defence

Missense mutation A mutation at one point in the genetic code in which one altered nucleotide base results in an altered amino acid code and formation of an altered protein structure

Mood disorder Also known as an affective disorder, this is a type of condition where a change in affect, or mood is apparent. Examples are major depressive disorder and bipolar disorder

Morningness-Eveningness Questionnaire (MEQ) A subjective measure of chronotype, or propensity towards morningness (early birds), eveningness (night owls) or intermediate types

Monoamine neurotransmitters These include serotonin, noradrenaline and dopamine and are derived from aromatic amino acids. They are involved in memory, emotion and arousal functions

Multifocal visual evoked potential (mfVEP) A visual evoked potential in which multiple areas of the visual field are stimulated simultaneously

Multiple Endocrine Neoplasia (MEN) A dominantly inherited syndrome of tumours (either benign or malignant) of multiple endocrine organs. There are several forms of MEN, each affecting a characteristic pattern of endocrine glands: MEN type I affects the pituitary, parathyroid glands and pancreas; MEN type II affects the thyroid, parathyroid glands and adrenal glands (types IIa and IIb have some differences in phenotypic presentation and inheritance). Familial medullary thyroid cancer is also a form of MEN.

Multiple Sclerosis (MS) A demyelinating disorder of the central nervous system that causes an array of motor and sensory symptoms. White matter plaques on neuroimaging which progress with time are diagnostic.

Multiple sleep latency test (MSLT) A standardised measurement of daytime sleep propensity. It evaluates a person's sleep latency, or how quickly they are able to fall asleep. It is used to distinguish hypersomnolence (excessive sleepiness) from general tiredness

Myelopathy A disorder of the spinal cord

Myopathy A disorder of muscle

Munich ChronoType Questionnaire (MCTQ) An evaluation of external factors on a person's circadian rhythms, which include social factors and seasons and the amount of sleep debt a person builds up, to determine their chronotype and sleep behaviours

Narcolepsy A neurological disorder characterised by episodes of sudden-onset sleep, which are usually associated with low hypocretin (orexin) levels

Neurofibroma A tumour of the neural sheath

Neurofibromatosis Type 1 A dominantly inherited condition in which tumours of the brain, spinal cord and peripheral nerves develops, usually in childhood. Common findings are skin neurofibromas (tumours), café-au-lait spots, learning disabilities, bony deformities and optic nerve gliomas

Neurofibromatosis Type 2 A dominantly inherited disorder that usually presents in adulthood of slow-growing tumours of the nerves. Common findings include hearing loss and balance problems due to an acoustic neuroma or vestibular schwannoma; optic nerve sheath meningiomas or schwannomas

Neuromyelitis optica spectrum disorder (NMOSD) An autoimmune inflammatory demyelinating condition of the optic nerves and spinal cord (transverse myelitis). Usual

presentations include visual disturbances and motor and sensory problems such as paraplegia, hemiplegia and numbness due to involvement of the spinal cord. Pain is also a common feature.

N-methyl-D-aspartic acid (NMDA) receptors An excitatory neurotransmitter receptor that is located throughout the central nervous system and is activated by both NMDA and glutamate. They are considered to have a role in synaptic plasticity, learning and memory, and in central sensitisation to pain in the spinal cord

Night terrors Also known as sleep terrors, a parasomnia of NREM sleep, in which vivid, frightening dreams occur, which may be accompanied by jerking of limbs, vocalisations and dream enactment

Non-arteritic anterior ischaemic optic neuropathy (NAION) An optic nerve pathology caused by ischaemia of the small vessels supplying the eye. In contrast to arteritic ischaemic optic neuropathy (AAION), it is not caused by inflammatory changes to the temporal artery or its subdivisions

No perception of light (NPL) A measure of visual acuity, in which conscious vision is completely absent – the individual is unable to discern a bright light being shone into the eye

Non-rapid eye movement (NREM) sleep This is defined by polysomnography and is known as quiescent sleep, in which sleep spindles and K complexes (biphasic waves) are present. It is divided into stages 1-4, which indicate progressive depth of sleep

Noradrenaline A monoamine neurotransmitter of the central and peripheral nervous system. It is also a catecholamine involved in the regulation of the sympathetic (autonomic) nervous system

Nucleus accumbens This forms part of the striatum of the basal ganglia, and is located in the basal forebrain, and is involved in reward, aversion, addiction, pain and sleep circuitry. Neurotransmitters in the nucleus accumbens include endogenous opiates. It forms a connection between the limbic and motor systems of the brain

Nucleus raphe magnus (NRM) This lies in the medulla oblongata and contains serotonergic neurones. It plays a role in motor control, pain signalling and endogenous analgesia

Obstructive sleep apnoea (OSA) Obstruction of the upper airway leading to episodes of apnoea (lack of breathing) during sleep

Oligodendrocyte (Pleural oligodendroglia) a myelin-producing cell of the central nervous system that provides support and electrical insulation to axons of nerve fibres

Olivary pretectal nucleus (OPN) A nucleus of the pretectum, in the midbrain, that forms part of the pupillary light response circuitry

Optic atrophy (OA) Loss of nerve fibres within the optic nerve, often characterised by a pale optic disc. It can be idiopathic, or can occur as the end result of compression, inflammation, trauma or ischaemia to the optic nerve

Optic chiasm The anatomical area where fibres from approximately half of each optic nerve cross over to form the optic tracts. The optic chiasm lies in close proximity to the pituitary gland and hypothalamus

Optical coherence tomography (OCT) An imaging technique used in ophthalmology using near-infrared light to create high resolution images of the retina and optic disc

Optic disc The portion of the optic nerve that is visible on fundoscopic examination of the eye – the nerve emerges at the back of the eye as a circular area with an outer rim and a central cup. The retinal arteries and veins emerge from the optic disc

Optic disc drusen (ODD) Congenital deposits of proteinaceous material in the optic nerve head which become calcified with age and can cause optic disc swelling. They can cause visual symptoms due to compression of the blood vessels at the optic disc

Optic nerve disorder (OND) A disorder of the optic nerve anywhere along its pathway from the optic disc to the optic chiasm

Optic nerve glioma An infiltrative tumour of the optic nerve that can occur sporadically or as part of a syndrome, for example neurofibromatosis type 1

Optic nerve hypoplasia (ONH) Underdevelopment of the optic nerve. It can occur sporadically or as part of a syndrome such as septo-optic dysplasia

Optic neuritis (ON) Inflammation of the optic nerve. This may be idiopathic, or due to a systemic condition, for example multiple sclerosis

Orexin Also known as hypocretin, this is a neuropeptide neurotransmitter produced by the hypothalamus that regulates wakefulness and satiety

Osteopetrosis An inherited syndrome of increased bone density and bony abnormalities. It can cause neural compression, including of the optic nerve. Other serious complications include low calcium levels, leading to seizures, and bone marrow failure

Parathyroid glands Four small glands that sit adjacent and posterior to the thyroid gland in the neck. They secrete parathyroid hormone and play a role in calcium and phosphate regulation

Parkinson disease (PD) A progressive neurological disorder which affects the dopaminergic neurones of the basal ganglia, leading to its stereotypic motor features of bradykinesia, rigidity and tremor. Other neural circuitry can be affected, leading to dementia, autonomic dysregulation and disordered sleep

Papilloedema Swelling of the optic discs in association with increased intracranial pressure

Parasomnia Atypical sleep behaviour, which occurs during NREM or REM sleep, and may be motor, perceptual or emotional in nature. This include somnambulation (sleep walking), bruxism (jaw clenching), sleep terrors and confusional arousals

Pattern electroretinogram (PERG) Use of a patterned visual stimulus to measure electrical responses of rods, cones and ganglion cells in the retina

Perception of light (PL) A measure of low visual acuity, in which the vision chart, counting fingers and hand movements cannot be discerned, although the presence or absence of a bright light shone into the eye can be detected

Periaqueductal grey matter (PAG) This is located in the midline of the midbrain and contains opioid receptors. The PAG has a role in pain transmission, chronic pain, and the analgesic "pain gate" mechanism, with projections to the raphe nuclei. It also has a role in response of the sympathetic nervous system to emotional and threatening stimuli

Perimetry A formal measure of visual fields – a visual field test, for example Humphrey perimetry, Goldmann perimetry

Periodic limb movement (PLM) A sleep disorder of recurrent jerking or twitching, particularly of the lower limbs, which may cause sleep disturbance for the sufferer or their bed partner

Peripapillary The area surrounding the optic disc

Peter anomaly Congenital corneal clouding due to malformation of the anterior segment of the eye, which affects the iris, Descemet membrane and corneal endothelium in Peter type I and in type II may be bilateral with the lens also affected

Photosensitive retinal ganglion cells (pRGCs) Non-image forming cells of the retina that contain the photopigment melanopsin and relay light information via the retinohypothalamic tract to the suprachiasmatic nuclei, the internal circadian pacemaker

Pittsburgh Sleep Quality Index (PSQI) A widely used subjective measure of sleep quality, in which a score greater than five indicates poor sleep quality (on a scale of 0-21)

Pituitary adenoma A tumour of the pituitary gland. It can cause endocrine dysfunction and visual field loss (most commonly bitemporal hemianopia) due to its proximity to the optic chiasm. They can cause pituitary insufficiency (under secretion) and hyperpituitarism (excessive secretion of pituitary hormones)

Pituitary insufficiency Also known as hypopituitarism, this is a disorder in which the pituitary gland secretes insufficient quantities of one or more of the hormones that it produces (TSH, ACTH, LH, FSH, prolactin, GH, ADH, oxytocin)

Pituitary macroadenoma A large (10mm or greater in diameter) tumour of the pituitary gland, which may cause endocrine dysfunction and visual field loss and are the most common cause of pituitary insufficiency

Pituitary microadenoma A tumour of the pituitary gland less than 10mm in diameter

Polydipsia Increased thirst drive leading to increased frequency of fluid intake

Polymorphism A variation in the genetic code for an allele. Some polymorphisms can result in coding for a different protein and a resulting genetic disorder

Polysomnography An objective measure of sleep wake that includes multiple parameters. These may include EEG, EOG, EMG, electrocardiogram, measurement of respiration with nasal and oral airflow transducers and pulse oximetry

Prefrontal cortex (PFC) An area at the anterior of the frontal lobe of the brain that is concerned with executive function, including personality, decision-making, complex awareness and social functioning

Primary angle closure glaucoma (PACG) A form of glaucoma in which the drainage angle between the iris and cornea is open. Intraocular pressure is increased, and there characteristic damage to the optic nerve. Loss of visual acuity and visual field can result

Primary open angle glaucoma (POAG) A form of glaucoma in which the drainage angle between the iris and cornea is narrowed or closed resulting in increased intraocular pressure and characteristic damage to the optic nerve. Loss of visual acuity and visual field can result

Prolactin A hormone secreted by the anterior pituitary gland. Its secretion stimulates milk production, and is associated with ovulation, sexual behaviours and appetite functions

Prolactinoma A tumour of the pituitary gland originating from lactrotrophic cells, which produce the hormone prolactin

Pupillary light response (PLR) The reflex response of the pupils to light, so that in bright light the pupil constricts. It is mediated by the photosensitive retinal ganglion cells of the retina, and the reflex arc includes the optic nerve, lateral geniculate nucleus, pretectal nucleus, Edinger Westphal nucleus and ciliary ganglion and oculomotor nerve. It can be used in locating lesions along this pathway

Putamen This forms part of the striatum, which in turn is part of the basal ganglia. It contains dopaminergic, GABAergic and cholinergic (acetylcholine) neurones and has a role in motor control, incidental and categorical learning and learning consolidation, and emotions of antipathy and contempt

Raphe nuclei These are serotonergic nuclei which lie in the midline of the medulla oblongata, pons and midbrain. They include the median raphe nucleus and dorsal raphe nucleus and project to the suprachiasmatic nuclei with roles in regulation of sleep wake, body temperature and appetite

Rapid eye movement (REM) sleep A stage of sleep characterised by rapid eye movements, with muscle atonia and a lack of central homeostatic regulation of body temperature, respiratory and circulatory function. Dreams tend to occur in this sleep stage

Rathke's pouch An embryological structure which originates from the buccal cavity, which gives rise to the anterior part of the pituitary gland. It is a precursor to the craniopharyngeal duct. Craniopharyngiomas are embryological tumours which can develop from this duct

Relative afferent pupillary defect (RAPD) A difference in the reflex response to light of one pupil compared to the contralateral pupil due to damage to neural fibres conducting the light impulse. This is frequently tested for in an assessment of ophthalmological and neurological disorders

REM sleep behaviour disorder (RBD) A condition of abnormal physical behaviours, vocalisations and limb jerking during sleep, and may feature dream enactment

REM sleep latency (REM latency) The amount of time between sleep onset and the first period of REM sleep, usually measured during polysomnography

Restless leg syndrome (RLS) A disorder in which there is an irrepressible urge to move the legs (the arms can also be affected). Abnormal sensations in the legs may be present and may increase in severity at night

Retinal nerve fibre layer (RNFL) The layer of the retina in which axons of ganglion cells lie. The axons of the RNFL are unmyelinated and converge at the optic disc to form the optic nerve

Retinohypothalamic tract (RHT) The pathway between the retina and the suprachiasmatic nuclei of the hypothalamus. It contains projections from photosensitive retinal ganglion cells which relay light information which entrains the internal circadian clock to day and night

Retinopathy of prematurity (ROP) A condition that affects premature babies born before 31 weeks' gestation. Abnormal growth of blood vessels in the retina can lead to scarring and retinal detachment, with later development of amblyopia and glaucoma

Schwannoma A tumour that arises from Schwann cells (cells that form the myelin sheath that surrounds neurones)

Sella (sella turcica) A saddle-shaped impression in the sphenoid bone in which the pituitary gland sits

Serotonin A monoamine neurotransmitter of the central nervous system that has a role in arousal, sleep and reward behaviours

Septo-optic dysplasia (SOD) A rare congenital condition of unknown aetiology in which optic nerve hypoplasia, dysgenesis of midline brain structures and abnormalities of pituitary function are present

Sclerocornea Congenital complete or partial opacification of the cornea, so that it is difficult to visually distinguish between the cornea and sclera

Septum pellucidum A membrane in the midline of the brain that lies below the corpus callosum and divides the anterior horns of the left and right lateral ventricles

SF-36 The Medical Outcome Study 36-Item Short Form Health Survey. It assesses quality of life in terms of physical, mental and emotional health, pain, energy and health perceptions

Sleep and circadian rhythm disorder (SCRD) A disorder of sleep wake which manifests as a shift in the circadian clock (the time a person goes to bed and wakes up). Examples include advanced phase sleep disorder (APSD), delayed phase sleep disorder (DPSD) and free running disorder (FRD)

Sleep-disordered breathing A range of disorders that cause an abnormal breathing pattern during sleep. An example is obstructive sleep apnoea

Sleep efficiency (SE) A formal measure of how effective a night's sleep has been. It is the ratio of the time spent asleep to the time spent in bed

Sleep latency (SL) A measure of the time it takes from being awake at rest before the onset of sleep

Sleep log/diary A record of sleep and wake times kept by an individual or their carer over a set period. It may also include a record of nightly sleep quality and night-time awakenings

Sleep terrors Also known as night terrors, a parasomnia of NREM sleep, in which vivid, frightening dreams occur, which may be accompanied by jerking of limbs, vocalisations and dream enactment

Snellen visual acuity A measure of visual acuity that uses black letters on a white chart. At the top of the chart, there is one large letter, and rows below this have sequentially smaller letters in greater numbers. The person undergoing the test stands 6 metres, or 20 feet from the chart and reads the letters with one eye covered

Somatotrophic tumour A tumour of the pituitary gland that originates from cells that produce growth hormone (somatotrophs)

Somnambulation Commonly known as sleepwalking, this is a NREM sleep parasomnia

Somniloquy Commonly known as sleep talking, this may be part of normal sleep, although it can also occur in disordered sleep and parasomnias, and may be comprehensible or unintelligible

Stage 1 sleep A stage of NREM sleep which occurs early after sleep onset, in which slow rolling eye movements and alpha waves occur

Stage 2 sleep A stage of NREM sleep in which a person is easily woken up and is characterised by the presence of K-complexes and sleep spindles

Stage 3 sleep A stage of NREM sleep. This is the initial stage of deep sleep, in which slow delta waves begin to appear

Stage 4 sleep A stage of NREM sleep that corresponds to deep sleep and slow, delta-wave activity

Striatum This comprises the caudate nucleus, the putamen and the nucleus accumbens, which are adjoining structures in the subcortical forebrain. It is a component of the basal ganglia and has roles in planning and consolidation of movement, impetus and appraisal of reward

Sturge Weber syndrome This is a congenital condition that is usually sporadic and is characterised by abnormal intracranial vascular malformations (leptomeningeal angiomas), port-wine stain birthmarks in the ophthalmic and maxillary distributions of the ipsilateral trigeminal nerve, seizures, glaucoma and developmental and learning disabilities

Subacute myelo-optic neuropathy An iatrogenic condition caused by exposure to clioquinol characterised by longstanding optic neuropathy, sensory, motor and autonomic dysfunction

Substantia nigra A pigmented structure in the midbrain with a high concentration of dopaminergic neurones. It forms part of the basal ganglia and is involved in the regulation of motor activity and reward behaviours

Suprachiasmatic nucleus/nuclei (SCN) Part of the hypothalamus located superior to the optic chiasm that acts as the "master clock" or primary regulator of the body's internal circadian rhythms

Slow wave activity (SWA) Also referred to as slow wave sleep (SWS), slow delta waves produced by the brain indicate deep sleep (NREM stages 3 and 4)

Slow wave sleep (SWS) This is deep sleep, in which delta waves are produced, and corresponds to NREM stage 3 and 4 sleep

Thalamus A large paired midline structure of the forebrain that serves as a relay centre with multiple nuclei with a wide range of functions. Its nuclei relay to the cortex, spinal tracts, basal ganglia and limbic systems. Information processed includes motor function, balance and fine motor activities, somatosensory interpretation, memory, learning, sleep wake, emotion, visual and auditory pathways and executive function

Theta-wave activity Rhythms of 4-8 Hz that are produced by the brain during relaxed wakefulness. They are associated with memory and emotional states and alterations in their production can be seen in transition between sleep and wakefulness

Thyroid stimulating hormone (TSH) A hormone secreted by the anterior pituitary gland that stimulates the thyroid gland to produce thyroxine. This, in turn, governs the basal metabolic rate of the body

Thyrotrophic tumour A tumour of the pituitary gland derived from cells that produce thyroid stimulating hormone (thyrotrophs)

Total sleep time (TST) A measure of the total amount of time spent asleep during the sleep period, not including periods of waking during sleep

Toxic optic neuropathy Damage to the optic nerve as a result of exposure to toxins, for example alcohol and chloroquine. It is usually bilateral and is more common in the presence of nutritional deficiencies

Trabecular meshwork A network of tissue located between the base of the cornea and the ciliary body. Its role is drainage of aqueous humour from the anterior chamber

Traumatic optic neuropathy Damage to the optic nerve caused by traumatic injury

Uveoscleral pathway A route through which aqueous humour leaves the anterior chamber of the eye. This is mostly across the tissues, such as the ciliary muscle, until it enters the choroidal vessels, emissarial veins and lymphatics

Vascular optic neuropathy An optic nerve disorder in which damage to the blood vessels supplying the nerve is interrupted. Examples include arteritic ischaemic optic neuropathy and non-arteritic ischaemic optic neuropathy

Ventrolateral preoptic area (VLPO) A nucleus of the anterior hypothalamus, which sits just anterolateral to the optic chiasm, that is active during NREM and REM sleep and contains GABA and galanin which suppress arousal systems in the brain

Vestibular schwannoma A tumour derived from the Schwann cells of the eighth cranial (vestibulocochlear) nerve

Visual acuity (VA) A measure of the clarity of the vision in each eye, usually from reading letters or numbers on a standardised chart from a set distance

Visual evoked potential (VEP) An electrical potential stimulated by a light or visual pattern (PVEP) which can be used to identify defects in the visual pathway

Visual field (VF) The range of peripheral and central vision of each eye

WAGR syndrome Wilms tumour, Aniridia, Genitourinary abnormalities, mental Retardation. This is associated with mutations or deletions of the *PAX6* gene

Wake after sleep onset (WASO) A measure of the amount of time a person spends awake after falling asleep during their night time sleep period

Wolfram syndrome (WS) A rare recessive genetic disorder which comprises diabetes mellitus, diabetes insipidus, optic atrophy, hearing loss in addition to renal and neurological problems

Zeitgeber An external cue that can influence the internal circadian rhythm, for example mealtimes, social and work routines and exercise. Light is the principal zeitgeber of the circadian clock.

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