The influence of diet on glycaemic control, sleep, and cognition

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Abstract

The overarching aim of this thesis was to examine the impact of diet on glycaemic control, cognition, and sleep using three different approaches. In Chapter 2, a systematic review of the effect of glycaemic load on acute cognition in children, adolescents, and adults was conducted. A meta-analysis of 15 studies revealed that the effect of breakfast glycaemic load on cognition was influenced by the timing of testing, sample age, glucose tolerance, and cognitive subdomain. Relative to a high glycaemic load, a low glycaemic load breakfast was associated with significantly better immediate episodic memory during the late postprandial period (>120 minutes). The beneficial effect of a low glycaemic load breakfast on episodic memory was greater in younger adults and those with better glucose tolerance. No differences in working memory and attention were revealed. A review of 16 studies involving children and adolescents suggested that a low glycaemic load breakfast may prevent a decline in episodic memory and accuracy of attention during the late postprandial period. The remaining five studies administered meals or drinks differing in glycaemic load after breakfast time, two of which reported that a high glycaemic load lunch benefitted performance. However, conclusions cannot be made given the paucity of studies.

In Chapter 3, the acute effects of consuming a HGL drink and LGL drink fifteen minutes before bedtime on sleep, sleep-dependent memory consolidation, and nocturnal glucose metabolism were examined in young, healthy males (n = 20). There was tentative evidence that measures of sleep architecture and continuity may be affected by the consumption of drinks differing in GL shortly before bedtime. However, most effects were either non-significant trends or no longer significant after controlling for multiple comparisons, which may reflect a lack of statistical power, the removal of several outliers, and the conservative nature of the Bonferroni correction.

In Chapter 4, the chronic effects of consuming cinnamon and turmeric/curcumin for three months were examined in apparently healthy middle-aged and older adults (n = 28). Primary outcome measures included glycaemic control and cognition, and secondary outcome measures included lipid profiles, c-reactive protein, mood, satiety, thirst, body mass index, and body fat percentage. There were no significant differences in any of these measures between the placebo group and active group after one, two, and three months of supplementation. It is likely that sample heterogeneity played a key role in the absence of significant effects.

A series of guiding principles were created by drawing from the strengths and limitations of the studies conducted as part of this thesis and past research. These guiding principles outline some of the factors that should be considered when designing studies. The goal of these guiding principles is to facilitate a better understanding of the complex relationship between blood glucose levels, cognition, and sleep in future.

Authors 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…….CGaylor……..(candidate)

Date……..28/03/2023……

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed…….CGaylor……..(candidate)

Date……..28/03/2023……

I hereby give my consent for my work, if relevant and accepted, to be available for photocopying and for inter-library loans **after expiry of a bar on access approved by the University.**

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The University's ethical procedures have been followed and, where appropriate, that ethical approval has been granted.

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Chapter 1

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List of abbreviations

GT = glucose tolerance	VAS = visual analogue scale
NGT = normal glucose tolerance	POMS-BI = Profile of Mood States-Bipolar
IGT = impaired glucose tolerance	WHO = World Health Organisation
IFG = impaired fasting glucose	OGTT = oral glucose tolerance test
T2DM = type 2 diabetes mellitus	MMSE = mini mental state examination
BMI = body mass index	HbA1c = haemoglobin A1C
GL = glycaemic load	PRISMA = preferred reporting items for systematic reviews and meta-analysis
HGL = high glycaemic load	ANOVA = Analysis of Variance
LGL = low glycaemic load	GRADE = grading of recommendations assessment, development, and evaluation
MGL = medium glycaemic load	SMD = standardised mean difference
GI = glycaemic index	CI = confidence intervals
HGI = high glycaemic index	PSG = polysomnography
LGL = low glycaemic index	SOL = sleep onset latency
MGI = medium glycaemic index	WASO = wake-after-sleep-onset
IAUC = incremental area under the curve	EOG = electrooculogram
AUC = area under the curve	EMG = electromyography
SGLUT 1 = sodium-dependent co-transporter 1	EEG = electroencephalogram
GLUT = glucose transporter	ECG = electrocardiogram
GLP-1 = glucagon-like peptide-1	REM = rapid eye movement
GIP = glucose-dependent insulinotropic polypeptide	NREM = non-rapid eye movement
BBB = blood brain barrier	AASM = American Academy of Sleep Medicine
HOMA-IR = homeostatic model assessment for insulin resistance	PSQI = Pittsburgh Sleep Quality Index
VLPO = ventrolateral preoptic nucleus	DASS-21 = Depression, Anxiety, and Stress Scale-21
GABA = gamma-aminobutyric acid	ESS = Epworth Sleepiness Scale
MCH = melanin concentrating hormone	LSEQ = Leeds Sleep Evaluation Questionnaire

Chapter 1.

1.1 General introduction

This chapter provides an overview of the key concepts covered in this thesis. The different approaches to classifying carbohydrates are first described, with a particular focus on glycaemic index (GI) and glycaemic load (GL). The digestion and absorption of carbohydrate is then briefly discussed, followed by peripheral and cerebral glucose metabolism. The relationship between glucose tolerance (GT) and diet is also briefly considered. The chapter ends with a review of the evidence for a relationship between GT and cognition.

1.2 Carbohydrate classification

1.2.1 Chemical classification

Carbohydrates can be categorised into one of four subtypes based on their degree of polymerisation (Cummings & Stephen, 2007). Monosaccharides are the most basic unit of a carbohydrate and contain one monomeric unit (e.g., glucose, fructose, and galactose), whereas disaccharides contain two monomeric units (e.g., sucrose, lactose, and maltose). Both monosaccharides and disaccharides are collectively referred to as sugars. Oligosaccharides are short-chain carbohydrates that contain between 3 to 9 monomeric units. Oligosaccharides can be further divided into malto-oligosaccharides (e.g., maltodextrins) and other oligosaccharides (e.g., raffinose and stachyose). Polysaccharides are long-chain carbohydrates that contain 10 or more monomeric units. A distinction can be made between starch polysaccharides which are digestible by enzymes in the small intestine (e.g., amylose and amylopectin) and non-starch polysaccharides (fibre) which are non-digestible (e.g., cellulose and pectin). Soluble fibres slow digestion, reduce cholesterol absorption, and lower postprandial glycaemia, whereas insoluble fibres have limited impact on metabolism. Some carbohydrates, such as inulin, exist in multiple forms and therefore do not fit into a specific subcategory. Dietary carbohydrates can also possess similar chemical properties but different physiological properties, rendering a chemical classification unsuitable at times.

1.2.2 Physiological classification

There are several ways to classify carbohydrates according to their physiology. For example, digestible (available) carbohydrates are digested and absorbed in the small intestine, whereas non-digestible (unavailable) carbohydrates are transported to the large intestine where they are fermented by gut microbiota. Carbohydrates can also be categorised as simple

(monosaccharides and disaccharides) or complex (oligosaccharides and polysaccharides). It was previously thought that postprandial glycaemia and insulinemia were determined by carbohydrate chain length and therefore complex carbohydrates were nutritionally superior to simple carbohydrates. However, complex carbohydrates produce a wide range of glycaemic responses, and in some cases simple carbohydrates produce smaller glycaemic responses than complex carbohydrates. After observing this variability, Jenkins et al. (1981) created the concept of GI, which quantifies the glycaemic response to a carbohydrate-containing food. GI and GL, a related concept, are discussed in detail in the next section.

1.2.2.1 Glycaemic index and glycaemic load

GI ranks carbohydrate-containing foods on a scale from 0 to 100 based on their postprandial glycaemic impact (Matthan et al., 2016). Carbohydrate-rich foods can be broadly classified as low GI (LGI; < 55), medium GI (MGI; 56-69), or high GI (HGI; > 70). Variations in GI are due to differences in the rate of digestion, absorption, and metabolism (Brouns et al., 2005). To calculate the GI of a food, fasted participants are required to consume 50 g of available carbohydrate from a test food on one occasion, followed by 50 g of available carbohydrate from a reference food (usually white bread or glucose) on another occasion. Two-hour blood glucose incremental area under the curves (IAUC) are determined by measuring capillary blood glucose levels every 15 to 30 minutes. Using the same participant, the GI is calculated by dividing the glucose IAUC of the test carbohydrate by the IAUC of the reference carbohydrate, multiplied by 100. Thus, the GI indicates the extent to which the available carbohydrate in a food raises blood glucose levels compared to an equal amount of a reference food. LGI foods are slowly digested and absorbed which elicits a smaller and slower rise and fall in postprandial glycaemia and insulinemia. Conversely, HGI foods are digested and absorbed quickly, producing a rapid rise and fall in glucose and insulin levels. The rapid release of insulin can result in a hypoglycaemic undershoot in some cases.

Although GI was originally developed as a tool to guide diabetics in their food choices, there is evidence that LGI diets may reduce the risk of type 2 diabetes mellitus (T2DM), heart disease, obesity, and mild cognitive impairment (Hodge et al., 2004; Power et al., 2015; Tavani et al., 2003). However, some LGI foods contain other nutrients that are beneficial to health, such as polyphenols, which may confound the health-promoting effects of LGI foods. Furthermore, some LGI foods contain high amounts of saturated fats, whilst some HGI foods are high in essential vitamins and minerals. The concept of GI has also been criticised for

failing to consider the quantity of carbohydrate consumed, which is an important determinant of the glycaemic response (Miller, 1993). For example, a larger portion of a LGI food can exert a greater impact on blood glucose levels than a smaller portion of a HGI food (Young & Benton, 2014a). Given this issue, the concept of GL was created. GL considers both the quality and quantity of a food and, as such, provides an overall measure of the total glycaemic impact of a specific portion of food (Aston et al., 2008). GL is calculated by multiplying the amount of available carbohydrate per serving of a food by its GI, divided by 100. Foods with a value of 10 or below are low GL (LGL), between 10 and 20 are medium GL (MGL), and 20 or above are high GL (HGL) (Aston, 2006). A HGI food can have a LGL if consumed in smaller quantities, whereas a LGI food can have a HGL if consumed in larger quantities. Studies have reported that GL is a stronger predictor of the glycaemic response than GI (Barclay et al., 2005), and stepwise increases in GL produce proportionate increases in postprandial glycaemia and insulinemia (Brand-Miller et al., 2003).

The practical usefulness of GI has been questioned because values are calculated using carbohydrates in isolation, yet carbohydrates are normally consumed as part of a mixed meal. Some studies have supported the predictability of GI in mixed meals (Wolever et al., 2006; Wolever et al., 1990), whereas others have not (Flint et al., 2004). However, it is important to note that GI and glycaemic response are not synonymous (Augustin et al., 2015). As such, the addition of protein, fat, fibre, or polyphenols to a meal changes the glycaemic response to that meal rather than its GI (Wolever et al., 1990). For example, fat stimulates the release of incretin hormones which results in a quicker clearance of glucose via increased insulin secretion (Carrel et al., 2011; Henry et al., 2005; Owen & Wolever, 2003). Fat, protein, fibre, and polyphenols can delay the absorption of carbohydrates by prolonging gastric emptying times, resulting in a lower glycaemic response (Blaak et al., 2012; Hlebowicz et al., 2007). Furthermore, certain polyphenols can inhibit pancreatic α-amylase enzymatic activity (Henry et al., 2005; Nayak et al., 2014; Wee & Henry, 2020).

1.3 Carbohydrate digestion and absorption

The chemical digestion of carbohydrate begins in the mouth via salivary α-amylase, which hydrolyses α-1,4-glycosidic bonds of starch into oligosaccharides of varying lengths (e.g., dextrins and maltotriose) and disaccharides (e.g., maltose). In the small intestine, where most carbohydrate digestion occurs, pancreatic α-amylase continues to cleave starch into smaller molecules. The end products of pancreatic α-amylase digestion are maltotriose, α-limit dextrins, and disaccharides. These are converted into their constituent monosaccharides by

brush border enzymes located on the surface of the intestinal epithelial cells. Lactase splits lactose into glucose and galactose, whilst maltase-glucoamylase hydrolyses maltotriose and maltose into glucose. Sucrase-isomaltase has two active sites. The sucrase site splits sucrose into fructose and glucose, whilst isomaltase hydrolyses the α-1,6-glucosidic bonds of α-limit dextrins into glucose. Thus, glucose, fructose, and galactose are the end products of carbohydrate digestion in the small intestine. Some carbohydrates (e.g., fibre) are not digested in the small intestine, but are instead fermented into short chain fatty acids by bacteria in the large intestine.

The absorption of glucose and galactose across the epithelium of the small intestine differs depending on their concentration in the intestinal lumen. When intestinal luminal concentrations are lower than in plasma, glucose and galactose are actively transported against the concentration gradient via the sodium-dependent co-transporter 1 (SGLUT 1). At high concentrations, transport is mediated by the facilitative glucose transporter (GLUT) 2 (Koepsell, 2020). Although GLUT 5 transports fructose via facilitated diffusion, GLUT 2 can also transport fructose when intestinal luminal concentrations are high (Fernández-Bañares, 2022). All three monosaccharides are then carried to the capillaries of the small intestine by GLUT 2. The capillaries connect with the hepatic portal vein, which transports the monosaccharides directly to the liver, where fructose and galactose are converted to glucose.

1.4 Glucose metabolism

1.4.1 Peripheral glucose metabolism

Glucose is the primary source of fuel for the human brain. During prolonged starvation (>48 hours), the brain switches to using ketone bodies for fuel so that glucose is spared for other tissues. Although the brain accounts for 2% of total body weight, it is highly active and consumes approximately 20% of energy derived from glucose at rest (Benton et al., 1996). Relative to the rate of glucose utilisation, glycogen stores in the brain are very small (Benton, 2001). Cerebral glycogen stores are rapidly depleted without a continuous source of glucose from the bloodstream, leading to symptoms such as dizziness, confusion, and impaired cognitive function (Guettier & Gorden, 2006). On the other hand, chronic hyperglycaemia can cause brain atrophy, nerve damage, and cognitive dysfunction (Allen et al., 2004; Asif, 2014; Yu et al., 2022). It is therefore crucial that blood glucose levels are kept within a narrow range of 4-6 mmol/L (Klover & Mooney, 2004).

Two pancreatic hormones with opposing actions play a key role in glucose homeostasis. Following the consumption of a carbohydrate-containing meal, elevated blood glucose levels stimulate the secretion of insulin from pancreatic β-cells. Insulin lowers the concentration of glucose in the blood by increasing the uptake of glucose into insulin-sensitive tissues. The uptake of glucose into muscle and adipose tissue is mediated by GLUT 4. Insulin also stimulates the synthesis of glycogen in the liver and muscles, termed glycogenesis. In healthy individuals, glycogen makes up approximately 10% of the total weight of the liver and 1-2% of skeletal muscle mass. When glycogen stores reach capacity, excess glucose is converted into fatty acids through a process of lipogenesis. Insulin also inhibits the synthesis of glucose from lactate and amino acids, termed gluconeogenesis (Röder et al., 2016).

Counterregulatory hormones are released in response to falling blood glucose levels (e.g., during sleep or prolonged exercise) to restore euglycemia. Glucagon is secreted from pancreatic α-cells, which stimulates the breakdown of glycogen to glucose in the liver, termed glycogenolysis. Insulin secretion is also suppressed which reduces the rate of glucose uptake and glycogenesis. Consequently, more glucose remains in circulation for uptake by the brain and body. During long periods of starvation, peripheral glycogen stores are eventually depleted. As amino acids and glycerol cannot directly influence blood glucose levels, they are converted to glucose via gluconeogenesis (Nuttall et al., 2008). Adrenaline also rapidly stimulates hepatic glycogenolysis and mobilises precursors for hepatic and renal gluconeogenesis (Sprague & Arbeláez, 2011). If glucose levels continue to fall, cortisol and growth hormone are released (Sprague & Arbeláez, 2011). Both hormones inhibit the release of insulin and stimulate lipolysis in adipose tissue and hepatic ketogenesis and gluconeogenesis (Brinkman et al., 2021; Thau et al., 2021).

The secretion of insulin, and suppression of glucagon, begins before glucose enters peripheral circulation via incretin hormones. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are rapidly secreted by endocrine cells in the epithelium of the small intestine after nutrient intake. GIP and GLP-1 are released into the bloodstream and stimulate pancreatic β-cells to release more insulin. Incretins also reduce gastric emptying. This phenomenon is called the incretin effect and it accounts for the removal of up to 80% of exogenous glucose (100 g) from circulation, thereby preventing excessive postprandial hyperglycaemia (Blaak et al., 2012). In addition, the peptide hormone amylin is co-secreted with insulin from β-cells. Amylin contributes to the lowering of blood glucose levels by inhibiting the secretion of glucagon and delaying gastric emptying (Martin, 2006).

1.4.2 Cerebral glucose metabolism

There is a positive correlation between extracellular glucose levels and blood glucose levels (Rostami & Bellander, 2011; van de Ven et al., 2012). Animal studies have shown that the concentration of glucose in the brain is 20-30% of that in the blood (Béland-Millar et al., 2017). There is also a time lag of up to 30 minutes between changes in peripheral glucose and changes in extracellular glucose (Abi-Saab et al., 2002; Gruetter et al., 1998). The transport of blood glucose across the blood brain barrier (BBB) is mediated by GLUT 1, which is highly expressed in the endothelial cells of the BBB (Koepsell, 2020). GLUT 1 transports glucose across the endothelial membrane of the BBB and into the brain extracellular fluid via facilitative diffusion. The expression of GLUT 1 and hence the rate of glucose transport across the BBB can change under certain circumstances. For example, the expression and activity of GLUT 1 in the endothelial cells of the BBB has been shown to increase in response to hypoglycaemia and decrease in response to hyperglycaemia (Patching, 2017). Astrocytes take up a considerable proportion of glucose via GLUT 1, where it is stored as glycogen, whilst GLUT 3 facilitates the uptake of glucose from extracellular fluid into neurons (Koepsell, 2020). The rate of glucose utilisation varies throughout the brain and is directly related to neuronal activity (Benton et al., 1996).

1.5 Glucose tolerance

GT is defined as the ability to appropriately regulate blood glucose levels and remove glucose from the bloodstream (Lamport et al., 2011). The gold standard method of measuring GT is a 2-hour oral glucose tolerance test (OGTT) (WHO, 2006). Following an overnight fast, a maximum of 75 g of glucose (1.75 g per kg of body weight) is consumed and blood glucose levels are measured every 30 minutes. The test is used to determine whether an individual has normal GT (NGT), impaired fasting glucose (IFG), impaired GT (IGT), or T2DM. The World Health Organisation (WHO, 1999) diagnostic criteria is shown in Table 1.

Table 1. World Health Organisation (1999) diagnostic criteria for normal glucose tolerance, impaired glucose tolerance, impaired fasting glucose, and type 2 diabetes.

	Fasting plasma glucose concentration (mmol/L)	2-hour plasma glucose concentration[1] (mmol/L)
NGT	<6.1	<7.8
IFG	6.1 to 6.9	<7.8
IGT	<7.0	≥7.8 to <11.1
T2DM	≥7.0	≥11.1

Note. 1 = 2-hours post-OGTT.

T2DM is a complex metabolic disease characterised by chronic hyperglycaemia and abnormal protein and lipid metabolism (Smushkin & Vella, 2010). T2DM is associated with impaired insulin secretion from pancreatic β-cells and diminished insulin action in insulin-sensitive tissues, termed insulin resistance. In the early stages of the disease, the pancreas secretes more insulin to compensate for hepatic and muscle insulin resistance. However, over time, β-cell dysfunction occurs, leading to impaired insulin secretion and hyperglycaemia (Sasaki et al., 2020). Additional factors that compound the hepatic and muscle insulin resistance include adipose tissue insulin resistance, increased glucagon secretion, reduced incretin secretion and sensitivity, and a reduced suppression of glucagon secretion during the postprandial state (Nauck & Meier, 2018).

IGT is an asymptomatic prediabetic state characterised by postprandial blood glucose levels that are higher than normal, but not to the extent that a diagnosis of T2DM is warranted. T2DM is always preceded by IGT, but IGT does not always lead to T2DM (Rao et al., 2004). IGT is caused by insulin resistance, whilst β-cell dysfunction contributes primarily to the transition from IGT to T2DM (Cai et al., 2019). IFG, on the other hand, is characterised by abnormally elevated fasting glucose levels. Both IFG and IGT are caused by insulin resistance, but the site of insulin resistance differs. Hepatic insulin resistance is severe in those with IFG, whereas skeletal muscle insulin resistance is severe in those with IGT (Abdul-Ghani et al., 2006). Furthermore, both IFG and IGT are associated with reduced early-phase (30 minutes post-OGTT) insulin secretion but only IGT is associated with reduced late-phase (60-120 minutes post-OGTT) insulin secretion (Abdul-Ghani et al., 2006).

1.5.1 Glucose tolerance and diet

Diet is one of many lifestyle factors that can influence GT. Given the impact of foods high in GL/GI on postprandial glycaemia, it is commonly recommended that individuals with abnormal glucose metabolism should consume diets high in fibre and low in GL/GI (Chiavaroli et al., 2021; Salas-Salvadó et al., 2011; Salmerón et al., 1997; Zafar et al., 2019). For example, a pooled analysis of three large cohort studies indicated that the risk of T2DM was 33% higher in those in the highest quantile of dietary GI, and 10% higher in those in the highest quantile of dietary GL, compared to those in the lowest quantile (Bhupathiraju et al., 2014). Similarly, a meta-analysis of 29 studies revealed that the consumption of a LGL/LGI diet (>3 weeks) significantly improved haemoglobin A1C (HbA1C) and fasting glucose levels in patients with T2DM (Chiavaroli et al., 2021).

Other aspects of diet can also influence GT. Polyphenols are a diverse group of naturally occurring compounds found in plant-based foods (e.g., fruits, herbs, spices, legumes, and coffee) that possess a range of biological activities that are beneficial to health (Costa et al., 2017; Kim et al., 2016; Sun et al., 2020). Polyphenols can be broadly categorised into four different groups according to the number of phenol rings and the way in which the rings are bound together, including flavonoids, lignans, phenolic acids, and stilbenes (Bahadoran et al., 2013). Due to their polyphenol content, studies have examined both the immediate effects of a single dose of cinnamon or turmeric on postprandial glycaemia, as well as their long-term effects on GT. For example, the consumption of yoghurt containing either cinnamon or turmeric significantly lowered peak glucose levels by nine percent relative to normal yoghurt in healthy participants (Pavalakumar et al., 2021). The addition of cinnamon or turmeric to high glycaemic breakfast cereals has also been shown to lower postprandial insulin levels (Wang et al., 2021) and glucose levels (Magistrelli & Chezem, 2012; Thota et al., 2018). Similar improvements in postprandial glycaemia have been demonstrated by administering cinnamon shortly before an OGTT (Solomon & Blannin, 2007; Solomon & Blannin, 2009).

The chronic effects of cinnamon or turmeric on GT are discussed in detail in Section 4.1.1 and 4.1.2, respectively. Briefly, studies have shown that chronic supplementation (>1 month) with cinnamon can improve fasting glucose, postprandial glucose, and HbA1c levels in type 2 diabetics (Akilen et al., 2010; Crawford, 2009; Lu et al., 2012; Mang et al., 2006; Mirmiranpour et al., 2020; Radhia et al., 2010; Sahib, 2016; Vafa et al., 2012) and individuals with IGT (Anderson et al., 2016; Romeo et al., 2020). Improvements in GT have also been reported in

healthy participants (Kizilaslan & Erdem, 2019; Solomon & Blannin, 2009). In contrast, improvements in GT have not yet been demonstrated in healthy participants following turmeric supplementation (Cox et al., 2015; Cox et al., 2020; Nieman et al., 2012; Oza, 2017; Tang et al., 2008). However, improvements have been reported in prediabetics and type 2 diabetics (de Melo et al., 2018; Yuan et al., 2022). Overall, these findings suggest that supplementation with cinnamon and turmeric offers a promising strategy for improving glycaemic control and preventing the onset of IGT or T2DM.

1.5.2 Glucose tolerance and cognition

Given the importance of glucose for brain functioning (Benton et al., 1996; Klover & Mooney, 2004), it is unsurprising that a relationship between GT and cognition exists. The nature of this relationship has been examined using cross-sectional and longitudinal designs. Studies investigating the glucose facilitation effect have also considered the influence of individual differences in GT. The different forms of evidence for a relationship between cognition and GT will be discussed separately in this section.

1.5.2.1 Longitudinal studies

Longitudinal studies have provided compelling evidence that T2DM increases the risk of cognitive decline and dementia (Allen et al., 2004; Cominetti et al., 2022; Fontbonne et al., 2001; Kanaya et al., 2004; Kumari & Marmot, 2005; Makino et al., 2021; Paile-Hyvärinen et al., 2009; Wang et al., 2022). However, T2DM is strongly associated with a number of comorbidities, such as obesity, hypertension, dyslipidaemia, and cardiovascular and cerebrovascular disease, which are independently associated with cognitive dysfunction (Iglay et al., 2016; Lamport et al., 2009). The confounding effect of these factors is likely to be weaker in those with IGT (Lamport et al., 2009). Longitudinal evidence for a relationship between IGT and cognition is mixed. Some studies have reported no differences in cognitive performance between individuals with NGT and IGT (Kumari & Marmot, 2005; Paile-Hyvärinen et al., 2009; Scott et al., 1998; Wang et al., 2022). In contrast, Kanaya et al. (2004) reported that verbal fluency declined over four years in females with IGT at baseline, but not males, despite no differences in cognition at baseline. A limitation of this study is that whilst cognition was measured at both baseline and follow-up, GT was only assessed at baseline. Vanhanen et al. (1998) reported that individuals with IGT at baseline and 3.5 years later had poorer Mini Mental State Examination (MMSE) scores and long-term memory scores than those with persistent NGT. No differences in verbal fluency and attention were reported. When the sample was split

according to gender, only males with IGT had poorer MMSE scores. Vanhanen et al. (1998) measured GT at baseline and follow-up, allowing individuals who were no longer prediabetic to be removed from the analysis. Given that the reproducibility of IGT diagnoses is poor (Balion et al., 2007), this may partly account for the non-significant associations reported in other longitudinal studies (Paile-Hyvärinen et al., 2009; Scott et al., 1998; Wang et al., 2022). Another factor that may be of importance is age. At baseline, the participants included in Kumari and Marmot (2005), Paile-Hyvärinen et al. (2009), and Wang et al. (2022) were approximately ten years younger than the participants included in Vanhanen et al. (1998) and Kanaya et al. (2004). Therefore, it is possible that the relationship between cognition and GT is influenced by age.

The association between IFG and cognition has also been examined. Relative to females with NGT, females with IFG had poorer psychomotor performance and immediate verbal memory at baseline, and poorer psychomotor performance at the 4-year follow-up (Yaffe et al., 2004). The risk of developing dementia over four years was also 40% higher in those with IFT. Fontbonne et al. (2001), on the other hand, reported no differences in cognition at baseline and during the 2- and 4-year follow-up visits. In this study, participants with MMSE scores below 27 were excluded, despite scores between 25 and 30 being considered normal. The use of stricter exclusion criteria may therefore play a role in the non-significant findings.

More recently, studies have investigated the relationship between cognition and elevated blood glucose levels within the normal range. Mortby et al. (2013) examined the relationship between fasting blood glucose levels and cognitive decline in healthy older adults (>68 years). The authors reported that higher fasting glucose levels at baseline were associated with lower grey and white matter regional volumes at the 12-year follow-up visit which, in turn, were associated with poorer working memory, executive function, processing speed, and language function. Anstey et al. (2015) reported that elevated HbA1c levels at the 5-year follow-up were associated with poorer memory at the 12-year follow-up in younger males (25-59 years) but not older males (>60 years). No differences were observed between younger and older females, and no relationship was reported between memory and fasting glucose levels. A limitation of these studies is that GT was only assessed at baseline, therefore these findings should be interpreted with caution. Ravona-Springer et al. (2012) also reported that elevated HbA1c levels at baseline were associated with lower MMSE scores 2.5 years later in a sample of cognitively healthy older adults (>75 years at baseline). The authors reported a decrease of 1.37 MMSE points per 1% increase in HbA1c. A strength of this study is that HbA1c and MMSE

performance was measured at baseline and the 2.5-year follow-up, enabling individuals with abnormal HbA1c and MMSE scores to be removed from the analysis.

1.5.2.2 Cross-sectional studies

Cross-sectional studies have also provided strong evidence that type 2 diabetics have impaired cognition (Dybjer et al., 2018; Teixeira et al., 2020; Zhou et al., 2015). For example, Palta et al. (2014) conducted a meta-analysis of 24 cross-sectional studies. Reductions in verbal memory, motor function, visual memory, processing speed, and executive function were reported in those with T2DM compared to those with NGT. A review of cross-sectional studies also reported that cognitive impairments in type 2 diabetics are greater in older adults and those with poorer glycaemic control (Awad et al., 2004). Cross-sectional studies in those with IGT have produced mixed findings. Dybjer et al. (2018) reported that older adults with IGT had slightly poorer processing speed, executive function, and memory than individuals with NGT. Nazaribadie et al. (2013) also reported that pre-diabetic adults, aged between 35 to 60 years, had poorer immediate and delayed memory than healthy controls, however no differences in attention were reported. In contrast, numerous studies have reported no differences in cognition between those with IGT and NGT (Fuh et al., 2007; Hiltunen et al., 2001; Kalmijn et al., 1995). Although Fuh et al. (2007) administered additional cognitive tests, these three studies administered the MMSE. Whilst the MMSE is a useful tool for detecting clinically impaired cognition, it is unlikely that this test is sensitive enough to detect subtle differences in cognition that might be expected between those with prediabetes and NGT (Lamport et al., 2009). It is also likely that the cognitive test battery administered in Fuh et al. (2007) lacked sensitivity, as no differences in cognitive performance were observed between those with NGT and T2DM.

The aforementioned studies largely classified participants as having NGT, IGT, and T2DM using the WHO diagnostic criteria (WHO, 1999). Another approach involves assessing cognitive performance in individuals with higher or lower blood glucose levels within the normal range. In the following studies, only non-diabetic adults were recruited, and GT and cognition were assessed on separate days. Perticone et al. (2021) divided healthy middle-aged and older adults into two groups based on whether their 1-hour postprandial glucose levels were above or below 8.6 mmol/L. Individuals with poorer GT performed worse on tasks of immediate and delayed episodic memory, whereas no differences in MMSE scores were reported. Vanhanen et al. (1997) divided elderly participants into two groups based on whether their glucose levels 2-hours after a 75 g OGTT were higher or lower than the median. Those

with poorer GT had impaired immediate and delayed episodic memory, attention, verbal fluency, and visuomotor speed. Furthermore, there were no differences in cognitive performance between those with poorer GT and type 2 diabetics. Messier et al. (2003) separated participants into two GT groups using a glucose recovery index (1-hour glucose minus baseline glucose). Older adults (>72 years) with poorer GT performed worse on tasks of working memory, episodic memory, and executive function. Awad et al. (2002) divided young adults into two groups based on the change in blood glucose levels from 1 to 2 hours following a 75 g OGTT. Immediate and delayed episodic memory scores were worse in participants with poorer GT.

Rather than arbitrarily dividing normoglycemic participants into two GT groups, several studies have correlated cognitive performance with indices of GT. Dahle et al. (2009) measured fasting blood glucose levels in adults aged between 18 to 78 years. Elevated fasting glucose levels, within the normal range, were associated with poorer delayed episodic memory on the most difficult memory task. When the sample was split according to sex, males with higher fasting glucose levels had slower working memory reaction times, whereas females with higher fasting glucose levels had poorer working memory accuracy. Wright et al. (2015) also reported that higher fasting glucose levels were associated with poorer immediate episodic memory, but only in men. Rolandsson et al. (2008) reported a negative association between episodic memory, but not semantic memory, and fasting and 2-hour glucose levels in non-diabetic females. No significant associations were found in men. Raizes et al. (2016) reported that higher fasting blood glucose levels in older adults were associated with slower reaction times. However, the influence of biological sex was not considered in this study. In healthy female undergraduates, Donohoe and Benton (2000) reported a negative correlation between vigilance and peak blood glucose levels during testing, and a positive correlation between memory and the speed at which a person's blood glucose levels returned to baseline after the nadir. A limitation of this study is that participants consumed their habitual breakfast on the morning of cognitive testing, however differences in breakfast composition have been shown to influence postprandial cognitive performance (Chapter 2).

Convit et al. (2003) also performed a correlational analysis using data from non-diabetic middle-aged and older adults. However, memory was assessed during an intravenous GT test. There was a negative correlation between fasting glucose, 2-hour glucose, and glucose area under the curve (AUC) and immediate and delayed paragraph recall. Similarly, Young and Benton (2014b) measured cognitive performance during an OGTT. Healthy middle-aged (41

to 60 years) and older (61 to 85 years) adults were classified as having poorer GT if their 2-hour OGTT glucose level was above 7 mmol/L. Older adults with poorer GT forgot more words from a word list than older adults with better GT. No significant differences in the rate of forgetting were reported in younger adults. As discussed in Section 1.5.2.3, the methodological approach taken by Young and Benton (2014b) could be considered problematic as the consumption of a glucose drink can ameliorate differences in cognitive performance between individuals with poorer and better GT. However, this method biases against, rather than favours, the detection of significant differences between GT groups.

1.5.2.3 Glucose tolerance and the glucose facilitation effect

During the last 40 years, a considerable number of studies have reported that the consumption of a glucose drink, relative to a placebo drink, enhances cognitive performance during the postprandial period. Studies have shown that episodic memory is particularly sensitive to the effects of glucose (Hall et al., 1989; Mantantzis et al., 2018; Messier, 2004; Owen et al., 2013; Smith et al., 2011; Stollery & Christian, 2015; Sünram-Lea et al., 2001, 2002). However, improvements in other cognitive domains/subdomains have also been reported, such as visuospatial memory (Stollery & Christian, 2016), working memory (Hall et al., 1989; Kennedy & Scholey, 2000; Meikle et al., 2004; Owen et al., 2013), and attention (Benton et al., 1994; Brown et al., 2020; Messier et al., 1997). The glucose facilitation effect is influenced by methodological factors such as age (Hall et al., 1989; Mantantzis et al., 2018; Meikle et al., 2004), the quantity of glucose administered (Gold, 1986; Sünram-Lea et al., 2011), and task difficulty (Scholey et al., 2001; Smith et al., 2011; Sünram-Lea et al., 2002). In this section, the impact of variations in GT, within the normal range, on the glucose facilitation effect will be covered.

In healthy undergraduates, Messier et al. (1999) compared episodic memory after the consumption of a glucose drink (50 g) or placebo drink. Participants with poorer GT (1-hour glucose minus baseline glucose) performed worse on tests of word list and paragraph recall after the placebo drink. The consumption of a glucose drink ameliorated this deficit, whereas performance in those with better GT was unaffected. Similarly, the consumption of a glucose drink improved deficits in word order recall in undergraduate students with poorer GT (Awad et al., 2002) and verbal and working memory in older adults with poorer GT but not middle-aged adults with poorer GT (Messier et al., 2003). In contrast, Riby et al. (2008) reported that the consumption of a 50 g glucose drink benefitted executive function in middle-aged adults

with better GT. Similarly, Smith and Foster (2008a) reported that the consumption of glucose enhanced delayed episodic memory in healthy adolescents under conditions of divided attention, but only in those with better GT (glucose AUC). Sünram-Lea et al. (2008) reported that glucose improved recognition memory in young adults, but measures of GT did not correlate with the number of hits or false alarms. However, this is the only study that administered 25 g of glucose, which may not be large enough to reveal differences in GT in young healthy adults.

Craft et al. (1994) extended these findings by examining the interaction between GT and age. Glucose improved memory in older males with better GT but had no effect in older males with poorer GT. In younger males, glucose improved memory in those with poorer GT and compromised memory in those with better GT. Older males with better GT and younger males with poorer GT had similar blood glucose levels, suggesting that a glucose facilitation effect is more likely to occur when postprandial blood glucose levels are within a specific range. However, more studies are needed that concurrently examine how age and GT influence the glucose facilitation effect.

1.5.2.4 Summary of findings

In summary, the link between T2DM and cognitive dysfunction is well established (Palta et al., 2014), whereas the evidence for cognitive deficits in those with IGT is inconsistent (Lamport et al., 2011). Conversely, there is strong cross-sectional evidence for cognitive deficits in individuals with elevated blood glucose levels within the normal range, suggesting that cognitive decline can occur even before the diagnostic criteria for IGT is met. It is, however, important to note that some participants in these studies had clinically defined IGT, potentially influencing the results. Nonetheless, impairments in a range of cognitive domains and subdomains have been reported in this population, including attention, working memory, verbal fluency, and executive function (Awad et al., 2004; Dahle et al., 2009; Donohoe & Benton, 2000; Messier et al., 2003; Raizes et al., 2016; Vanhanen et al., 1997). However, episodic memory deficits are most commonly reported (Awad et al., 2004; Convit et al., 2003; Dahle et al., 2009; Donohoe & Benton, 2000; Perticone et al., 2021; Rolandsson et al., 2008; Vanhanen et al., 1997; Young & Benton, 2014b).

Two methodological factors may have contributed to the discrepancies between IGT and NGT studies. Firstly, studies that examined cognitive performance in individuals with normoglycaemia utilised a wide range of GT parameters, such as fasting glucose, HbA1c, or

the change in blood glucose levels between two specific time points. Although this approach increases the likelihood of producing significant correlations by chance, it provides insight into how different GT indices relate to different aspects of cognition. Secondly, several studies involving individuals with IGT administered the MMSE. This test is designed to screen for dementia rather than detect subtle differences in cognition between individuals with NGT and IGT (Allen et al., 2004). Therefore, small but important decrements in cognition may have been missed in those with IGT.

Counterintuitively, the consumption of a glucose drink, which increases peripheral glucose levels, facilitates cognitive performance during the postprandial period (Hall et al., 1989; Kennedy & Scholey, 2000; Meikle et al., 2004; Sünram-Lea et al., 2008; Sünram-Lea et al., 2001). There is also evidence that the glucose facilitation effect is influenced by variations in age and GT within the normal range. However, the exact way in which these factors influence the glucose facilitation effect is unclear, as beneficial effects have been reported in young, middle-aged, and older adults with better and poorer GT (Awad et al., 2002; Craft et al., 1994; Messier et al., 1999; Messier et al., 2003; Riby et al., 2008; Smith & Foster, 2008a). Differences in the amount of glucose administered (ranging from 25 to 75 g), definitions of poorer and better GT, task difficulty, and task domain are likely to play a role in these inconsistencies.

1.6 Aims of thesis

- To perform a systematic review and meta-analysis of the effect of GL on postprandial cognition in children, adolescents, and adults, and to determine the influence of the timing of testing, cognitive subdomain, GT, and age (Chapter 2).
- To compare the effects of a HGL and LGL pre-bedtime drink on sleep, sleep-dependent memory consolidation, and nocturnal glucose metabolism in a sample of healthy young adults (Chapter 3).
- To investigate the chronic effects of cinnamon and turmeric/curcumin supplementation on glycaemia, cognition, lipids, inflammation, mood, thirst, satiety, body mass index (BMI), and body fat percentage in apparently healthy middle-aged and older adults (Chapter 4).
- To create a series of guiding principles for future research (Chapter 5).

Chapter 2

A systematic review and meta-analysis of the effect of breakfast glycaemic load on acute cognitive performance in adults.

The systematic review and meta-analysis of breakfast studies included in this chapter were published in the following paper: Gaylor, C., Benton, D., Brennan, A., & Young, H. A. (2022). The impact of glycaemic load on cognitive performance: a meta-analysis and guiding principles for future research. *Neuroscience & Biobehavioural Reviews,* 141, 104824.

2.1 Introduction

As discussed in Chapter 1, the consumption of a glucose drink can improve cognitive performance during the postprandial period (Hall et al., 1989; Kennedy & Scholey, 2000; Meikle et al., 2004; Sünram-Lea et al., 2008; Sünram-Lea et al., 2001). However, this paradigm lacks ecological validity as glucose is rarely consumed in isolation and as part of a normal diet (Gilsenan et al., 2009). Alternatively, studies have examined whether cognition is influenced by differences in the rate of carbohydrate digestion and absorption during the postprandial period. One way that this has been achieved is by administering meals or drinks differing in GI and GL (Cooper et al., 2012; Ingwersen et al., 2007; Young & Benton, 2014a, 2015). As GL provides an overall measure of the total glycaemic impact of a specific portion of food, and more strongly predicts the glycaemic response to food than GI (Barclay et al., 2005), it will be the focus of this systematic review and meta-analysis.

It has been hypothesised that a LGL meal or drink may benefit cognition 2 to 3 hours after consumption, reflecting a continuous source of glucose for the brain (Benton et al., 2003; Cooper et al., 2012; Young & Benton, 2014a). Conversely, a HGL meal or drink produces a rapid rise and fall in blood glucose levels which may disrupt cognitive performance, particularly if glucose concentrations fall below baseline (Nilsson et al., 2009; Young & Benton, 2014a). Indeed, mild hypoglycaemia (3.1 to 3.6 mmol/L) in healthy adults is associated with impairments in vigilance, short-term memory, and psychomotor performance (Fruehwald-Schultes et al., 2000; Stevens et al., 1989). The vast majority of studies have examined this hypothesis by manipulating the composition of breakfast (Anderson et al., 2020; Benton & Nabb, 2004; Deng et al., 2021; Lamport et al., 2013a; Lamport et al., 2009; Lee et al., 2019; Mahoney et al., 2005; Nabb & Benton, 2006a, 2006b; Young & Benton, 2014a, 2015). A smaller number of studies have manipulated the composition of meals or drinks consumed after

breakfast time (Akhavan et al., 2014; Drozdowska et al., 2021; Jansen et al., 2020; Keesing et al., 2019; Marchand et al., 2020).

Studies examining the effect of breakfast GL on cognition have produced mixed findings. For example, the consumption of a LGL breakfast, compared to a HGL breakfast, has been shown to benefit episodic memory, working memory, and attention (Benton et al., 2003; Cooper et al., 2012; Ingwersen et al., 2007; Mahoney et al., 2005; Nabb & Benton, 2006a; Nilsson et al., 2012; Wesnes et al., 2003; Young & Benton, 2014a, 2015). Other studies have reported the opposite effect (Dye et al., 2010; Nabb & Benton, 2006a; Smith & Foster, 2008b; Young & Benton, 2014a) or no effect of breakfast GL (Kaplan et al., 2001; Lamport et al., 2014). Similarly, inconsistent findings have also been reported by studies that manipulated the GL of meals or drinks consumed after breakfast time (Akhavan et al., 2014; Drozdowska et al., 2021; Jansen et al., 2020; Keesing et al., 2019; Marchand et al., 2020).

To date, only one published review has examined the effect of GL on acute cognitive performance (Gilsenan et al., 2009). The authors concluded that there was insufficient evidence to support an effect of breakfast GL on cognitive performance in children, adolescents, and adults. However, several studies have since been published, potentially enabling a quantitative synthesis of the literature (Anderson et al., 2020; Anderson et al., 2018; Anderson et al., 2021; Deng et al., 2021; Lee et al., 2019; Sanchez-Aguadero et al., 2020; van der Zwaluw et al., 2014; Young & Benton, 2014a, 2015). In Chapter 1, it was established that the glucose facilitation effect is influenced by sample age, task domain, and GT. It is plausible that these methodological factors have also contributed to discrepancies within this literature. Another factor that may be of importance is the length of time between meal or drink consumption and cognitive testing (Benton et al., 2003; Ingwersen et al., 2007; Wesnes et al., 2003; Young & Benton, 2014a). The impact of these factors on the relationship between GL and cognition has not yet been systematically explored via meta-analysis.

2.1.1 Aims of systematic review and meta-analysis

The primary aim of this chapter was to conduct an up-to-date systematic review and, for the first time, a meta-analysis of the impact of breakfast GL on acute cognitive performance in children, adolescents, and adults. The secondary aim was to examine the impact of methodological factors on the relationship between breakfast GL and postprandial cognition, including the timing of cognitive testing, sample age, task domain, and GT. Given the number

of studies that administered nutritional interventions after breakfast time, it was decided that the meta-analysis would only include studies that manipulated the GL of breakfast. A systematic review of studies that manipulated the GL of meals or drinks consumed after breakfast time was conducted instead (see Section 2.3.5 and 2.3.8).

2.2 Method

This systematic review and meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. PRISMA 2020 checklists are provided in Appendix 1. A study protocol was registered with PROSPERO (CRD42021229575).

2.2.1 Search strategy and selection criteria

A systematic search for studies published up to 31st January 2023 was conducted using PubMed, Scopus, and Cochrane Library. To identify relevant publications, the following search terms were used: 'cognitive function' or 'cognition' or 'cognitive performance' combined with 'glycaemic index' or 'glycaemic load' or 'breakfast' or 'lunch' or 'carbohydrate' or 'glucose' or 'sucrose' or 'isomaltulose'. The search was restricted to English-language articles only, and both British and American spellings of key search terms were used. Reference lists from articles and reviews identified during the electronic search were checked for additional studies. The British Library of Electronic Theses Online Service (http://ethos.bl.uk) was also searched to identify unpublished studies. Titles and abstracts were read to check for duplicates and to determine whether the study potentially met the inclusion criteria. Studies that did not fulfil the inclusion criteria or were clearly irrelevant to the review were eliminated. The remaining articles were read to establish their suitability. The systematic search was conducted by two independent individuals. Any disagreements were resolved by discussion.

Breakfast was defined as the first meal or drink of the day consumed between 6 and 10am after an overnight fast. For the purpose of this systematic review and meta-analysis, acute cognitive effects were defined as effects that were measured on the same day that a nutritional intervention was consumed. Consequently, studies that examined the second meal cognitive effect were excluded from the present review. Other than excluding non-breakfast studies from the meta-analysis, the same inclusion and exclusion criteria were used for the meta-analysis and systematic review.

The following inclusion criteria were applied:

- Studies that investigated the acute cognitive effects of variations in GL or studies that provided adequate information from which GL could be calculated.
- Randomised or non-randomised studies.
- Published or unpublished studies.
- Studies that used objective measures of cognition.
- Studies involving children/adolescents (5 to 17 years) or adults (>18 years) who were healthy (i.e., no diagnosis of disease) or had IGT or T2DM.

The following exclusion criteria were applied:

- Reviews or meta-analyses.
- Cross-sectional studies.
- Studies examining the second meal cognitive effect.
- Studies examining the chronic effects of dietary GL on cognition.
- Studies comparing food/drink intake with water, artificial sweeteners, or food/drink omission (e.g., breakfast consumption versus omission).

2.2.2 Data extraction

Two independent individuals extracted the following information using a standardised data spreadsheet: first author name, year of publication, participant characteristics (age, gender, and GT status), study characteristics (sample size, type of design, counterbalancing, randomisation, blinding, length of overnight fast, adjustment for confounding factors, length of washout period between test sessions, number of withdrawals, and control for previous days meal consumption/physical activity levels), characteristics of nutritional interventions (GL, GI, macronutrient content, and energy content), timing of blood glucose/cognitive tests, type of cognitive domain/subdomain assessed, name of cognitive test, and results of study.

The GL of a nutritional intervention was calculated using the reported GI value multiplied by the amount of available carbohydrate per serving and divided by 100. If the GI of a meal or drink was not reported, it was estimated using values provided by Atkinson et al. (2021) or Sydney Universities Glycaemic Index Research Service (SUGiRS). The two nutritional interventions with the largest difference in GL were categorised as the HGL or LGL interventions. Remaining meals or drinks were categorised as MGL interventions.

For the meta-analysis, means and standard deviations (SD) of each cognitive outcome, at each postprandial time point, after the LGL and HGL breakfast interventions were extracted. Sample sizes were recorded and, where possible, both adjusted and unadjusted means were extracted. Authors were contacted when data were missing or only change scores were reported. When an author did not respond, data were estimated from figures, or the study was not included in the meta-analysis.

2.2.3 Organisation process

Using the framework described by Harvey (2019), data were first categorised into one of the following cognitive domains and subdomains: memory (episodic, working, visuospatial, and semantic), attention (selective and sustained), processing speed, executive function (reasoning, problem solving, and inhibitory control), and psychomotor function. Next, as cognitive performance was measured at various time points throughout the postprandial period, data were further categorised into one of three time windows: early postprandial period (testing commenced between 10 – 59 minutes), mid postprandial period (60 – 119 minutes), or late postprandial period (120 minutes or later). These time windows were chosen to reflect specific points in the typical postprandial glycaemic response.

2.2.4 Risk of bias and certainty of evidence

Risk of bias was assessed by two independent individuals using The Cochrane Risk of Bias 2 tool (Sterne et al., 2019) for within-subjects and between-subjects trials. Disagreements were resolved through discussion. The following sources of bias were assessed: randomisation process (selection bias), deviations from intended interventions (performance bias), missing outcome data (attrition bias), measurement of outcome (measurement bias), selection of the reported results (reporting bias), and overall bias. Studies were classified as either 'low risk of bias', 'high risk of bias', or 'some concerns of bias'. To obtain additional information, theses and study protocols were checked and study authors were contacted where possible. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2008). Each cognitive subdomain was assessed based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. There were four possible outcomes: very low, low, moderate, or high.

2.2.5 Data handling and statistical analysis

Meta-analyses were conducted using a generic inverse variance method in Review Manager 5.3 [Computer programme]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. All analyses used a random effects model. Effect sizes reflected the standardised mean difference (SMD) between the HGL and LGL breakfast interventions, with 95% confidence intervals (CI). A minimum of three studies per analysis were required. Using the guidelines reported by Cohen (2013), SMD were interpreted as trivial (< 0.2), small (between 0.2 and 0.6), moderate (between 0.6 and 1.2), or large (between 1.2 and 2.0). A p value of <0.05 was considered significant, whilst a p value between 0.06 and 0.1 was considered a trend. Heterogeneity was examined using the I^2 statistic, a value above 50% indicated substantial heterogeneity which required exploration.

Studies involving adults were analysed separately from studies involving children and adolescents. To examine the influence of time, three separate meta-analyses were performed for each postprandial time window where possible (early postprandial period = 10 – 59 minutes, mid-postprandial period = 60 – 119 minutes, or late postprandial period = 120 minutes or later). Two a priori subgroup analyses were also performed where data were available. To examine the influence of age in adults, studies were categorised into either the younger or older subgroup based on whether the mean age of the sample was below or above 35 years of age. This cut-off value was chosen because it achieved the most equal subgroup sample sizes, however there is evidence that certain aspects of cognitive function peak at approximately 35 years of age (Hartshorne & Germine, 2015; Strittmatter et al., 2020). To examine the influence of GT in adults, participants were classified as having better or poorer GT if fasting glucose was below or above 6.1 mmol/L and/or 2-hour glucose was below or above 7 mmol/L. Due to an insufficient number of studies, the influence of age and GT was not examined in children and adolescents. For the same reason, the following post hoc subgroup analyses were not performed: a) use of dairy and b) difference in GL between HGL and LGL nutritional interventions.

To determine the influence of each individual study on pooled effect sizes and p values, sensitivity analyses were conducted using the leave-one-out method. The effect of removing studies that did not match both the macronutrient and energy content of breakfast interventions was also examined, as well as the effect of including either unadjusted or adjusted means in the analysis. Publication bias was assessed by visual inspection of funnel plots; a minimum of

10 studies were required. The Cochrane Handbook for Systematic Reviews of Interventions states that change scores and post-scores should not be analysed as SMD together. Therefore, separate analyses were performed when necessary. In cases where the same cognitive domain was measured twice within the same postprandial time window, the measurement taken at the time closest to the other studies was used.

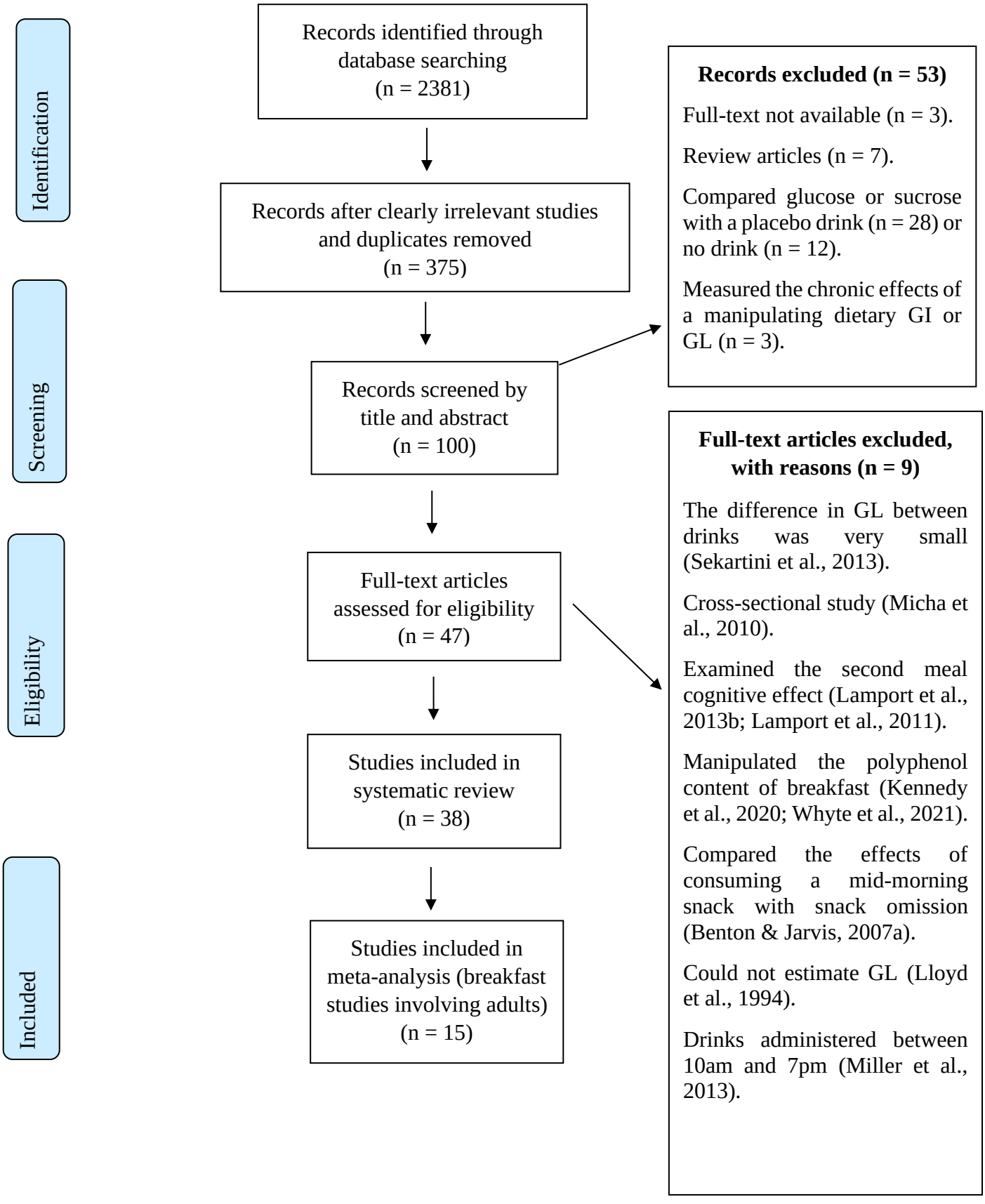


Figure 1. PRISMA flow diagram of the screening and literature selection process.

2.3 Results

2.3.1 Study selection and characteristics

As shown in Figure 1, 2381 publications were initially identified, of which 47 were potentially eligible. These studies were read fully, and a further nine studies were excluded. A total of 38 studies met the inclusion criteria. Thirty-three studies manipulated the GL of breakfast. Seventeen studies involved adults (Table 2) and 16 studies involved children and adolescents (Table 4). The remaining five studies administered nutritional interventions after breakfast time. Of the two studies involving adults (Table 3), one study manipulated the GL of lunch (Marchand et al., 2020) and the other manipulated the GL of an afternoon drink (Keesing et al., 2019). Of the three studies involving children, two studies manipulated the GL of a lunchtime meal (Drozdowska et al., 2021; Jansen et al., 2020) and one a mid-morning snack (Akhavan et al., 2014). These studies are summarised in Table 6. A systematic review of non-breakfast studies involving adults and children and adolescents can be found in Section 2.3.5 and 2.3.8, respectively.

For the meta-analysis, data were obtained from 15 adult studies for measures of episodic memory, working memory, and attention. Dye et al. (2010) and Kaplan et al. (2000) were not included in the meta-analysis as data were not available. Several other cognitive domains/subdomains were assessed, but these were also not included in the meta-analysis due to limited data. A detailed discussion of these cognitive outcomes can be found in Section 2.3.4. Data were obtained from 11 studies involving children/adolescents for measures of episodic memory, working memory, and attention. However, for several reasons, a meta-analysis of the data was considered inappropriate. Firstly, data were not obtained from five studies (Benton et al., 2007b; Cooper et al., 2012, 2015; Lee et al., 2019; Taib et al., 2012). Secondly, in some cases, data were available but only for certain cognitive subdomains (Ingwersen et al., 2007; Mahoney et al., 2005; Wesnes et al., 2003). Thirdly, three studies only reported change scores (Brindal et al., 2012; Brindal et al., 2013; Wesnes et al., 2003). As change scores and post-scores were analysed separately, this reduced the number of studies included in each analysis, often to the point that there were no longer enough studies to perform a meta-analysis (i.e., less than 3 studies). Consequently, only a systematic review of the literature was performed, which can be found in Section 2.3.7.

2.3.2 Breakfast studies involving adults

2.3.2.1 Study characteristics

All studies were randomised, of which four used a between-subjects design and 13 used a within-subjects design. Mean age ranged from 20.36 years (Nabb & Benton, 2006a) to 78 years (van der Zwaluw et al., 2014), and sample sizes ranged from 18 (Lamport et al., 2014) to 189 participants (Nabb & Benton, 2006a). Four studies were double-blind (Deng et al., 2021; Dye et al., 2010; Ginieis et al., 2018; Young & Benton, 2014a). In Kaplan et al. (2000), participants were blinded to the glucose drink condition. The majority of studies recruited healthy participants, several of which examined the influence of GT on the relationship between breakfast GL and cognition using a range of GT parameters (Anderson et al., 2018; Anderson et al., 2021; Kaplan et al., 2000; Nabb & Benton, 2006a, 2006b; Nilsson et al., 2009, 2012; van der Zwaluw et al., 2014; Young & Benton, 2014a). Two studies recruited participants with clinically diagnosed T2DM (Lamport et al., 2013a; Papanikolaou et al., 2006), and one study recruited participants with IGT (Lamport et al., 2014). Cognitive tests were administered at various times throughout the postprandial period, ranging from 15 minutes (Ginieis et al., 2018) to 225 minutes post-breakfast (Nilsson et al., 2012). Other than Benton et al. (2003), all studies measured more than one cognitive domain/subdomain. Deng et al. (2021), Ginieis et al. (2018), and van der Zwaluw et al. (2014) were the only authors to administer one cognitive test battery.

GL was manipulated using various methods. Five studies sweetened meals or drinks using sugars differing in GL, including glucose, sucrose, isomaltulose, or fructose (Deng et al., 2021; Dye et al., 2010; Ginieis et al., 2018; van der Zwaluw et al., 2014; Young & Benton, 2014a). Two studies administered breakfasts matched for carbohydrate quantity (50 g of available carbohydrate) but differing in carbohydrate quality (Kaplan et al., 2000; Papanikolaou et al., 2006). Nilsson et al. (2009) also provided 50 g of available carbohydrate from a glucose drink which was consumed either as a bolus to simulate a HGL drink or sipped in small amounts for 150 minutes to simulate a LGL drink. In a later study, Nilsson et al. (2012) compared the effects of white bread supplemented with or without guar gum, which slows the rate of absorption. Benton et al. (2003) administered meals differing in slowly available glucose and rapidly available glucose. The remaining seven studies administered realistic meals or drinks, some of which were matched for macronutrient and energy content (Anderson et al., 2018; Anderson et al., 2021; Lamport et al., 2014; Lamport et al., 2013a; Nabb & Benton, 2006a, 2006b; Sanchez-Aguadero et al., 2020).

2.3.2.2 Risk of bias and certainty of evidence

The results of the risk of bias assessment are summarised in Appendix 2. Overall, five studies showed a low risk of bias, and 12 studies showed some concerns of bias. Studies were generally judged with some concerns of bias for the following reasons: a) the method of randomisation and/or allocation concealment was not reported, b) a pre-registered study protocol was not found; therefore, it is unclear whether statistical analysis plans were changed and/or whether certain cognitive outcomes were selectively reported, and c) it was unclear whether the researcher(s) administering the cognitive tasks were aware of which breakfast intervention was consumed. For the 'deviations from intended interventions' domain, studies that used a within-subjects design were judged as having a high risk of bias if participants were clearly not blinded. The certainty of evidence assessment is reported in Appendix 3. Assessments ranged from very low (working memory and attention) to low (episodic memory). The main issues were risk of bias, as discussed above, and imprecision.

Table 2. Summary of breakfast studies involving adults.

Author (Year)	Participant characteristics	Study design	Breakfast intervention	Cognitive test	Timing of cognitive and glucose tests	Results	Comments
Anderson et al. (2018)	86 healthy participants (57 female, 29 male). Mean age = 21.09 (SD = 2.48). GT status = fasting BGLs at each test session (continuous variable).	WS. Randomised. Counterbalanced. Overnight fast. 48-hour minimum washout period. Prior to testing, no exercise or alcohol consumption (24 hours).	1. HGL = 237 mL of apple juice (120 kcals, 29 g CHO, 0 g PRO, 0 g fat, 11.3 GL[3]) 2. LGL = 237 mL of 1% fat milk (110 kcal, 12 g CHO, 8 g PRO, 2.5 g fat, 4 GL[3]) 3. Control = water	Go-no-go task (executive function - inhibitory control), RMCPT (working memory), and SCPT (sustained attention).	Cognition = 30, 90, and 120 minutes. Glucose levels = fasted only.	Go-no-go task = those with fasting BGLs above 104.97 mg/dL made fewer omission errors, at 30 minutes, after the LGL drink vs. HGL drink. RMCPT = those with higher fasting BGLs displayed better performance (RT and accuracy) 30 minutes after the LGL drink vs. HGL drink. Opposite pattern occurred for those with lower fasting BGLs.	Drinks had different macronutrient profiles but provided similar amounts of energy. Included BMI and biological sex as covariates. Fasting glucose included as a repeated factor.

Anderson et al. (2021)	44 participants (22 female, 22 male). Mean age = 30.81 years (SD = 8.36). GT status = fasting BGLs at each test session and change in plasma glucose levels from baseline to 30 minutes after drinking juice.	WS. Randomised. Counterbalanced. Overnight fast. 48-hour minimum washout period. Prior to testing, no exercise or alcohol (24 hours), tobacco (1 hour), and caffeine (8 to 12 hours).	1. HGL = 237 mL of apple juice (120 kcal, 29 g CHO, 0 g PRO, 0 g fat, 11.3 GL^3) 2. LGL = 237 mL of 2% fat milk (122 kcal, 12 g CHO, 8 g PRO, 5 g fat, 4.4 GL^3) 3. Control = water	CNS Vital Signs battery: Stroop task, symbol digit coding, shifting attention task, CPT, and 4-part CPT. Created five composite scores: working memory, processing speed, executive function, complex attention, and simple attention.	Cognition = 00, 30, 90, and 150 minutes. Glucose levels = 00, 30, 60, 90, 120, 150, and 180 minutes.	No effect of GL on any cognitive measure. Complex attention = there was a trend (non-significant) towards a GL X GT interaction. At 30 minutes, performance was better after consuming the LGL drink in those with higher fasting glucose, whereas performance was better after the HGL drink in those with lower fasting glucose. At 150 minutes, this pattern reversed.	Drinks had different macronutrient profiles but provided similar amounts of energy. Included biological sex, BMI, and baseline cognitive performance as covariates. Both measures of GT status were included as repeated factors in separate analyses.

Benton et al. (2003)	71 healthy female participants. Mean age = 21 years. GT status not assessed.	BS. Randomised. Overnight fast.	1 of 2 meals PLUS sugar-free orange drink, decaffeinated coffee/tea, and skimmed milk, if required. 1. HGL = cereal bar (219.5 kcal, 31.3 g CHO, 3.65 g PRO, 8.85 g fat, 20 GL[4]) 2. LGL = biscuit (230 kcal, 34 g CHO, 3.3 g PRO, 8.8 g fat, 14 GL[4])	WLR task (immediate and delayed episodic memory).	Immediate memory = 30, 90, 150, and 210 minutes (delayed memory was assessed 10 minutes after each test). Glucose levels = 00, 20, 50, 80, 140, 200, and 230 minutes.	Higher global memory scores[1] at 150 and 210 minutes after consuming the LGL breakfast vs. HGL breakfast. No significant difference at 30 and 90 minutes.	Meals provided similar amounts of PRO and fat but different amounts of CHO and energy. Differences in performance occurred when BGLs were similar.
Deng et al. (2021)	55 healthy participants (41 female, 14 male).	WS. Randomised. Counterbalanced.	1. HGL = carbonated water sweetened with 50 g of sucrose with 250 μL lemon flavouring (32 GL[4])	ROCF (immediate and delayed visuospatial memory),	Cognition = 60 minutes. Glucose levels	No effect of GL on any cognitive measure.	Macronutrient content of drinks were matched.

	Mean age = 25.5 years (SD = 5.7). GT status not assessed.	1-week minimum washout period. Overnight fast. Double-blind. Prior to testing, no vigorous exercise or alcohol (24 hours).	2. LGL = carbonated water sweetened with 50 g of isomaltulose with 250 μL lemon flavouring (16 GL[4]) 3. Control = sucralose lemon drink	HVLT (WLR - immediate and delayed episodic memory), a self-developed Trail-Making Part B task (attention and executive function), and Stroop task (executive function – inhibitory control).	(measured using a different group of participants who did not undergo cognitive testing) = 00, 30, 60, 90, 120, and 150 minutes.		Administered one cognitive test battery, at a time when BGLs were almost identical. Regression adjusted for order of drink consumption, quality of previous night's sleep, and the degree of drowsiness and hunger before test
Dye et al. (2010)	24 healthy male participants.	WS. Randomised. Overnight fast.	1. HGL = 429 mL of a milk-based drink sweetened with 50 g of sucrose (325 kcal, 11.2% CHO, 1.3%	VVLT (immediate and delayed episodic memory, word recognition, and	Cognition = 00, 35, and 115 minutes.	Serial Sevens task = faster responses 35 minutes following the HGL drink vs. LGL drink in those with slower baseline response times. No effect of GL	Drinks had identical macronutrients and energy profiles.

	Mean age = 23.4 years (range = 18 – 32 years). GT status not assessed.	Counterbalanced. Double-blind. Standardised evening meal. Prior to testing, no exercise or alcohol consumption (24 hours).	PRO, 2.1% fat, 32 GL[5]) 2. LGL = 429 mL of a milk-based drink sweetened with 50 g of isomaltulose (325 kcal, 11.2% CHO, 1.3% PRO, 2.1% fat, 16 GL[5]) 3. Control = 429 mL of water	learning of word list), Serial Sevens task (working memory), and a self-developed psychomotor test (psychomotor speed).	Glucose levels = continuous glucose monitor inserted at baseline in 12 participants.	in those with faster baseline response times. No effect of GL on the remaining tests.	Baseline cognitive performance included as a covariate. Adjusted for the influence of visit and order of drink consumption. Used a milk-based vehicle – insulinotropic.
Ginieis et al. (2018)	49 healthy participants (28 female, 21 male). Mean age of fasting group =	WS. Randomised. Double-blind. Counterbalanced.	1. HGL = 26 g of glucose (25 kcal, 0 PRO, 0 fat, 0 fibre, 24.9 GL[5]) 2. MGL = 14.5 g of sucrose (14 kcal, 0	SRT task (speed of processing), arithmetic processing task (speed of processing and problem	Cognition = 20 minutes. Glucose levels = 00, 25, and 50 minutes.	SRT task = slower performance following the HGL drink vs. LGL drink for both the fasted and non-fasted group, and slower performance vs. MGL drink but only in the fasted group.	Drinks matched for PRO, fat, and fibre. Contained different amounts of CHO.

	22.6 years (SD = 4.2) and non-fasting group = 24.3 years (SD = 4.9). GT status not assessed.	1-week washout period. Participants either fasted overnight or ate and drank as normal.	PRO, 0 fat, 0 fibre, 8.7 GL[5]) 3. LGL = 13 g of fructose (12 kcal, 0 PRO, 0 fat, 0 fibre, 1.56 GL[5]) 4. Control = sucralose lemon drink	solving), and Stroop task (attention and executive function - inhibitory control).		Arithmetic task = slower performance after the HGL drink vs. LGL and MGL drink, but only in the fasted group. Stroop task = slower RTs after the HGL and MGL drink vs. LGL drink for both the fasted and non-fasted group. No differences in error rates between drink conditions.	Only measured cognition during the early PPP. Adjusted for the influence of order of drink consumption.
Kaplan et al. (2000)	20 healthy elderly participants (10 female, 10 male). Mean age = 72.3 years (SD = 1.4,	WS. Randomised. Blind to glucose and placebo condition. Overnight fast.	50 g of available CHO from: 1. HGL = 300 mL glucose lemon drink (0 g PRO, 0 g fat, 50 GL[4])	WLR task (immediate episodic memory) and paragraph recall task (immediate and delayed episodic memory).	Cognition = 15, 60, and 105 minutes (testing started shortly after blood glucose sampling).	No effect of GL on any cognitive measure. Poorer baseline performance and poorer β cell function = associated with enhancements in immediate and delayed paragraph recall after the consumption of 50 g of CHO,	Breakfasts provided identical amounts of available CHO. Barley and mashed potatoes contained similar amounts of PRO and fat.

	range = 60 – 82 years). GT status = β cell function, insulin resistance, and glucose AUC.	Counterbalanced.	2. MGL = 312 g of mashed potatoes with 2.5 g of butter to use as required (4 g PRO, 2 g fat, 41.50 GL[4]) 3. LGL = 196 g of barley with 2.5 g of butter to use as required (5 g PRO, 2 g fat, 12.50 GL[4]) 4. Control = 300 mL lemon flavoured saccharin drink.	*During delay periods:* Trail-Making Part B (attention and executive function) and video clip task (sustained attention).	Glucose levels = 00, 15, 60, and 105 minutes.	regardless of its source, compared to a placebo. Poorer β cell function = associated with improvements in Trails Part B performance after the consumption of 50 g CHO. LGL meal consumption was most strongly related to improvements in memory performance.	Included biological sex as a between-subjects factor. 91.3% of barley, and 75% of mashed potato, was not consumed – possibly contributed to non-significant findings.
Lamport et al. (2013a)	24 clinically diagnosed T2DM patients (12 female, 12 male) and	WS. Randomised.	1. HGL = Lucozade energy drink (307 kcal, 75 g CHO, 0 g PRO, 0 g fat, 0 g fibre, 71 GL[3])	VSLT (immediate and delayed visuospatial memory),	Cognition = 30 and 120 minutes.	No effect of GL on any cognitive measure.	Breakfasts had different macronutrient profiles but provided identical

10 healthy controls (6 female, 4 male). Mean age of T2DM = 61 years (SD = 1.9) and controls = 56.2 years (SD = 2). GT status = WHO criteria for NGT and T2DM.	1-week washout period. Overnight fast. Counterbalanced. Standardised evening meal.	2. LGL = toast, yoghurt, and margarine (307 kcal, 37.3 g CHO, 20.9 g PRO, 9.3 g fat, 5 g fibre, 12 GL^3) 3. Control = water	VVLT (immediate and delayed episodic memory, and word recognition), paragraph recall (immediate and delayed episodic memory), Corsi Block Tapping test (spatial memory), Tower of Hanoi (executive function – planning ability), self-developed psychomotor test	Glucose levels = 00, 15, 30, 60, 90, 120, 150, and 180 minutes.	amounts of energy. Statistical adjusted for the influence of biological sex. Lucozade Energy Original contained 48 mg of caffeine, potentially masking the negative effects of the HGL drink.

				(psychomotor skill), and Grooved Peg Board test (psychomotor skill).			
Lamport et al. (2014)	18 females with IGT and 47 females with NGT. Mean age of IGT/LWC = 38.56 years (SD = 4.89), IGT/ HWC = 41 years (SD = 6.54), NGT/LWC = 36.2 years (SD = 5.2), and NGT/ HWC =	WS. Randomised. 1-week washout period. Overnight fast. Counterbalanced. Standardised evening meal	1. HGL = Lucozade energy drink (307 kcal, 75 g CHO, 0 g PRO, 0 g fat, 0 g fibre, 71 GL^3) 2. LGL = toast, yoghurt, and margarine (307 kcal, 37.3 g CHO, 20.9 g PRO, 9.3 g fat, 5 g fibre, 12 GL^3) 3. Control = water.	VSLT (immediate and delayed visuospatial memory), VVLT (immediate and delayed episodic memory, and word recognition), paragraph recall (immediate and delayed episodic memory), Corsi	Cognition = 30 and 120 minutes. Glucose levels = 00, 15, 30, 60, 90, 120, 150, and 180 minutes.	VVLT (immediate) = in the IGT/HWC group, more words were recalled during the most demanding trial at 120 minutes following the LGL breakfast vs. HGL breakfast. VSLT (delayed) = scores were lower after the HGL breakfast at 120 minutes in the IGT/HWC group compared to NGT/LWC group. This pattern was not observed after consuming the LGL breakfast.	Breakfasts had different macronutrient profiles but provided identical amounts of energy. NGT group possibly underpowered due to small sample size.

	37.91 years (SD = 5.96). GT status = WHO criteria for IGT and NGT. Waist circumference (low = <80 cm, high = >80cm.			Block Tapping test (spatial memory), Tower of Hanoi (executive function – planning ability), self-developed psychomotor test (psychomotor skill), and Grooved Peg Board test (psychomotor skill).		The remaining cognitive tasks were not affected by GL.	Lucozade Energy Original contained 48 mg of caffeine, potentially masking the negative effects of the HGL drink.
Nabb and Benton (2006a)	189 female participants.	BS. Randomised.	1 of 8 meals containing low or high CHO (24 or 59 g), fat (1 or 16 g),	Self-developed WLR task (immediate and delayed episodic	Cognition = 30, 75, and 120 minutes.	WLR task = better GT/LP had higher global memory scores[1] vs. better GT/HP and poorer GT/LP. Those who ate LP and	Macronutrient and energy composition of

	Mean age = 20.36 (SD = 3.48) GT status = fasting BGLs below or above 5 mmol/L.	Overnight fast.	and PRO (2 or 10 g), and a sugar-free orange drink, decaffeinated coffee/tea, and skimmed milk, if required. Kcal range = 114 - 407, CHO range = 24.2-59.6 g, PRO range = 1.7-9.9 g, fat range = 1-16.5 g, GL range = 12.23-52.66[3].	memory), Hick paradigm (SRT and CRT – speed of processing), and RIPT (sustained attention).	Glucose levels = 00, 20, 50, 95, and 140 minutes.	had better GT also had the lowest BGLs. Global memory scores[1] were higher in those with better GT/LCLF vs. poorer GT/LCLF. Hick paradigm = better GT/HCLP had faster decision times vs. better GT/LCLP. RIPT = better GT/HCHF made more correct responses vs. better GT/LCHF. Poorer GT/LCHF also made more correct responses vs. better GT/LCHF.	certain meals differed.
Nabb and Benton (2006b)	168 female participants. Mean age = 20.41 (SD = 1.99).	BS. Randomised. Overnight fast.	1 of 8 meals containing low, medium, or high CHO (10/30/50 g) and fibre (1.5/6/13 g), and a sugar-free	Self-developed WLR task (immediate and delayed episodic memory), Hick paradigm (SRT	Cognition = 30 and 90 minutes. Glucose levels = 00,	WLR task = fewer words forgotten[2] in those with poorer GT/LC vs. poorer GT/HC. Higher global memory scores[1] in those with poorer GT/medium fibre vs. poorer GT/low fibre.	Macronutrient and energy composition of certain meals differed.

	GT status = fasting BGLs below or above 6 mmol/L.		orange drink, decaffeinated coffee/tea, and skimmed milk, if required. Kcal range = 81.80 - 274.90, CHO range = 14.45-49.84 g, PRO range = 4.26-14.06 g, fat range = 0.34-2.08 g, GL range = 3.01 - 35.45[5].	and CRT – speed of processing), and RIPT (sustained attention).	20, 50, 80, and 110 minutes.	Hick paradigm = in those with better GT, decision times were faster when medium CHO or high CHO was consumed with low fibre. No effect of GL on sustained attention.	Did not assess cognitive performance during the late PPP.
Nilsson et al. (2009)	40 healthy participants (20 female, 20 male).	WS. Randomised. Counterbalanced. Overnight fast.	1. Simulated HGL = 50 g of glucose in 450 mL of water consumed as a bolus (within 10 – 12 minutes)	Self-developed working memory test (verbal working memory) and picture test (visual selective	Working memory = 35, 90, 120, and 150 minutes.	Working memory task = better accuracy scores 90 minutes after the LGL drink vs. HGL drink. At 35 minutes, there was an order effect, whereby performance was better on the second day of testing. Analysis	GL of drinks could not be calculated due to the method of manipulating breakfast GL.

	Mean age = 59 years (range = 49 – 70 years). GT status = above or below median split of BGLs 3-hours after 50 g bolus. (5.4 mmol/L).	Standardised evening meal. 1-week minimum washout period.	2. Simulated LGL = 50 g of glucose in 450 mL of water, divided into six equal parts and sipped every 30 minutes for 150 minutes	attention and RT).	Selective attention = 170 minutes. Glucose levels = 00, 15, 35, 45, 60, 90, 150, 170, and 180 minutes.	of day 1 data indicated that performance was similar at 35 minutes, but better 90 and 120 minutes after the HGL drink vs. LGL drink. Selective attention task = better accuracy scores 170 minutes after consuming the LGL drink vs. HGL drink. No differences in RT occurred.	Did not report whether there was an interaction between GT and GL. Order of meal consumption included as a between-subjects factor, and GT included as a covariate.
Nilsson et al. (2012)	40 healthy participants (28 female, 12 male). Mean age = 62.9 years (SD = 5,	WS. Randomised. Counterbalanced. Overnight fast.	50 of available starch from: 1. HGL = 124 g of white wheat flour-based bread (100 GI)	Self-developed working memory test (verbal working memory) and picture test (selective	Working memory = 90, 135, 180, and 225 minutes. Selective attention =	Selective attention task = better accuracy scores 120 minutes after the LGL bread vs. HGL bread. When only the most difficult part of the test was analysed, the difference in performance was greater. Specifically, accuracy scores	Meals provided similar amounts of macronutrients and energy. Did not report whether there was an interaction

	range = 49-71 years). GT status = above or below median split of glucose incremental AUC.	Standardised evening meal. 1-week minimum washout period.	2. LGL = 179 g of white wheat flour-based bread supplemented with guar gum (45 GI)	attention and RT).	75, 120, 165, and 210 minutes. Glucose levels = 00, 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes (measured using another group of participants).	were better after consuming the LGL bread vs. HGL bread at each time point (75-210 minutes). No effect of GL on sustained attention RTs or working memory scores.	between GT and GL. Order of meal consumption included as a between-subjects factor.
Papanikolaou et al. (2006)	21 clinically diagnosed T2DM patients (11 female, 10 male).	WS. Randomised. 1-week washout period.	50 g of available CHO from: 1. HGL = white bread, cheese, and	HVLT (WLR - immediate and delayed episodic memory) and WMS (paragraph	Cognition = 15, 62, and 100 minutes.	HVLT = better immediate recall, and delayed recall at 100 minutes, after consuming the LGL meal vs. HGL meal.	Meals provided identical amounts of available CHO, but different amounts of PRO and fat.

	Mean age = 65 years (SD = 7.29). Fifteen participants were medicated (taken directly before meal consumption)	Overnight fast.	tomato sauce (37 GL^6) 2. LGL = pasta, cheese, and tomato sauce (22 GL^6) 3. Control = water	recall - immediate and delayed episodic memory). *During first and second delays:* Digit span forward task (working memory), Trail-Making test (Part A = attention and processing speed, Part B = attention and executive function), and Test of	Glucose levels = 00, 5, 15, 62, 100, and 138 minutes.	WMS = delayed paragraph recall (62 and100 minutes) was better after consuming the LGL meal vs. HGL meal. Digit span forward test = performance better after the LGL meal vs. HGL meal, but only during the first delay (prior to 62 minutes). Trails Part B = larger improvement in performance from the first to the second administration of the test after consuming the LGL meal vs. HGL meal. No effect of GL on Test of Everyday Attention and Trails Part A performance.	No control group – unclear what effects may have occurred in healthy participants. Regression included HbA1c values, depression scores, intelligence scores, and visit as covariates where appropriate (also checked whether BMI and age needed to be included).

				Everyday Attention (Part A = sustained attention, Part B = auditory selective attention).			
Sanchez-Aguadero et al. (2020)	40 healthy participants (20 female, 20 female). Mean age = 28.1 years (range = 20-40 years). GT status not assessed.	WS. Randomised. 1-week washout period. Participants required to maintain stable dietary habits between test sessions.	1. HGL = white bread, jam, grape juice, and water (315 kcal, 72 g of CHO, 3.9 g PRO, 0.9 g fat, 1.6 g fibre, 46.08 GL[4]) 2. LGL = low fat yoghurt, an apple, three walnuts,72% dark chocolate, and water (356 kcal, 31.5 g CHO, 9.7 g PRO,	WLR (immediate and delayed episodic memory), phonological fluency task (semantic memory), and Trail-Making test (Part A = attention and processing speed, Part B = attention and	Cognition = 00, 60, and 120 minutes. Glucose levels = 00, 60, and 120 minutes.	Phonological fluency = at 120 minutes, there was a decline in phonological fluency scores after the LGL breakfast but not the HGL breakfast. No effect of GL on the remaining tasks.	Meals had different macronutrient and energy profiles. Statistically adjusted for age and educational level. There was a hypoglycaemic undershoot 60 minutes after

		Limited physical activity, smoking, and alcohol consumption 24 – 48 hours prior to testing.	19.9 g fat, 6 g fibre, 9.26 GL[4]) 3. Control = water	executive function).			consuming the LGL breakfast, which is not typically observed.
van der Zwaluw et al. (2014)	43 older adults with self-reported memory complaints (27 female, 16 male). Mean age – 77.7 years (SD = 5.6). GT status = above or below median split of	WS. Randomised. 1-week minimum washout period. Overnight fast.	1. HGL = 250 mL of water sweetened with 100 g of sucrose and lemon flavouring (0 g PRO, 0 g fat, 0 g fibre, 65 GL[5]) 2. LGL = 250 mL of water sweetened with 50 g of glucose and lemon flavouring (0 g PRO, 0 g fat, 0 g fibre, 50 GL[5])	Administered a large battery of tests: RAVLT, digit span forwards and backwards, TAP (LDST, Flexibility, and Alertness subtests), story recall subset of the Rivermead Behavioural Memory tests, PAL test, Stroop	Cognition = 15 minutes. Glucose levels = 00, 15, 30, 60, and 90 minutes.	Working memory = better performance after the HGL drink vs. LGL drink. No significant difference in attention and information processing composite scores. However, within this domain, performance on the flexibility subtest of the TAP was faster after the HGL drink vs. LGL drink.	Drinks provided identical amounts of PRO and fat. The HGL drink contained twice as many calories and CHO. Assessed cognitive performance at one time point. Both drinks produced similar

	incremental AUC after glucose consumption.		3. Control = water with artificial sweeteners	test, and phonological fluency test. Created four composite scores: episodic memory, working memory, attention and information processing speed, and executive functioning.		No effect of GL on the remaining cognitive tests/compositive scores.	glycaemic responses (no significant difference in BGLs at any time point).
Young and Benton (2014a)	155 healthy participants (96 female, 58 male).	BS. Randomised. Double-blind.	1. HGL = breakfast sweetened with 15 g of glucose, and an orange drink sweetened with 25 g	Self-developed WLR task (immediate and delayed episodic memory),	Cognition = 30, 105, and 195 minutes.	WLR task = the better GT/above baseline group had better memories 30, 105, and 195 minutes after consuming the LGL breakfast vs. MGL	Meals had identical macronutrient and energy profiles.

Mean age = 55.35 years (SD = 10.63, range = 45-80 years). GT status = OGTT performed on a separate day (poorer GT or better GT = above or below 7 mmol/L at 120 minutes, then further divided into above or below fasting glucose).	of glucose (275 kcal, 56.4 g CHO, 9.3 g PRO, 1.45 g fat, 45.4 GL^3) 2. MGL = breakfast sweetened with 15 g of sucrose, and an orange drink sweetened with 25 g of sucrose (275 kcal, 56.4 g CHO, 9.3 g PRO, 1.45 g fat, 34.9 GL^3) 3. LGL = breakfast sweetened with 15 g of isomaltulose, and an orange drink sweetened with 25 g of isomaltulose (275	phonological fluency task (semantic memory), Serial Sevens task (working memory), RIPT (sustained attention), and Hick paradigm (SRT and CRT – speed of processing).	breakfast, and 105 and 195 minutes after consuming the LGL breakfast vs. HGL breakfast. The better GT/below baseline group had higher episodic memory scores 195 minutes after consuming either the LGL or MGL breakfast vs. HGL breakfast. The poorer GT/above baseline group had higher episodic memory scores 30 minutes after consuming the HGL breakfast vs. LGL breakfast. Serial Sevens task = the better GT/above baseline group made more errors 195 minutes after	Did not measure BGLs. GT included as a between-subjects factor, and cognitive performance on day 1 as a covariate (also checked whether age, biological sex, and BMI needed to be included as covariates).

	kcal, 56.4 g CHO, 9.3 g PRO, 1.45 g fat, 24.3 GL[3])	consuming the HGL breakfast vs. LGL breakfast. No other effects reported.

Note. 1 = calculated by summing immediate and delayed memory scores, 2 = difference between immediate and delayed memory scores, 3 = GL values reported by study authors, 4 = GL values calculated using reported GI values multiplied by amount of CHO or available CHO, 5 = GL values calculated using published GI tables, and 6 = GL values taken from Philippou and Constantinou (2014). BS = between-subjects design, WS = within-subjects design, LWC = low waist circumference, HWC = high waist circumference, OGTT = oral glucose tolerance test, BMI = body mass index, BGLs = blood glucose levels, AUC = area under the curve, 00 = baseline, GT = glucose tolerance, IGT = impaired glucose tolerance, NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus, RT = reaction time, SRT = simple RT, CRT = choice RT, WLR = word list recall, CHO = carbohydrate, PRO = protein, LP = low protein, HP = high protein, LC = low carbohydrate, HC = high carbohydrate, LF = low fat, HF = high fat, LGL = low glycaemic load, MGL = medium glycaemic load, HGL = high glycaemic load, RAVLT = Rey Auditory Verbal Learning Test, HVLT = Hopkins Verbal Learning Test, WMS = Wechsler Memory Scale, TAP = Test for Attentional Performance, LDST = Letter Digit Substitution Test, PAL = Paired Associate Learning, RIPT = Rapid Information Processing Task, VVLT = Visual Verbal Learning Test, VSLT = Visual Spatial Learning Test, ROCF = Rey-Osterrieth Complex Figure, CPT = continuous performance test, RMCPT = running-memory CPT, SCPT = standard CPT, PPP = postprandial period, HbA1c = haemoglobin A1C.

2.3.3 Meta-analysis

A meta-analysis was performed to determine the effect of breakfast GL on immediate episodic memory, delayed episodic memory, working memory (accuracy), and attention (accuracy and speed). Note that Nabb and Benton (2006a) and Nilsson et al. (2009) were excluded from all GT subgroup analyses because the authors defined poorer GT using a particularly low cut-off point. Although Young and Benton (2014a) compared the cognitive effects of breakfast GL across four glucoregulatory groups (Table 2), data from only the poorer GT and better GT group were analysed. Data were extracted from figures for one study (Papanikolaou et al., 2006).

2.3.3.1 Immediate episodic memory

2.3.3.1.1. The influence of the timing of testing

Forest plots of effect sizes with 95% CI are shown in Figure 2. During the early postprandial period (15 – 30 minutes), there was no significant difference in immediate episodic memory scores between the HGL and LGL nutritional interventions (SMD = 0.05, 95% CI = -0.09 – 0.19, p = 0.51, I^2 = 0%), nor during the mid-postprandial period (60 - 105 minutes; SMD = 0.08, 95% CI = -0.07 – 0.23, p = 0.31, I^2 = 0%). However, during the late postprandial period (120 – 195 minutes), immediate episodic memory was significantly better following a LGL breakfast compared to a HGL breakfast (SMD = 0.16, 95% CI = -0.00 – 0.32, p = 0.05, I^2 = 5%). Heterogeneity was low for all analyses.

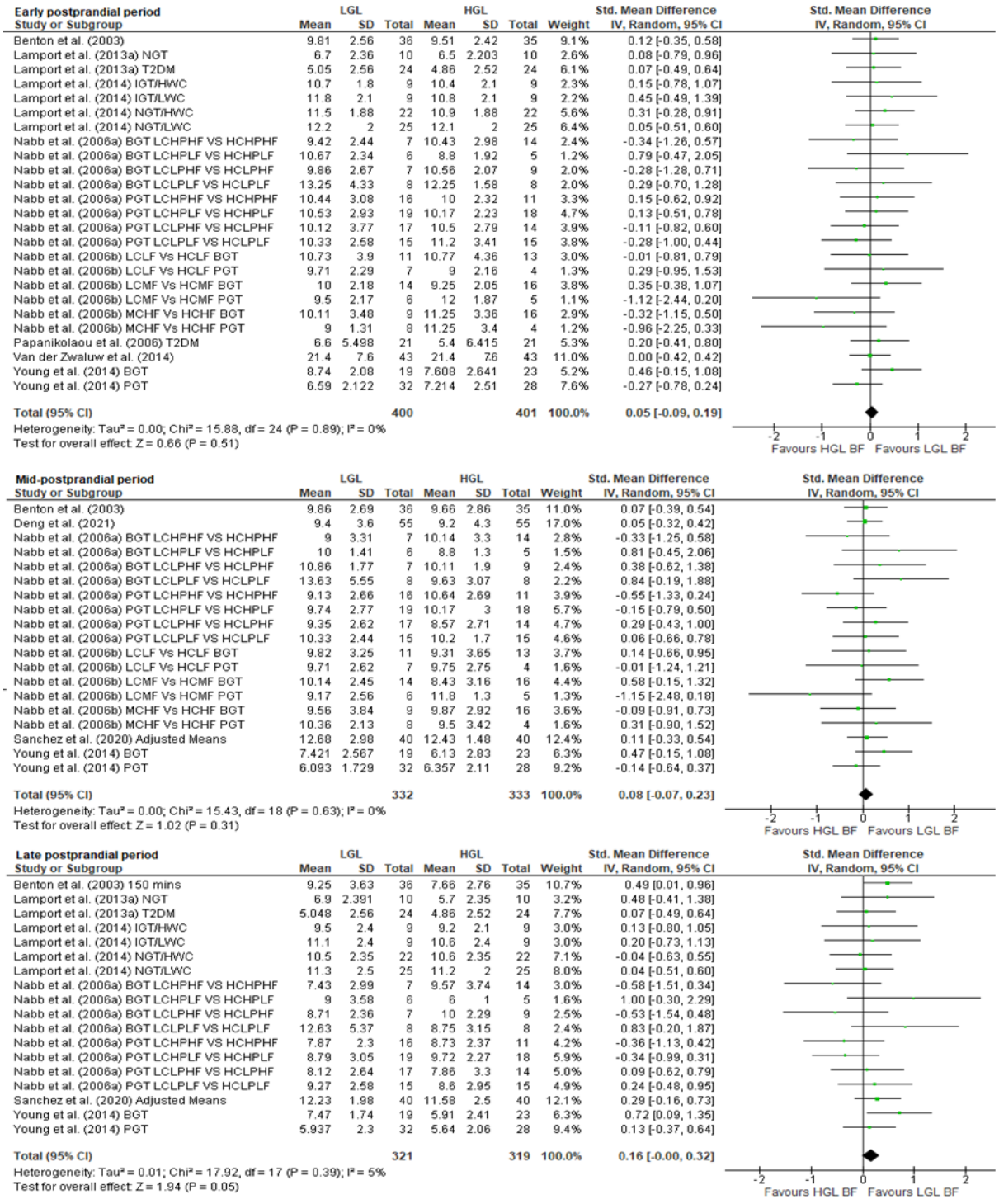


Figure 2. Forest plot of the effect of glycaemic load on immediate episodic memory during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. A significant beneficial effect of a LGL breakfast on immediate episodic memory was observed, but only during the late postprandial period (p = 0.05). NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus, IGT = impaired glucose tolerance, HWC = high waist circumference, LWC = low waist circumference, BGT = better glucose tolerance, PGT = poorer glucose tolerance, LC =

low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that Nabb and Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

2.3.3.1.2. The influence of sample characteristics

Subgroup analyses indicated that GT was related to the effect of breakfast GL on immediate episodic memory, but only during the late postprandial period (120 – 195 minutes; Figure 3). In those with better GT, performance was significantly better following a LGL breakfast compared to a HGL breakfast (SMD = 0.31, 95% CI = 0.09-0.54, p = 0.007, I^2 = 0%), whereas there were no differences in performance in those with poorer GT (SMD = 0.12, 95% CI = –0.21–0.45, P = 0.47, I^2 = 0%). Age did not influence the effect of breakfast GL on immediate episodic memory.

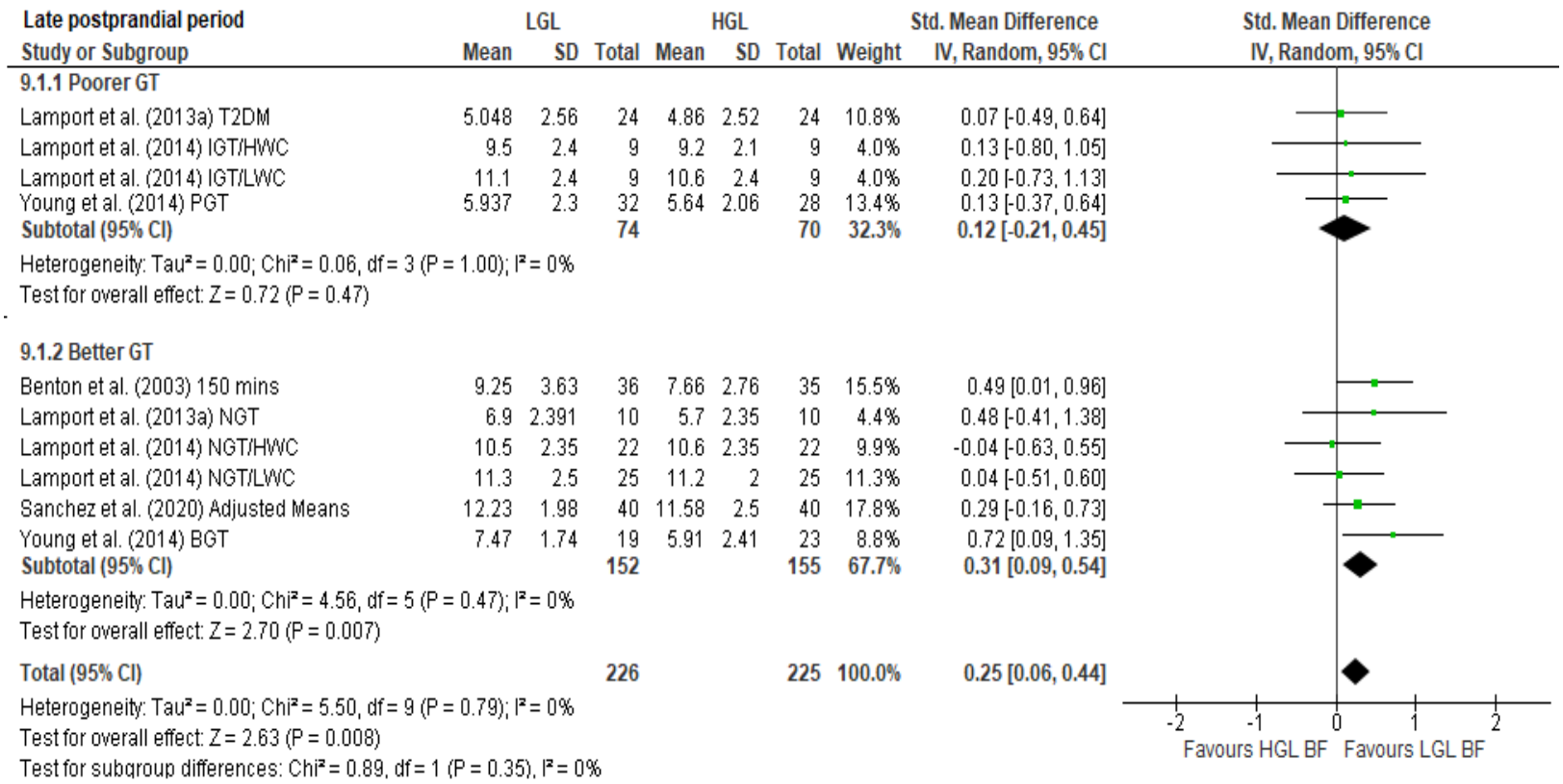


Figure 3. Forest plot of the effect of glycaemic load on immediate episodic memory during the late postprandial period in participants with poorer or better glucose tolerance. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. A significant beneficial effect of a LGL breakfast on immediate episodic memory was observed, during the late postprandial period, in those with better GT (p = 0.007) but not poorer GT (p = 0.47). NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus, IGT = impaired glucose tolerance, HWC = high waist circumference, LWC = low waist circumference, BGT = better glucose tolerance, and PGT = poorer glucose tolerance.

2.3.3.2 Delayed episodic memory

2.3.3.2.1 The influence of the timing of testing

As shown in Figure 4, there was no effect of breakfast GL on delayed episodic memory during the early postprandial period (35 - 59 minutes; SMD = 0.09, 95% CI = -0.08 – 0.27, p = 0.30, I^2 = 6%), nor during the mid-postprandial period (62 - 119 minutes; SMD = 0.11, 95% CI = -0.02 – 0.24, p = 0.10, I^2 = 0%). However, during the late postprandial period (150 - 220 minutes), there was a trend towards better performance following a LGL breakfast compared to HGL breakfast (SMD = 0.14, 95% CI = -0.01 – 0.30, p = 0.07, I^2 = 0%). Heterogeneity was low for all analyses.

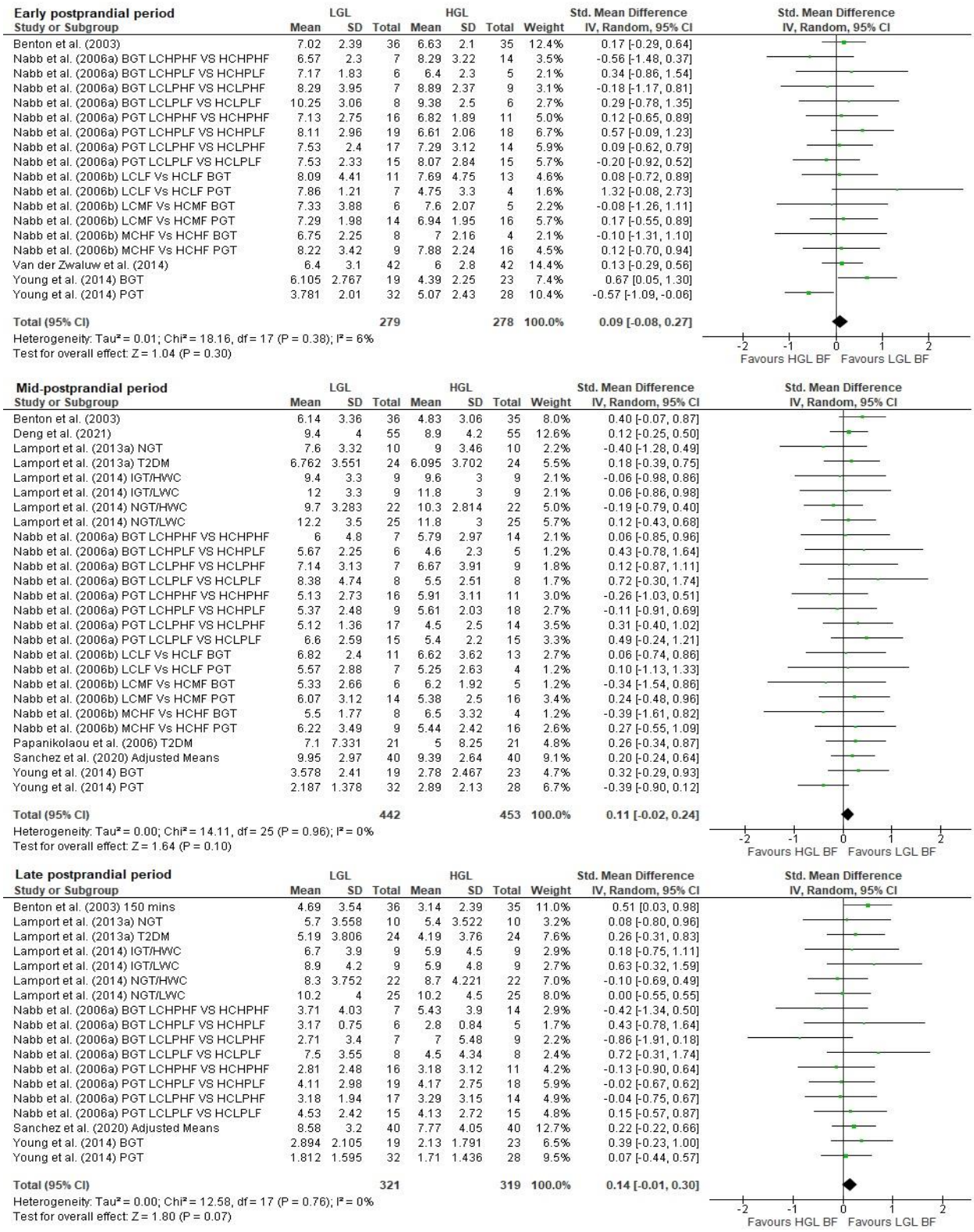


Figure 4. Forest plot of the effect of glycaemic load on delayed episodic memory during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. There was a trend towards a beneficial effect of a LGL breakfast on delayed episodic memory, but only during the late

postprandial period (p = 0.07). NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus, IGT = impaired glucose tolerance, HWC = high waist circumference, LWC = low waist circumference, BGT = better glucose tolerance, PGT = poorer glucose tolerance, LC = low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that Nabb and Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

2.3.3.2.2 The influence of sample characteristics

GT influenced the effect of breakfast GL on delayed episodic memory, but only during the late postprandial period (150 - 220 minutes; Figure 5). In the better GT subgroup, there was a trend towards better delayed episodic memory following the consumption of a LGL breakfast compared to a HGL breakfast (SMD = 0.22, 95% CI = -0.01 – 0.44, p = 0.06, I^2 = 0%), whereas no trend was observed in the poorer GT subgroup (SMD = 0.21, 95% CI = -0.12 – 0.54, p = 0.20, I^2 = 0%).

Subgroup analyses by age could not be performed during the early postprandial period due to an insufficient number of studies. Age was related to the effect of GL on delayed episodic memory, but only during the mid-postprandial period (Figure 6). Specifically, performance was significantly better after a LGL breakfast compared to a HGL breakfast in the younger subgroup (SMD = 0.18, 95% CI = 0.01 – 0.35, p = 0.04, I^2 = 0%), but not the older subgroup (SMD = -0.00, 95% CI = -0.21 – 0.21, p = 0.99, I^2 = 0%). To check whether this was due to the inclusion of participants with T2DM in the older subgroup, a separate analysis was performed with data from these participants excluded. There was still no significant effect of breakfast GL in the older subgroup (SMD = -0.08, 95% CI = -0.33 – 0.17, p = 0.53, I^2 = 0%).

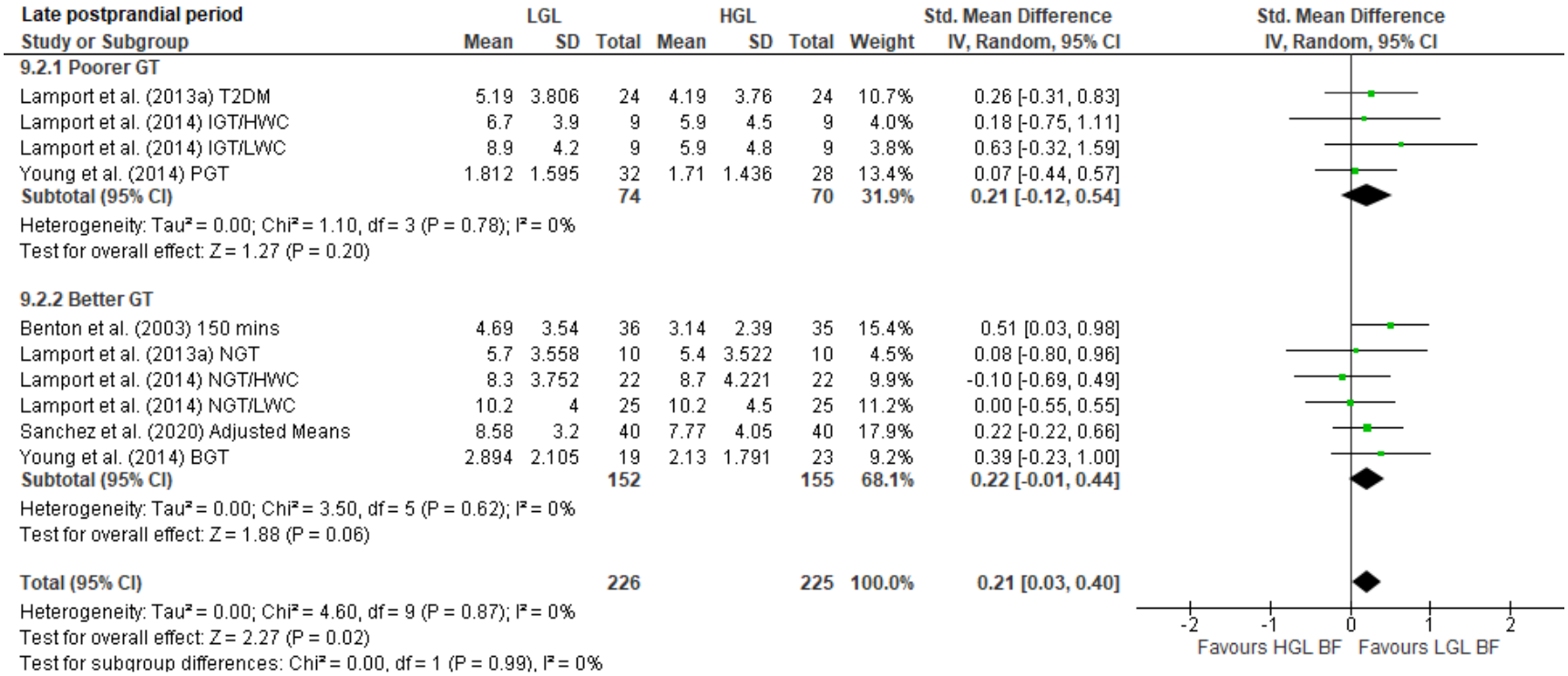


Figure 5. Forest plot of the effect of glycaemic load on delayed episodic memory during the late postprandial period in participants with poorer or better GT. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. There was a trend towards a beneficial effect of a LGL breakfast on delayed episodic memory, during the late postprandial period, in those with better GT (p = 0.06) but not poorer GT (p = 0.20). NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus, IGT = impaired glucose tolerance, HWC = high waist circumference, LWC = low waist circumference, BGT = better glucose tolerance, and PGT = poorer glucose tolerance.

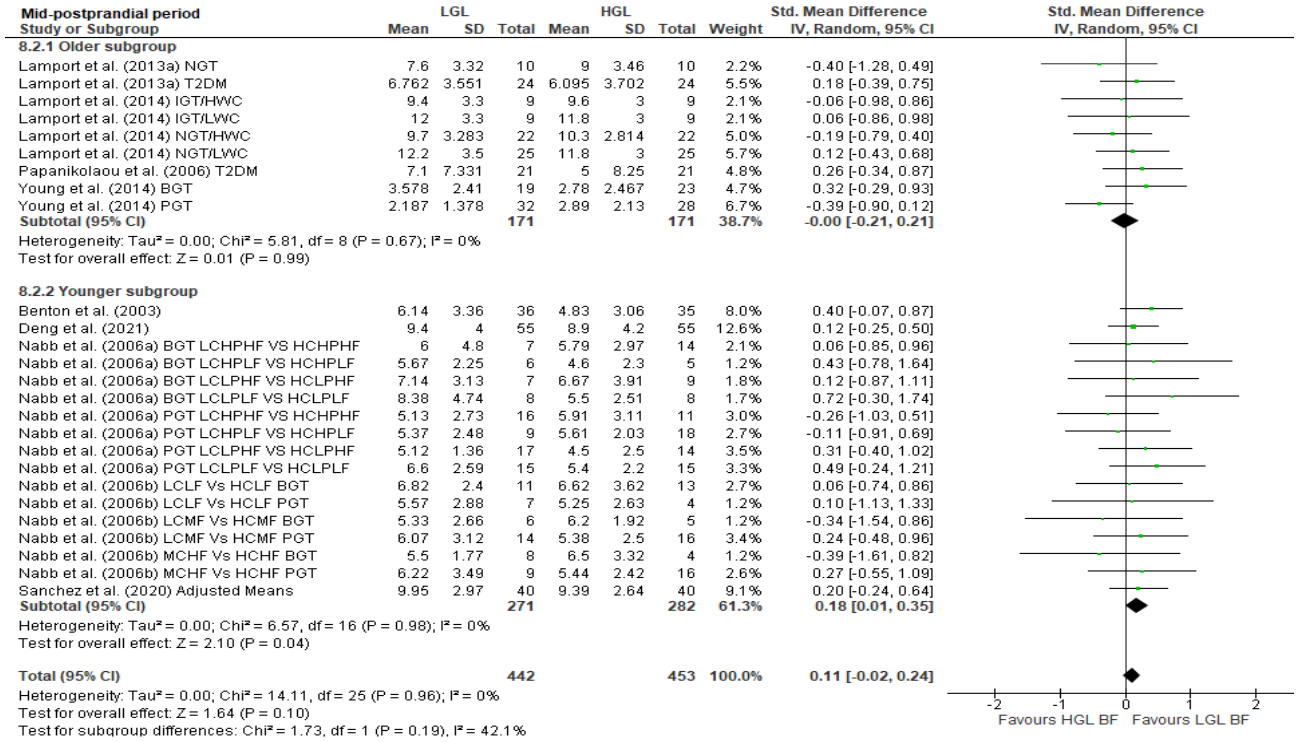


Figure 6. Forest plot of the effect of glycaemic load on delayed episodic memory during the mid-postprandial period in studies with a mean age above or below 35 years. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. A significant beneficial effect of a LGL breakfast on delayed episodic memory, during the mid-postprandial period, was observed in studies with a mean age <35 years (p = 0.04) but not >35 years (p = 0.99). NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus, IGT = impaired glucose tolerance, HWC = high waist circumference, LWC = low waist circumference, BGT = better glucose tolerance, PGT = poorer glucose tolerance, LC = low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that Nabb and Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

2.3.3.3 Accuracy of working memory

2.3.3.3.1 The influence of the timing of testing

As shown in Figure 7, there were no significant differences in performance between the HGL and LGL nutritional interventions during the early (30 – 35 minutes; p = 0.30), mid (90 – 105 minutes; p = 0.32), or late postprandial period (120 – 195 minutes; p = 0.78). There was also no evidence of heterogeneity (I^2 = 0%).

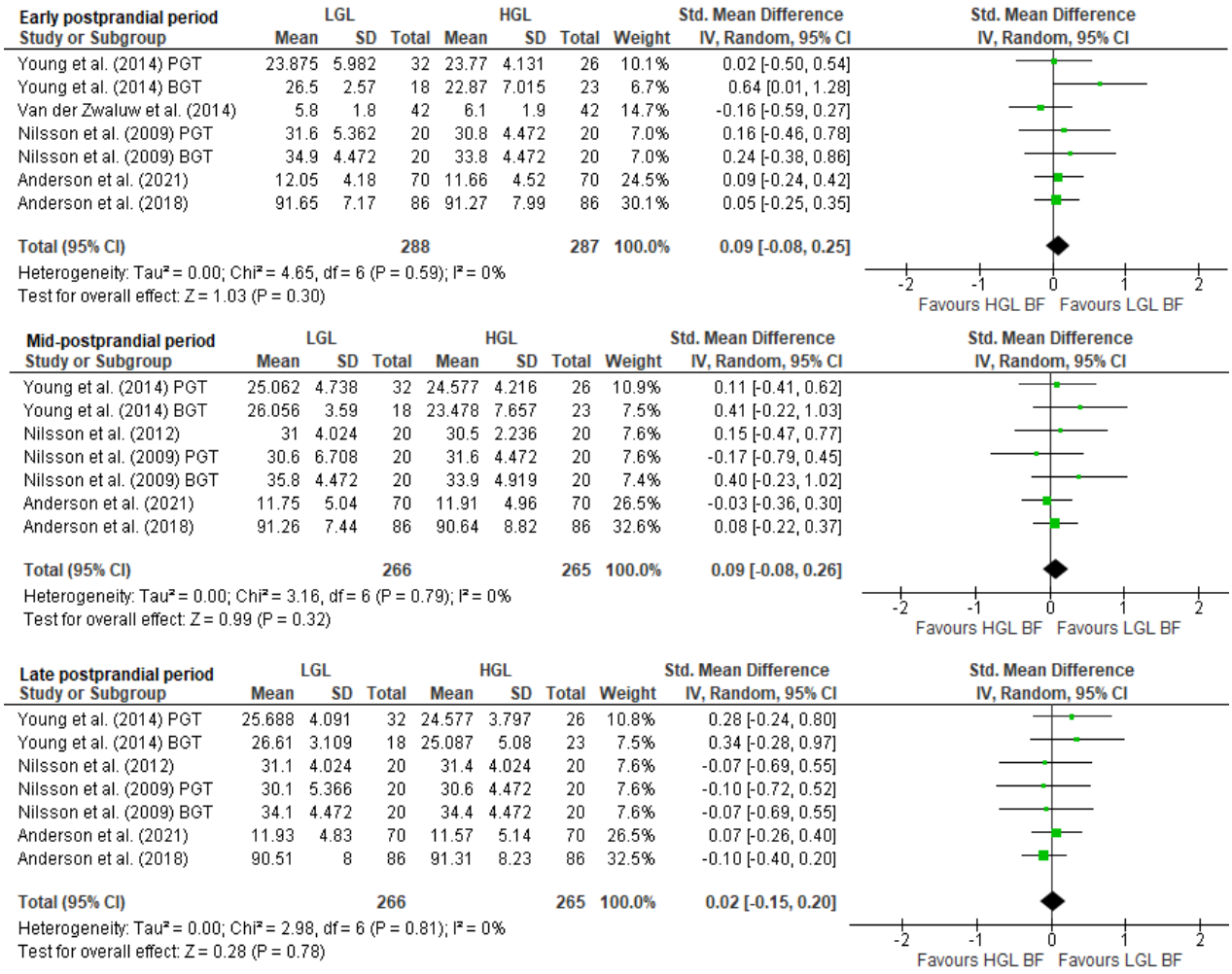


Figure 7. Forest plot of the effect of glycaemic load on accuracy of working memory during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. Breakfast GL was not significantly associated with accuracy of working memory during the early, mid, or late postprandial period. BGT = better glucose tolerance and PGT = poorer glucose tolerance.

2.3.3.3.2 The influence of sample characteristics

GT and age did not influence the effect of breakfast GL on accuracy of working memory (all p = NS).

2.3.3.4 Speed of attention

2.3.3.4.1 The influence of the timing of testing

The RIPT was used in three studies (Nabb & Benton, 2006a, 2006b; Young & Benton, 2014a). This task detects changes in performance over time by measuring attention every minute for five minutes. To reduce the number of data points taken from these studies, data from the first and fifth minute were extracted, and separate analyses were performed for each minute. When one-minute RIPT reaction time scores were included in the analysis (Figure 8), there was no significant effect of breakfast GL during the early (15 – 35 minutes; p = 0.52), mid (60 – 105 minutes; p = 0.77), or late postprandial period (120 – 195 minutes; p = 0.21). Similarly, when five-minute RIPT reaction time scores were included in the analysis (Figure 9), there was no effect of breakfast GL during the early (15 – 35 minutes; p = 0.57), mid (60 – 105 minutes; p = 0.64), or late postprandial period (120 – 195 minutes; p = 0.26). Heterogeneity was not substantial for any analysis.

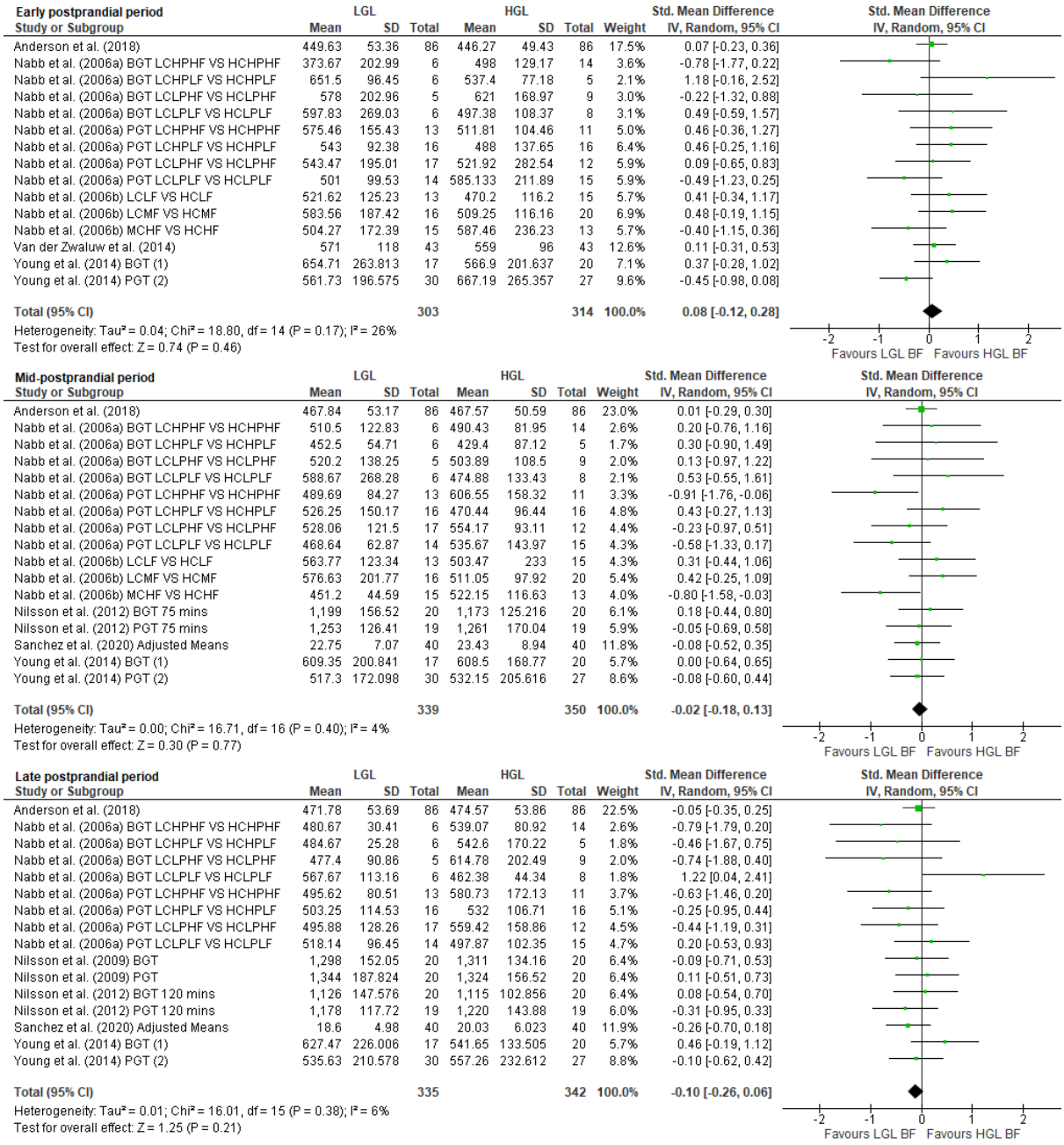


Figure 8. Forest plot of the effect of glycaemic load on speed of attention, using one-minute RIPT reaction times, during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. Breakfast GL was not significantly associated with speed of attention during the early, mid, or late postprandial period. Analyses include one-minute data from Nabb and Benton (2006a), Nabb and Benton (2006b), and Young and Benton (2014a). BGT = better glucose tolerance, PGT = poorer glucose tolerance, LC = low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that Nabb and

Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

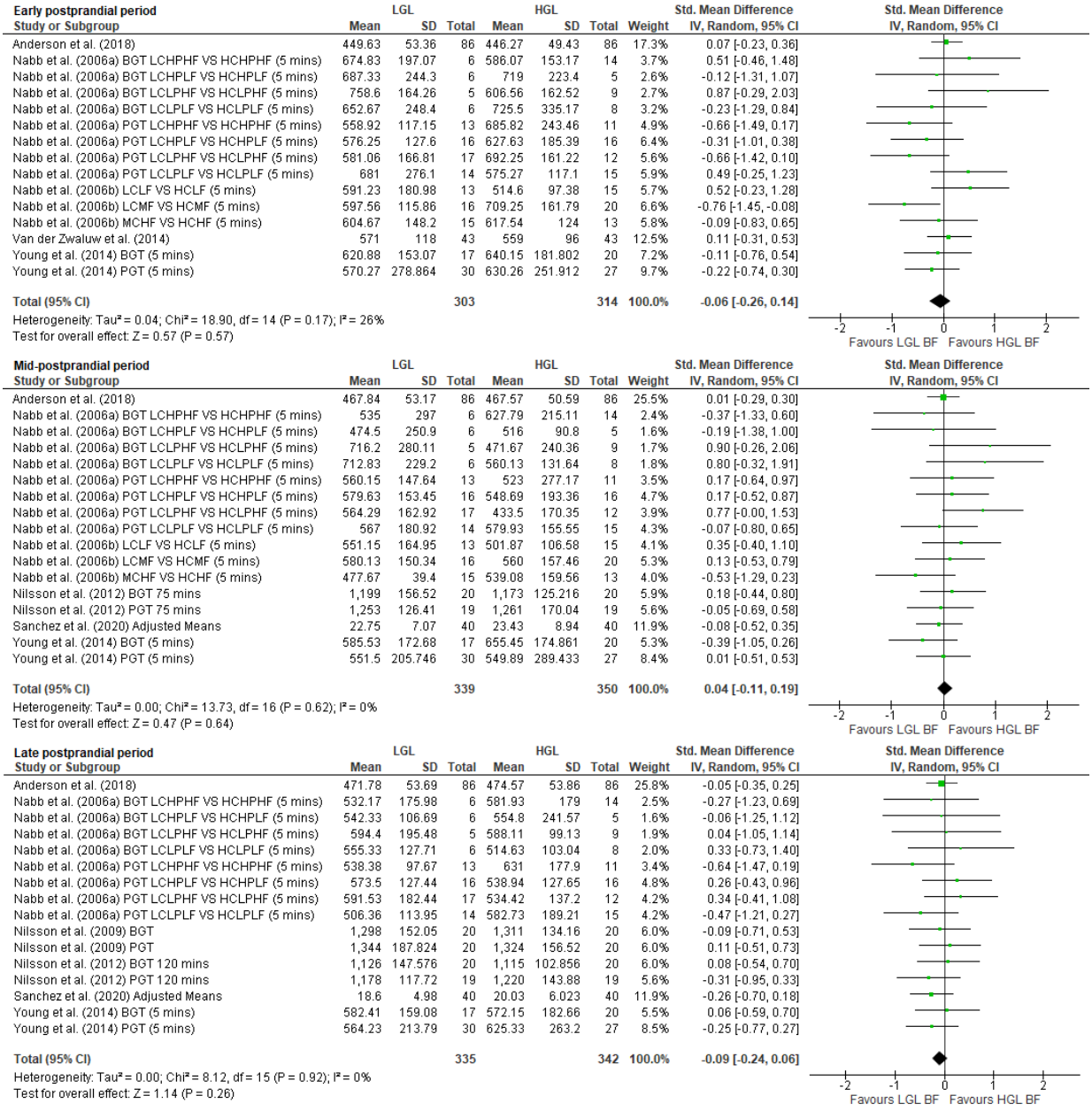


Figure 9. Forest plot of the effect of glycaemic load on speed of attention, using five-minute RIPT reaction times, during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. Breakfast GL was not significantly associated with speed of attention during the early, mid, or late postprandial period. Analyses include five-minute data from Nabb and Benton (2006a), Nabb and Benton (2006b), and Young and Benton (2014a). BGT = better glucose tolerance, PGT = poorer glucose tolerance, LC = low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that Nabb and

Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

2.3.3.4.2 The influence of sample characteristics

GT and age were not related to the effect of breakfast GL on speed of attention (all p = NS).

2.3.3.5 Accuracy of attention

2.3.3.5.1 The influence of the timing of testing

When one-minute RIPT reaction time scores were included in the analysis (Figure 10), there was no effect of breakfast GL on accuracy of attention during the early (30 – 35 minutes; p = 0.84). mid (60 – 105 minutes; p = 0.48), or late postprandial period (120 – 195 minutes; p = 0.54). Similarly, when five-minute RIPT reaction time scores were included in the analysis (Figure 11), there was no effect of GL during the early (30 – 35 minutes; p = 0.81), mid (60 – 105 minutes; p = 0.91), or late postprandial period (120 – 195 minutes; p = 0.71). There was no evidence of substantial heterogeneity.

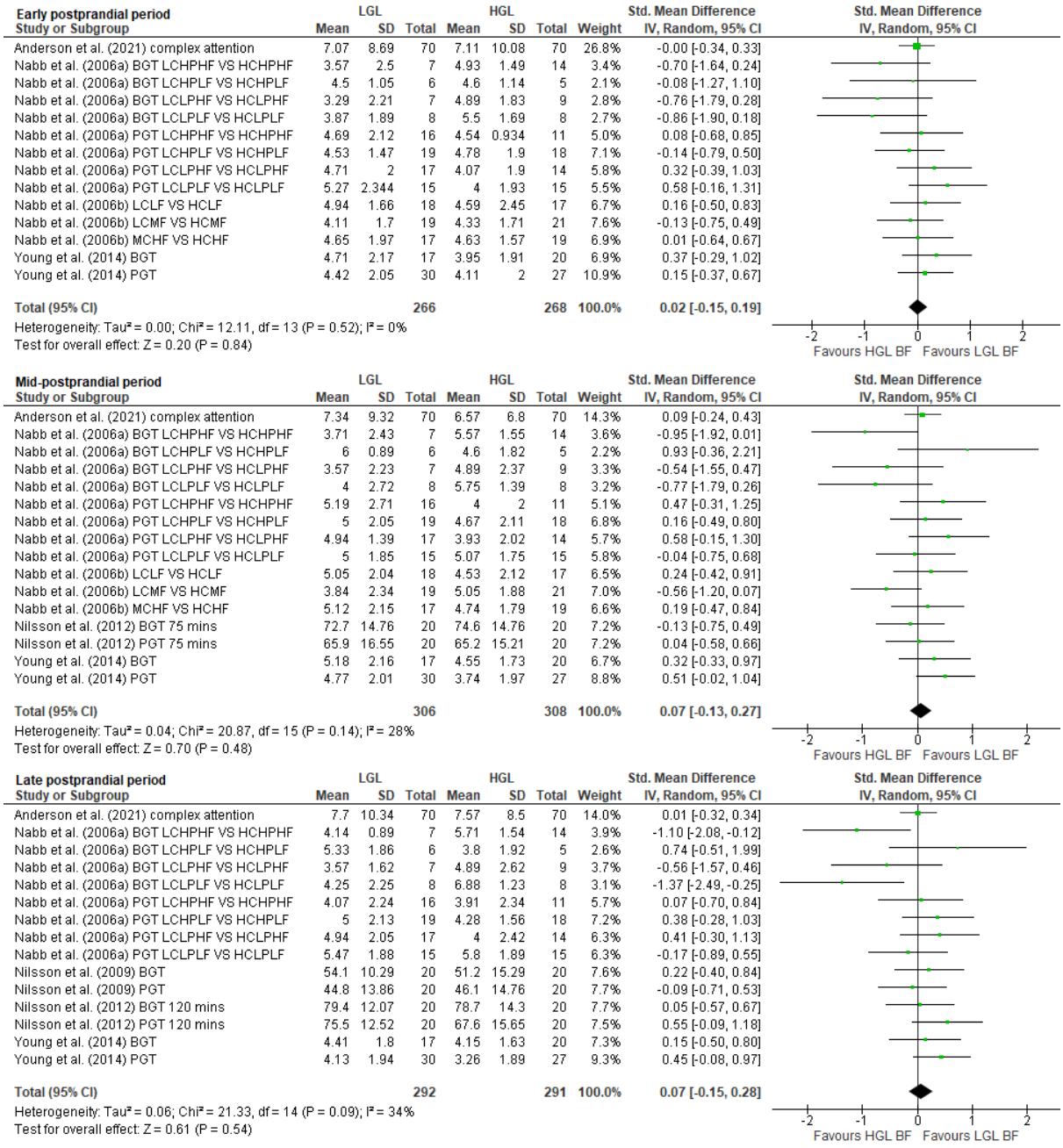


Figure 10. Forest plot of the effect of glycaemic load on accuracy of attention, using one-minute RIPT reaction times, during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. Breakfast GL was not significantly associated with accuracy of attention during the early, mid, or late postprandial period. Analyses include one-minute data from Nabb and Benton (2006a), Nabb and Benton (2006b), and Young and Benton (2014a). BGT = better glucose tolerance, PGT = poorer glucose tolerance, LC = low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that

Nabb and Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

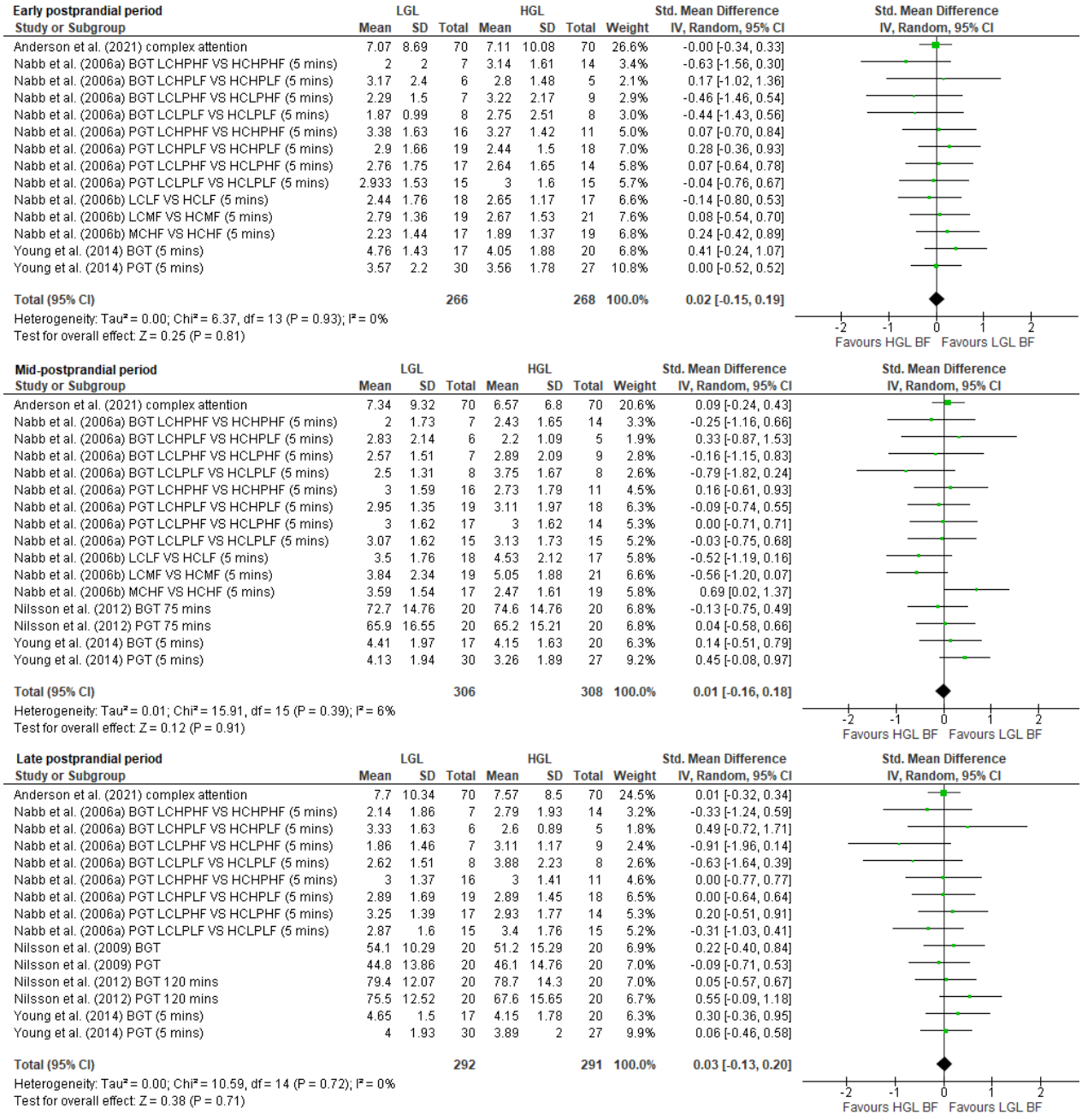


Figure 11. Forest plot of the effect of glycaemic load on accuracy of attention, using five-minute RIPT reaction times, during each postprandial time window. Effect sizes reflect the SMD with 95% CIs. The size of the plotted squares reflects the statistical weight of each study. Breakfast GL was not significantly associated with accuracy of attention during the early, mid, or late postprandial period. Analyses include five-minute data from Nabb and Benton (2006a), Nabb and Benton (2006b), and Young and Benton (2014a). BGT = better

glucose tolerance, PGT = poorer glucose tolerance, LC = low carbohydrate, HC = high carbohydrate, LP = low protein, HP = high protein, LF = low fat, and HF = high fat. Note that Nabb and Benton (2006b) manipulated the carbohydrate and fibre content of meals hence LF = low fibre, HF = high fibre, and MF = medium fibre.

2.3.3.5.2 The influence of sample characteristics

GT and age were not related to the effect of breakfast GL on accuracy of attention (all p = NS).

2.3.3.6 Sensitivity analyses

The results of the leave-one-out analysis are reported in Appendix 4. For brevity, the impact of individually removing studies on significant/trending analyses will only be discussed here. With regards to immediate episodic memory (late postprandial analysis), removal of 13 out of 18 studies reduced the pooled effect size and resulted in the analysis no longer being significant. The removal of Benton et al. (2003) most strongly affected the pooled effect size and p value, followed by the removal of Young and Benton (2014a) (better GT subgroup) and Sanchez-Aguadero et al. (2020). Conversely, removal of some data from Nabb and Benton (2006a) and Lamport et al. (2014) reduced the significance value and increased the pooled effect size. With regards to delayed episodic memory (late postprandial analysis), removal of Benton et al. (2003) also produced the largest change in significance and pooled effect size, followed by Young and Benton (2014a) (better GT subgroup) and Sanchez-Aguadero et al. (2020).

In most cases, removal of studies that did not match the macronutrient and energy composition of breakfast interventions lowered p values and increased effect sizes (data not reported). For accuracy of attention scores, removal of these studies revealed a trend towards a beneficial effect of a LGL breakfast during the late postprandial period (SMD = 0.23, 95% CI = -0.01 – 0.48, p = 0.06, I^2 = 0%). Adjusted and unadjusted means were obtained from one study (Sanchez-Aguadero et al., 2020). The inclusion of adjusted or unadjusted means did not influence effect sizes (data not reported).

2.3.3.7 Publication bias

Funnel plots were generated for immediate episodic memory, delayed episodic memory, accuracy of attention, and speed of attention (Appendix 5). Due to an insufficient number of studies, funnel plots for accuracy of working memory scores were not created. There was some degree of asymmetry for accuracy of attention (early and late postprandial period), speed of

attention (early and late postprandial period) and delayed episodic memory (early postprandial period).

2.3.3.8 Summary of findings from meta-analysis of breakfast studies involving adults

- The influence of the timing of testing: immediate episodic memory was significantly better after a LGL breakfast, compared to a HGL breakfast, but only during the late postprandial period (120 – 195 minutes). There was a similar non-significant trend for delayed episodic memory, whereby performance was better during the late postprandial period (150 – 220 minutes) following a LGL breakfast relative to a HGL breakfast.
- The influence of GT: during the late postprandial period, immediate episodic memory was significantly better following a LGL breakfast, but only in those with better GT. No differences were observed in those with poorer GT. A similar non-significant trend was observed for delayed episodic memory, whereby performance was better after a LGL breakfast, in those with better GT, during the late postprandial period. No trend was observed in the poorer GT subgroup.
- The influence of age: during the mid-postprandial period (62 – 119 minutes), delayed episodic memory was significantly better following a LGL breakfast, but only in the younger subgroup. No differences were observed in the older subgroup.
- There was no effect of breakfast GL on accuracy of working memory, accuracy of attention, or speed of attention.

2.3.4 Review of breakfast studies involving adults

In this section, the effect of breakfast GL on the cognitive domains and subdomains that could not be included in the meta-analysis are systematically reviewed according to the timing of testing, including semantic memory, visuospatial memory, executive functions, processing speed, and psychomotor function.

2.3.4.1 Memory

2.3.4.1.1 Semantic memory

Three studies measured semantic memory using a verbal fluency test. No study reported a difference in performance between the LGL and HGL breakfast conditions during the early postprandial period (van der Zwaluw et al., 2014; Young & Benton, 2014a), mid-postprandial period (Sanchez-Aguadero et al., 2020; Young & Benton, 2014a), and late postprandial period (Sanchez-Aguadero et al., 2020; Young & Benton, 2014a). However, at 120 minutes, there was

a significant decline in semantic memory relative to baseline, but only after the consumption of the LGL breakfast (Sanchez-Aguadero et al., 2020).

2.3.4.1.2 Visuospatial memory

Visuospatial memory was not affected by the consumption of breakfasts differing in GL in two studies during the early postprandial period (Lamport et al., 2014; Lamport et al., 2013a), one study during the mid-postprandial period (Deng et al., 2021), and one study during the late postprandial period (Lamport et al., 2013a). Lamport et al. (2014) reported that delayed visuospatial memory was poorer during the late postprandial period (120 minutes) following the HGL meal in the IGT/higher waist circumference group compared to the NGT/lower waist circumference group, a pattern that was not observed following the LGL breakfast.

2.3.4.2 Executive function

2.3.4.2.1 Inhibitory control

Three studies measured inhibitory control. Ginieis et al. (2018) reported faster Stroop reaction times 20 minutes after the consumption of a LGL drink compared to a HGL drink, but no differences in accuracy rates. Similarly, Anderson et al. (2018) reported fewer omission errors 30 minutes after the consumption of a LGL drink, compared to a HGL drink, in those with higher fasting glucose levels only. However, no differences in reaction times were reported. No differences in inhibitory control were reported during the mid (Anderson et al., 2018; Deng et al., 2021) or late postprandial period (Anderson et al., 2018).

2.3.4.2.2 Planning ability

Two studies measured participants planning abilities using the Tower of Hanoi task during the early (30 minutes) and late (120 minutes) postprandial period. The consumption of breakfasts differing in GL did not influence performance (Lamport et al., 2014; Lamport et al., 2013a).

2.3.4.2.3 General executive function

General executive function was measured by four studies during the early postprandial period (Anderson et al., 2021; Kaplan et al., 2000; Papanikolaou et al., 2006; van der Zwaluw et al., 2014), five studies during the mid-postprandial period (Anderson et al., 2021; Deng et al., 2021; Kaplan et al., 2000; Papanikolaou et al., 2006; Sanchez-Aguadero et al., 2020), and three studies during the late postprandial period (Anderson et al., 2021; Kaplan et al., 2000; Sanchez-Aguadero et al., 2020). Only one study reported that breakfast GL influenced general executive function scores. In type 2 diabetic patients, a larger improvement in scores from the first test

(15 minutes) to the second test (62 minutes) was observed following a LGL breakfast compared to HGL breakfast (Papanikolaou et al., 2006).

2.3.4.3 Speed of information processing

Six studies measured speed of information processing during the early postprandial period (Anderson et al., 2021; Ginieis et al., 2018; Nabb & Benton, 2006a, 2006b; van der Zwaluw et al., 2014; Young & Benton, 2014a), of which only one study reported an effect of breakfast GL. Ginieis et al. (2018) reported that simple and arithmetic reaction times were faster 20 minutes after the consumption of a LGL drink compared to a HGL drink. No study reported an effect of breakfast GL during the mid-postprandial period (Anderson et al., 2021; Nabb & Benton, 2006a, 2006b; Young & Benton, 2014b) or late postprandial period (Anderson et al., 2021; Nabb & Benton, 2006a; Young & Benton, 2014b). Two studies reported an effect of breakfast GL which interacted with GT. In those with better GT, Nabb and Benton (2006a) reported that decision times were faster after the consumption of a high carbohydrate, low protein meal compared to a low carbohydrate, low protein meal. Another study by the same authors reported that those with better GT had faster performance after consuming a medium or high carbohydrate meal with low fibre (Nabb & Benton, 2006b).

2.3.4.4 Psychomotor function

Three studies measured psychomotor function during the early (Dye et al., 2010; Lamport et al., 2014; Lamport et al., 2013a), mid (Dye et al., 2010), and late postprandial period (Lamport et al., 2014; Lamport et al., 2013a). No effect of breakfast GL was reported at any time.

2.3.4.5 Summary of findings from systematic review of breakfast studies involving adults

- A range of cognitive domains and subdomains have been examined using various cognitive tests.
- Although semantic memory, visuospatial memory, inhibitory control, general executive function, and speed of information processing were influenced by differences breakfast GL, in most cases effects were only demonstrated by one study.
- No studies reported that breakfast GL influenced psychomotor function or planning abilities.
- The timing of testing, participants age, and GT were not consistently related to the effect of breakfast GL.

2.3.5 Review of non-breakfast studies involving adults

Due to a lack of studies, the effect of manipulating the GL of meals or drinks consumed after breakfast time on cognitive performance could not be examined via meta-analysis. The results of these studies are therefore systematically reviewed in this section.

2.3.5.1 Study characteristics

As shown in Table 3, both Marchand et al. (2020) and Keesing et al. (2019) were within-subjects, randomised, and double-blind. A standardised meal was administered in both studies prior to the experimental meal/drink. Marchand et al. (2020) manipulated the GL of a lunchtime dessert (12pm) by sweetening the dessert with either sucrose or isomaltulose. Keesing et al. (2019) administered drinks differing in GL during the afternoon (2pm). The drinks also contained either sucrose or isomaltulose. Neither study examined whether GT moderated the effect of GL on cognition.

2.3.5.2 Memory

2.3.5.2.1 Episodic memory

Marchand et al. (2020) examined immediate and delayed episodic memory, using a world list recall task, 60- and 120-minutes post-lunch consumption. The authors reported no differences in episodic memory following the HGL and LGL desserts. Keesing et al. (2019) examined immediate episodic memory using a word list recall task and a video clip task. No differences in performance were reported 30-, 80-, and 130-minutes post-drink consumption.

2.3.5.2.2 Working memory

Using a letter-number sequencing task, Marchand et al. (2020) reported that differences in GL did not influence working memory performance 60- and 120-minutes post-consumption.

2.3.5.2.3 Visuospatial memory

Marchand et al. (2020) reported no differences in visuospatial memory, using a self-developed task, 60- and 120-minutes after consuming the HGL and LGL desserts.

2.3.5.3 Executive function

Marchand et al. (2020) examined executive function using the Trails Part B task. The HGL dessert was associated with faster performance, by approximately 8 seconds, 60 minutes post-consumption. Keesing et al. (2019) administered the same task 140 minutes post-drink consumption. However, no differences in performance were reported.

Table 3. Summary of non-breakfast involving adults.

Author (Year)	Participant characteristics	Study design	Nutritional intervention	Cognitive test	Timing of cognitive and blood glucose tests	Results	Comments
Keesing et al. (2019)	70 healthy participants (57 female, 13 male). Mean age = 21.9 years (SD = 0.64, range = 18-60 years). GT status not assessed.	WS. Randomised. Double-blind. 1-week washout period. Administered drinks at 2pm. Standardised lunch followed by a 2-hour fast.	1. LGL = 500 mL of carbonated water sweetened with 50 g of isomaltulose and 50 uL of lemon flavour (0 g PRO, 0 g fat, 0 g fibre, 16 GL^2) 2. HGL = 500 mL of carbonated water sweetened with 50 g of sucrose and 50 uL of lemon flavour (0 g PRO, 0 g fat, 0 g fibre, 32 GL^2)	Video clip task (immediate episodic memory), WLR task (immediate episodic memory), and Trails Part B (attention and executive function).	Video clip task and WLR task = 30, 80, and 130 minutes. Trails Part B = 140 minutes.	No effect of GL on any cognitive measure.	Macronutrient content, volume, and appearance matched. Measured the glycaemic response to drinks on a separate day to cognitive testing, using a subset of the participants. Glucose levels declined after the

		Participants instructed not to exercise between lunch and afternoon drink.					consumption of isomaltulose.
Marchand et al. (2020)	65 healthy participants (57 female, 8 male). Mean age = 21.9 years (SD = 5.8). GT status not assessed.	WS. Randomised. Double-blind. Lunchtime intervention. 2 to 3-week washout period. Standardised breakfast.	1. LGL = trifle sweetened with isomaltulose (601 kcal, 98.8 g CHO, 16.1 g PRO, 15.3 g fat, 32.60 GL[1]) 2. HGL = trifle sweetened with sucrose (601 kcal, 98.8 g CHO, 16.1 g PRO, 15.3 g fat, 43.47 GL[1])	WLR task whilst simultaneously performing a motor task (immediate recall, short delay recall, and long delay recall), letter-number sequencing task (working memory), self-developed visuospatial task (visuospatial memory), and Trails Part B	Cognition = 00, 60, and 120 minutes. Trails Part B = 60 minutes only. Glucose levels = 00, 60, and 120 minutes.	The HGL meal was associated with faster performance (7.7 seconds) on the Trails Part B task compared to the LGL meal at 60 minutes. No other effects of GL were reported.	Macronutrients content, energy, appearance, and volume were matched. Regression adjusted for baseline performance, English as second language, special diet, and order.

	Fasted after breakfast until 12pm.	(attention and executive function).

Note. 1 = GL values reported by study authors and 2 = GL values calculated using reported GI values multiplied by amount of CHO or available CHO. WS = within-subjects design, BGLs = blood glucose levels, 00 = baseline, GT = glucose tolerance, RT = reaction time, SRT = simple RT, CRT = choice RT, WLR = word list recall, GL = glycaemic load, LGL = low glycaemic load, MGL = medium glycaemic load, HGL = high glycaemic load, PRO = protein, CHO = carbohydrate.

2.3.6 Breakfast studies involving children and adolescents

As mentioned above, data from studies conducted in children and adolescents were not deemed suitable for meta-analysis. However, children and adolescents are an important population in which to consider the cognitive consequences of breakfast GL. Therefore, a systematic review of the literature was conducted instead, which systematically considered the influence of the timing of testing.

2.3.6.1 Study characteristics

Participants mean age ranged from 5.58 years (Taib et al., 2012) to 15.65 years (Smith & Foster, 2008b), and sample sizes ranged from 19 (Benton et al., 2007b) to 84 participants (Anderson et al., 2020). One study was unpublished (Ingwersen, 2011). Two studies used a between-subjects design, two used a mixed-subjects design, and 12 used a within-subjects design. All studies were randomised, other than both studies by Mahoney et al. (2005). Four studies were double-blind (Brindal et al., 2013; Micha et al., 2011; Taib et al., 2012; Young & Benton, 2015). The experimenter was blinded in three studies (Anderson et al., 2020; Mahoney et al., 2005).

The majority of studies administered realistic breakfasts differing in GL, such as breakfast cereals, some of which were matched for macronutrient and/or energy composition (Anderson et al., 2020; Benton et al., 2007b; Brindal et al., 2012; Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007; Mahoney et al., 2005; Micha et al., 2011; Smith & Foster, 2008b; Wesnes et al., 2003). Two studies manipulated GL by sweetening drinks or meals with sugars differing in GL (Brindal et al., 2013; Young & Benton, 2015). Taib et al. (2012) provided young children with a standard growing-up milk, a reformulated GUM, an isomaltulose-sweetened GUM, and a glucose-maltodextrin drink. Lee et al. (2019) provided 50 g of available carbohydrate from mashed potatoes, white rice, French fries, hash browns, or baked beans.

2.3.6.2 Risk of bias

The results of the risk of bias assessment are summarised in Appendix 6. Overall, four studies showed a low risk of bias, and 12 studies showed some concerns of bias. Studies were generally judged with some concerns of bias for the same reasons reported in Section 2.3.2.2. For the 'bias arising from period and carryover effects' domain, studies were judged as having some concerns of bias or a high risk of bias if the study was unbalanced and/or participants were

tested on consecutive days. For the ‘deviations from intended outcome’ domain, studies were judged as showing a high risk of bias if participants were clearly not blinded.

Table 4. Summary of breakfast studies involving children and adolescents.

Author (Year)	Participant characteristics	Study design	Breakfast intervention	Cognitive test	Timing of cognitive and blood glucose tests	Results	Comments
Anderson et al. (2020)	84 healthy children (46 female, 38 male). Mean age = 10.18 years (SD = 1.35, range = 8-12 years). GT status = fasting BGLs at the beginning of each test session (analysed as a continuous	WS. Randomised. Counterbalanced Overnight fast. 1-week minimum washout period. Experimenter blinded to breakfast conditions.	1. HGL = 237 mL of apple juice (120 kcal, 29 g CHO, 0 g PRO, 0 g fat, 10 GL[1]) 2. LGL = 237 mL of 1% fat milk (110 kcal, 12 g CHO, 8 g PRO, 2.5 g fat, 4 GL[1])	Go-no-go task (executive function - inhibitory control). RMCPT (working memory). SCPT (sustained attention).	Cognition = 00, 30, 90, and 120 minutes. Glucose levels = 00, 30, 60, 90, and 120 minutes.	Go-no-go task = in those with higher fasting BGLs, RTs were faster after consuming the LGL drink vs. HGL. The difference in performance increased as fasting BGLs increased. No impact on accuracy scores. RMCPT = in females, consumption of the HGL drink improved accuracy vs. LGL drink, whereas the opposite pattern emerged for males (trend only). No impact on speed scores.	Drinks had different macronutrient profiles but provided similar amounts of energy. Statistically adjusted for the influence of visit, biological sex, and GT.

	variable using a linear mixed model).					SCPT = in females, consumption of the LGL drink was associated with faster performance, whereas the opposite pattern emerged for males (trend only). No impact on accuracy scores.	
Benton et al. (2007b)	19 healthy children (10 female, 9 male). Mean age = 6 years and 10 months (range = 5 – 7 years). GT status not assessed.	WS. Randomised. Unbalanced. Overnight fast. No washout period (4-week breakfast club).	Breakfast club provided one of three meals (based on the average amount consumed): 1. HGL = Cornflakes with semi-skimmed milk, two spoons of sugar, one waffle, and one tablespoon of maple syrup (196 kcal, 33.9 g CHO,	British Ability Scale – object name recall (immediate and delayed episodic memory). British Ability Scale – object location recall (immediate and delayed	Cognition = between 140 – 210 minutes.	No effect of GL on cognition (ANOVA). Object name recall = negative correlation between immediate word recall and GL. A lower GL predicted better performance, whereas PRO, fat, and CHO did not. Paradigm of Shakow = positive correlation between the number of lapses of	Breakfasts had different macronutrient and energy profiles. Only administered one cognitive test battery. Did not measure BGLs.

		School-based study (two days of testing per dietary condition)	4.7 g PRO, 1.7 g fat, 17.86 GL[1]) 2. MGL = scrambled egg, one slice of bread, low fat spread, and jam (168 kcal, 21.7 g CHO, 8.9 g PRO, 5.2 g fat, 12.09 GL[1]) 3. LGL = low calorie yoghurt, ham, cheese, bread, and low fat spread (157 kcal, 5.7 g CHO, 10.8 g PRO, 10.2 g fat, 2.85 GL[1])	visuospatial memory). Paradigm of Shakow (sustained attention).		attention (difficult trials only) and GL. A lower GL predicted better sustained attention (difficult trials only). No associations between GL and immediate/delayed visuospatial memory and delayed episodic memory.	Statistically tested for the influence of biological sex and order of meal consumption.
Brindal et al. (2012)	39 healthy children (13	WS. Randomised.	1) HGL = white bread, margarine, vegemite or jam, and	Administered an extensive battery of cognitive tests:	Cognition = 00, 60, 120,	No effect of GL on any of the cognitive tasks.	Meals provided similar amounts of fat and

female, 26 male). Mean age = 11.6 years (SD = 0.7, range = 10 – 12 years). GT status not assessed.	Overnight fast. Tested on consecutive days. Laboratory-based study.	fruit drink. (313 kcal, 50 g CHO, 7 g PRO, 9 g fat, 33 GL[1]) 2) MGL = low fat yogurt, full fat cheese, white bread, vegemite or jam, and fruit drink. (312 kcal, 45 g CHO, 14 g PRO, 9 g fat, 24 GL[1]) 3) LGL = full fat milk, low fat yogurt, full fat cheese, white bread, and vegemite or jam. (315 kcal, 38 g CHO, 18 g PRO, 10 g fat, 18 GL[1])	SRT task, CRT task, odd-man-out RT task, attention switching task, letter cancellation task, RAVLT WLR, WISC digit span backward task, and visual inspection time task. Created six composite scores: speed of processing, attention switching, perceptual speed, short-term memory, working	and 180 minutes. Glucose levels = continuous glucose monitor inserted at baseline.	energy but different amounts of PRO and CHO. Used a milk-based vehicle - insulinotropic. Included biological sex, BMI, z-score, age, baseline cognitive scores, and visit as covariates.

				memory, and inspection time.			
Brindal et al. (2013)	40 healthy children (21 female, 19 male). Mean age = 11.6 years (SD = 0.13, range = 10 – 12 years). GT status = median split of blood glucose responses to the glucose drink.	WS. Randomised. Double-blind. Overnight fast. Tested on consecutive days. Laboratory-based study. No vigorous exercise prior to testing.	1. HGL = 65 g of glucose with water (254 kcal, 0 g PRO, 0 g fat, 65 GL[1]) 2. MGL = 200 g of whole milk and 32 g of glucose (259 kcal, 42 g CHO, 7 g PRO, 8 g fat, 35 GL[1]) 3. LGL = 400 g of whole milk (260 kcal, 19 g CHO, 13 g PRO, 15 g fat, 5 GL[1])	Administered a large battery of cognitive tests: SRT task, CRT task, odd-man-out RT task, attention switching task, letter cancellation task, RAVLT WLR, WISC digit span backward task, and visual inspection time task. Created six composite scores: speed of processing,	Cognition = 00, 60, 120, and 180 post-breakfast. Glucose levels = continuous glucose monitor inserted at baseline.	Short term memory = there was an interaction between breakfast GL and biological sex. Relative to baseline, females recalled more words overall after consuming the MGL or LGL drink vs. HGL drink.	Drinks provided similar amounts of energy but different amounts of PRO, fat, and CHO. Used a milk-based vehicle – insulinotropic. Included biological sex, BMI z-score, age, GT status, baseline cognitive scores,

				attention switching, perceptual speed, short-term memory, working memory, and inspection time.			and visit as covariates.
Cooper et al. (2012)	41 healthy children (23 female, 18 male). Mean age = 12.8 years (SD = 0.4, range = 12 – 14 years). GT status not assessed.	WS. Randomised. Counterbalanced. Overnight fast. 1-week washout period. School-based study.	1.5 g of available CHO per kg body mass. For a 50 kg participant: 1. HGL = Cornflakes, 1% fat milk, white bread, and margarine (422 kcal, 75 g CHO, 14.3 g PRO, 7.2 g fat, 54 GL[1]) 2. LGL = Muesli, 1% fat milk and	Stroop task (executive function - inhibitory control). Sternberg task (working memory/ speed of processing). Flanker task (selective attention).	Cognition = 30 and 120-minutes. Glucose levels = 00, 15, 30, 60, and 120 minutes.	Stroop task = overall RTs were faster following the HGL meal vs. the LGL meal. Conversely, there was a larger decline in accuracy scores from 30 to 120 minutes after the HGL meal vs. LGL meal. Sternberg task = RTs remained similar across the morning following the HGL meal, whereas there was a larger improvement across the morning following the	Meals provided identical amounts of CHO, and similar amounts of energy, PRO, and fat.

		Same meal consumed evening before testing. No unusually vigorous exercise for 24 hours.	apple (420 kcal, 75 g CHO, 15.5 g PRO, 6.4 g fat, 36 GL[1]) 3. No breakfast.			LGL meal. Accuracy scores on the complex trials were maintained across the morning following the LGL meal but declined following the HGL meal. No difference in accuracy scores on the easier levels. Flanker task = on the complex trials, accuracy scores were better maintained across the morning following the LGL breakfast vs. HGL breakfast.	
Cooper et al. (2015)	42 healthy adolescents (22 female, 20 male).	Mixed design (WS = exercise or rest and BS = HGL or LGL meal).	1.5 g of available CHO per kg body mass. For a 50 kg participant:	Stroop task (executive function - inhibitory control). Sternberg task	Cognition = 30 and 120-minutes. Glucose levels = 00,	Stroop task = no effect of GL alone. On the complex trials, RT improved across the morning after the LGL breakfast on both exercise and rest days. The largest	Meals provided identical amounts of CHO, and similar amounts

Mean age = 12.4 (SD = 0.5, range = 11-13 years). GT status not assessed.	Randomised Counterbalanced. Overnight fast. 1-week washout period. School-based study. Same meal consumed evening before testing. No unusually vigorous exercise for 24 hours.	1. HGL = Cornflakes, 1% fat milk, white bread, and margarine (422 kcal, 75 g CHO, 14.3 g PRO, 7.2 g fat, 54 GL[1]) 2. LGL = Muesli, 1% fat milk and apple (420 kcal, 75 g CHO, 15.5 g PRO, 6.4 g fat, 36 GL[1]) 3. No breakfast	(working memory/ speed of processing). Flanker task (selective attention)	30, 60, and 120 minutes.	improvement was when the LGL breakfast was combined with exercise. No difference in performance accuracy. Sternberg task = RT improved across the morning after the LGL meal, regardless of exercise type, whereas RT only improved after the HGL meal on exercise days. Flanker task = no effect of GL alone.	of energy, PRO, and fat. Statistically tested for the influence of order of meal consumption.

Ingwersen et al. (2007)	64 healthy children (38 female, 26 male). Mean age = 9.3 years (range = 6 – 11 years). Two age groups = 6-8 years and 9 – 11 years. GT status not assessed.	WS. Randomised. Counterbalanced. Tested on consecutive days. Overnight fast. School-based study.	1. HGL = Coco Pops plus 125 ml of semi-skimmed milk (133 kcal, 29.8 g CHO, 1.6 g PRO, 0.9 g fat, 23 GL^2) 2. LGL = All Bran cereal plus 125 ml of semi-skimmed milk (98 kcal, 16.1 g CHO, 4.9 g PRO, 1.6 g fat, 7 GL^2) 3. No breakfast.	CDR Computerised Assessment Battery: WLR, SRT, CRT, digit vigilance, visuospatial and numeric working memory, word recognition, and picture recognition. Created composite scores: speed of attention, speed of memory, accuracy of attention, secondary memory, and working memory.	Cognition = 00, 10, 70, and 130 minutes.	Accuracy of attention = at 130 minutes, there was a sharp decline in scores following the HGL meal, whereas performance was maintained after the LGL meal. No difference at 10 and 70 minutes. Secondary memory = at 10 and 130 minutes, scores were better after the LGL vs. HGL meal. No difference at 70 minutes. No effect of GL on the remaining composite scores/ tests.	Meals provided similar amounts of fat but different amounts of PRO, CHO, and energy. Did not measure BGLs. Statistically tested for the influence of biological sex.
Ingwersen (2011)	38 healthy children (19	BS.	1. HGL = Coco Pops plus 125 ml of semi-	SRT and CRT task (speed of	Cognition = 00, 10, 70,	No effect of GL on any cognitive measure.	Meals provided similar amounts

.	female, 19 male). Mean age = 9 years and 5 months (range = 8 – 10 years). GT status not assessed.	Randomised. Overnight fast. School-based study.	skimmed milk (133 kcal, 29.8 g CHO, 1.6 g PRO, 0.9 g fat, 23 GL^2) 2. LGL = All Bran cereal plus 125 ml of semi-skimmed milk (98 kcal, 16.1 g CHO, 4.9 g PRO, 1.6 g fat, 7 GL^2) 3. No breakfast	information processing), Corsi Block Tapping test (spatial memory), Continuous Attention Task (sustained attention), and odd-one-out task (working memory)	and 130 minutes.		of fat but different amounts of PRO, CHO, and energy. Did not measure BGLs.
Lee et al. (2019)	22 healthy children (7 female, 15 male). Mean age = 12.4 years (SD = 0.3).	WS. Randomised. Counterbalanced. Minimum 4-day washout period.	50 g of available CHO from one of five meals*: 1. HGL = mashed potatoes with 17 g of unsalted butter (426 kcal, 5.2 g PRO,	WLR task (immediate episodic memory). Modified map task (visuospatial memory).	Cognition = 10, 30, 60, 120, and 180 minutes. Glucose levels = 00, 10, 30, 60,	WLR task = overall, more words recalled after French fries vs. mashed potatoes and white rice. No effect of GL on the remaining tests.	Some meals contained similar amounts of energy, fat, and PRO.

		20.7 g fat, 35.50 GL^3)	Digit span forwards and backwards test (working memory)	120, and 180 minutes.
GT status not assessed.	Overnight fast. Rescheduled test session if previous days physical activity level or sleep duration deviated from normal routine.	2. MGL = white rice with 25.9 g of unsalted butter added whilst boiling (413 kcal, 5.6 g PRO, 20.7 g fat, 34 GL^3) 3. MGL = French fries cooked in canola oil (424 kcal, 4.5 g PRO, 20.7 g fat, 31.50 GL^3) 4. MGL= oven-baked hash browns (515 kcal, 4.8 g	Finding A's test (speed of information processing).	

			PRO, 29.8 g fat, 28 GL^3) 5. LGL = baked beans with 24.5 g of unsalted butter (475.8 kcal, 15.5 g PRO, 20.7 g fat, 20 GL^3) 6. No breakfast				
Mahoney et al. (2005) Study 1.	30 healthy children (15 female, 15 male). Age range = 9 – 11 years. GT status not assessed.	WS. Non-randomised. Counterbalanced. Experimenter blind to breakfast conditions.	1. HGL = 36 g of ready-to-eat oatmeal with half cup skimmed milk (200 kcal, 36 g CHO, 22 g sugar, 5 g PRO, 1.5 g fat, 37.02 GL^3) 2. LGL = 43 g of oatmeal with half	Self-developed spatial map test (visuospatial memory), digit span forwards and backwards test (working memory), Rey Complex Figure Test (visual perception), CPT	Cognition = 60 minutes.	Digit span backward test = in females, more digits recalled after the LGL breakfast vs. HGL breakfast. No difference in performance in boys. No effects of GL on the remaining tests.	Meals provided identical amounts of energy, and similar amounts of CHO and fat. Statistically tested for the

		Overnight fast. Minimum 1-week washout period. School-based study.	cup skimmed milk (200kcal, 38 g CHO, 19 g sugars, 8 g PRO, 2 g fat, 31.66 GL[3]) 3. No breakfast	(visual and auditory attention), and paragraph recall task (episodic memory).			influence of biological sex. Only administered one cognitive test battery. Did not measure BGLs.
Mahoney et al. (2005) Study 2.	30 healthy children (15 female, 15 male). Age range = 6 – 8 years. GT status not assessed.	WS. Non-randomised. Counterbalanced. Experimenter blind to breakfast conditions.	1. HGL = 36 g of ready-to-eat cereal with half cup skimmed milk (200 kcal, 36 g CHO, 22 g sugar, 5 g PRO, 1.5 g fat, 1 g fibre, 37.02 GL[3]) 2. LGL = 43 g of oatmeal with half	Self-developed spatial map test (visuospatial memory), digit span forwards and backwards test (working memory), Rey Complex Figure Test (visual perception), CPT (visual and	Cognition = 60 minutes.	Digit span backward test = in females, more digits were recalled after the LGL breakfast vs. HGL. No effect in boys. CPT (auditory) = higher number of CR/fewer misses after LGL breakfast vs. HGL breakfast.	Meals provided identical amounts of energy, and similar amounts of CHO and fat. Statistically tested for the influence of biological sex.

		Overnight fast. Minimum 1-week washout period. School-based study.	cup skimmed milk (200 kcal, 38 g CHO, 19 g sugars, 8 g PRO, 2 g fat, 3 g fibre, 31.66 GL[3]) 3. No breakfast	auditory attention), and paragraph recall task (episodic memory).		No effect of GL on the remaining tests.	Only administered one cognitive test battery. Did not measure BGLs.
Micha et al. (2011)	74 healthy children (37 female, 37 male). Mean age = 12.6 years (SD = 0.1, range = 11-14 years). Created 32 matched pairs based on school	Mixed design (WS = HGI or LGI and BS = HGL or LGL). Randomised. Double-blind. Counterbalanced. Overnight fast.	1) HGL/LGI = Alpen muesli, milk, apple juice, and sugar (470 kcal, 86.6 g CHO, 14 g PRO, 7.1 g fat, 41 GL[1]) 2) HGL/HGI = Cornflakes, milk, apple juice, and sugar (470 kcal, 90.4 g CHO, 14 g PRO, 5.3 g fat, 55 GL[1])	Word generation task (semantic memory). WLR task (immediate and delayed episodic memory), Stroop task (executive function - inhibitory control), Matrices (visual reasoning), number search task (speed	Cognition = started between 101-105 minutes post-breakfast and finished 133-138 minutes post-breakfast. Glucose levels = 00,	Inclusion of confounding variables increased the number of significant results. Serial Sevens task = HGI meals predicted better performance. Stroop task = HGI meals predicted faster performance.	Some meals contained similar amounts of macronutrients and energy. Included order of meal consumption, biological sex, BMI, height, age, weight,

	year, sex, height, weight, mean age, and BMI.	2-week washout period. Same meal consumed evening before testing. No vigorous exercise for 24 hours School-based study.	3) LGL/LGI = Alpen muesli, milk, and sugar (281 kcal, 43.2 g CHO, 12.5 g PRO, 6.4 g fat, 21 GL[1]) 4) LGL/HGI = Cornflakes, milk, and sugar (276 kcal, 45.2 g CHO, 12 g PRO, 5.1 g fat, 28 GL[1])	of information processing), and Serial Sevens task (working memory).	92, and 147 minutes.	Number search task = HGI meals predicted better performance. Word generation task = LGI meals predicted better performance. No effect of GL on the remaining tests.	baseline mood, and baseline cortisol/glucose levels as covariates. Did not report Stroop accuracy scores. Faster RTs may reflect more impulsive responses.
Smith and Foster (2008b)	38 healthy participants (19 female, 19 male). Mean age = 15.65 years (SD	BS. Randomised. Overnight fast.	1. HGL = Cornflakes with 125 ml milk (172 kcal, 31.2 g CHO, 6.5 g PRO, 2 g fat, 24 GL[2])	CVLT, WLR task (immediate, short delay, and long delay episodic memory)	Cognition = 20 (immediate recall), 60 (short-delay free/cued recall), and	Participants in the HGL group recalled more words after the long delay vs. LGL group.	Breakfasts provided similar amounts of fat but different amounts of PRO, CHO, and energy.

	= 0.9, range = 14 – 17 years). GT status not assessed.		2. LGL = All Bran with 125 ml milk (158 kcal, 20.5 g CHO, 8.8 g PRO, 2.8 g fat, 6 GL^2)	Completed a secondary motor task whilst encoding word lists.	100 minutes (long-delay free/cued recall). Glucose levels = 00, 10, 50, and 90 minutes.		No difference in BGLs between groups at any time point.
Taib et al. (2012)	30 healthy children (12 female, 18 male). Mean age = 5.58 years and 4 months. GT status not assessed.	WS. Randomised. Counterbalanced. Double-blind. Overnight fast. 1-week washout period.	1. HGL = glucose - maltodextrin drink (160 kcal, 50 g CHO, 40 GL^2) 2. MGL = standard GUM (170 kcal, 26.40 g CHO, 5.88 g PRO, 5.32 g fat, 20 GL^2)	CDR Computerised Assessment Battery: visuospatial working memory, numeric working memory, and picture recognition. Also created two composite scores using speed	Cognition – 00, 60, 120, and 180 minutes.	Speed of attention = scores declined across the morning. However, scores improved 180 minutes after consuming the isomaltulose-GUM drink (non-significant). Working memory = spatial working memory scores declined across the morning following the consumption of all drinks; the decline was	GUM drinks had similar macronutrient and energy profiles. Did not measure BGLs. Used a milk-based vehicle – insulinotropic.

		School-based study. Children maintained a standard pattern of activity prior to testing.	3. MGL = reformulated GUM (174 kcal, 26.48 g CHO, 5.88 g PRO, 5.32 g fat, 14 GL[2]) 3. LGL = isomaltulose GUM (170 kcal, 26.44 g CHO, 5.88 g PRO, 5.36 g fat, 13.76 GL[2])	measures (speed of attention) and accuracy measures (accuracy of attention) from SRT, CRT, and digit vigilance tasks.		significantly smaller following the consumption of glucose. Numeric working memory also declined across the morning following the consumption of all drinks; the decline was smaller following the isomaltulose-GUM drink. Delayed picture recognition = overall performance declined across the morning in all groups except the isomaltulose-GUM group. Speed scores improved from baseline following the glucose drink only.	Baseline cognitive performance for each visit included as a covariate.
Wesnes et al. (2003)	29 healthy children (15 female, 14 male).	WS. Randomised.	1. HGL = 38.3 g of glucose in 330 ml orange-flavoured drink (38 GL[3])	CDR Computerised Assessment Battery: WLR, SRT, CRT, digit	Cognition = 00, 30, 90, 150, and 210 minutes.	Speed of attention and secondary memory = scores declined across the morning following the consumption of	Macronutrient and energy content of meals not reported.

		Counterbalanced.		vigilance,		a glucose drink or no	
	Mean age = 12.2 years (range = 9 – 16 years).	Tested on consecutive days.	2. LGL = Shreddies plus 125 ml of semi-skimmed milk (38.3 g total CHO, 15 GL[3])	visuospatial and numeric working memory, word recognition, and picture recognition.		breakfast, whereas the consumption of either LGL breakfast reduced the decline by more than half.	Did not measure BGLs.
	GT status not assessed.	Overnight fast.					Large age range of sample.
		Laboratory-based study.	3. LGL = Cheerio's plus 125 ml of semi-skimmed milk (28.7 g total CHO, 15 GL[3])	Created composite scores: speed of memory, speed of attention, accuracy of attention, working memory, and secondary memory.		Immediate WLR = relative to baseline, immediate WLR declined by 27% 210 minutes after consuming the glucose drink, whereas scores increased by 5% after Shreddies and 3% after Cheerio's.	
			4. No breakfast			No effect of GL on the remaining tests.	
Young and Benton (2015)	75 healthy children from four different schools (47	WS.	1. HGL = Cornflakes, skimmed milk, and glucose-sweetened	British Ability Scale – object name recall (immediate and	Cognition = 60 and 180 minutes.	Information processing speed = order of meal consumption interacted with breakfast GL. No difference in performance	Meals had identical macronutrient

	female, 28 male). Mean age = 8 years and 8 months (range = 5 – 11 years). GT status not assessed.	Counterbalanced. Overnight fast. Double-blind. 1-week minimum washout period. School-based study.	low-calorie yoghurt, fruit, and an orange drink (337 kcal, 73 g CHO, 9.2 g PRO, 1.9 g fat, 59.8 GL[1]) 2. LGL = Cornflakes, skimmed milk, and isomaltulose-sweetened low calorie yoghurt, fruit, and an orange drink (337 kcal, 73.3 g CHO, 9.2 g PRO, 1.9 g fat, 31.63 GL[1])	delayed episodic memory), British Ability Scale – object location recall (immediate and delayed visuospatial memory), Paradigm of Shakow (sustained attention), British Ability Scale (speed of information processing), and RTs.	Speed of information processing task also tested at baseline.	on day 1. However, on day 2, overall performance was better after the LGL meal vs. HGL meal. Object name recall (immediate) = similar performance at 60 minutes. However, at 180 minutes, performance following the LGL meal was maintained, whereas performance declined following the HGL meal. Object location recall = order of meal consumption interacted with breakfast GL. No difference in performance on day 1. However, on day 2, overall performance was	and energy profiles. Did not measure BGLs. Biological sex and order of meal consumption were included as additional between-subjects factors. Age, baseline cognitive performance (speed of processing only), and social deprivation were

		better after the LGL meal vs. HGL meal. No effect of GL on RTs or sustained attention.	included as covariates.

Note. 1 = GL values reported by study authors, 2 = GL values calculated using reported GI values multiplied by amount of CHO or available CHO, and 3 = GL values calculated using published GI tables. * = estimated GL values are not consistent with participants glycaemic responses. BS = between-subjects design, WS = within-subjects design, 00 = baseline, GL = glycaemic load, LGL = low GL, HGL = high GL, MGL = medium GL, GI = glycaemic index, CHO = carbohydrate, PRO = protein, GT = glucose tolerance, BMI = body mass index, BGLs = blood glucose levels, GUM = growing up milk, WLR = word list recall, RT = reaction times, SRT = simple RT, CRT = choice RT, CDR = cognitive drug research, CPT = continuous performance task, SCPT = standard CPT, RMCPT = running memory CPT, CVLT = California Verbal Learning Test, RAVLT = Rey Auditory Verbal Learning Test, WISC = Wechsler Intelligence Scale for Children, ANOVA = Analysis of Variance.

2.3.7 Review of breakfast studies involving children and adolescents

In this section, the effect of breakfast GL on memory, attention, executive function, and speed of information processing in children and adolescents is systematically reviewed according to the timing of testing during the postprandial period.

Table 5. Ratio of significant to non-significant breakfast studies involving children and adolescents.

	Early PPP (0-59 minutes)	Mid PPP (60-119 minutes)	Late PPP (>120 minutes)
Episodic memory[1]	1/4	1/11	4/9
Working memory[2]	0/7	2/10	3/11
Speed of attention[3]	0/5	0/8	1/8
Accuracy of attention	0/6	1/10	3/11

Note. Only studies that reported an effect of breakfast GL at a specific time point were included in this table. A main effect of breakfast GL was reported by 1 = Brindal et al. (2013), Lee et al. (2019), and Taib et al. (2012), 2 = Taib et al. (2012), and 3 = Anderson et al. (2020) and Taib et al. (2012). PPP = postprandial period.

2.3.7.1 Memory

2.3.7.1.1 Episodic memory

Twelve studies assessed episodic memory. As shown in Table 4, three studies reported no effect of breakfast GL during the early postprandial period (Lee et al., 2019; Smith & Foster, 2008b; Wesnes et al., 2003). In contrast, Ingwersen et al. (2007) reported that episodic memory scores were higher 10 minutes after consuming a LGL breakfast compared to HGL breakfast.

During the mid-postprandial period, 10 studies reported no effect of breakfast GL (Brindal et al., 2012; Brindal et al., 2013; Ingwersen et al., 2007; Lee et al., 2019; Mahoney et al., 2005; Micha et al., 2011; Taib et al., 2012; Wesnes et al., 2003; Young & Benton, 2015). Smith and Foster (2008b) were the only authors to report an effect of breakfast GL within this time window (100 minutes post-breakfast), whereby delayed episodic memory was better in the HGL group compared to the LGL group. The authors suggested that the beneficial effect of a HGL breakfast on delayed memory may be due to the increased availability of glucose to the brain during encoding. However, there were no significant differences in blood glucose levels

between the two groups at any postprandial time point, suggesting that differences in glycaemia may not account for differences in cognitive performance.

Nine studies measured episodic memory during the late postprandial period (120 minutes or later), of which five reported that breakfast GL did not influence performance (Brindal et al., 2012; Brindal et al., 2013; Lee et al., 2019; Micha et al., 2011; Taib et al., 2012). Using an Analysis of Variance (ANOVA), Benton et al. (2007b) also found that breakfast GL did not influence the memory of young children 140 minutes post-breakfast. However, there was a significant negative correlation between GL and immediate episodic memory scores. Furthermore, a lower GL predicted better episodic memory, whereas the amount of protein, fat, and carbohydrate did not. Young and Benton (2015) also recruited young children. Although immediate recall was similar 60 minutes post-breakfast, performance was significantly better during the second test battery (180 minutes) following the consumption of a LGL breakfast. Furthermore, performance only declined from the first test battery to the second test battery after the consumption of a HGL breakfast. Ingwersen et al. (2007) also found no effect of breakfast GL during the mid-postprandial period (70 minutes). However, during the late postprandial period (130 minutes), task accuracy was better after consuming a LGL rather than HGL breakfast. Similarly, Wesnes et al. (2003) found that a LGL breakfast benefited performance, but only during the late postprandial period. Immediate recall declined by 27% during the final test battery (210 minutes) after participants consumed a HGL breakfast but improved by 3 to 5% after a LGL breakfast. The ratio of significant to non-significant findings during the early, mid, or late postprandial period are shown in Table 5. The pattern of results suggests that the likelihood of detecting differences in episodic memory may be greater during the late postprandial period, rather than early or mid-postprandial period.

Three studies reported significant effects of breakfast GL that were not time dependent. Taib et al. (2012) reported an overall decline in delayed memory across the morning after the consumption of all drinks other than an isomaltulose-sweetened drink (lowest GL). Interestingly, overall task speed improved across the morning after the consumption of a glucose drink (highest GL) compared to reformulated growing-up milk. In contrast, Wesnes et al. (2003) and Ingwersen et al. (2007) reported that task speed was not influenced by breakfast GL. Brindal et al. (2013) reported that the effect of breakfast GL interacted with participant's biological sex. Relative to baseline, females recalled more words overall after consuming a LGL or MGL breakfast compared to a HGL breakfast. There was no effect of GL in male children. No effect of time was also reported by Lee et al. (2019). However, participants

recalled more words overall after consuming a meal with a lower estimated GL (French fries) compared to a higher estimated GL (mashed potatoes or white rice). As glycaemic responses were higher after the consumption of French fries than mashed potatoes, it suggests that estimated GL values are incorrect. Therefore, these findings should be interpreted with caution.

2.3.7.1.2 Working memory

A total of 13 studies assessed working memory. Nine studies reported that breakfast GL did not influence task performance during the early postprandial period (Anderson et al., 2020; Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Wesnes et al., 2003), mid postprandial period (Anderson et al., 2020; Brindal et al., 2012; Brindal et al., 2013; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Taib et al., 2012; Wesnes et al., 2003), and/or late postprandial period (Anderson et al., 2020; Brindal et al., 2012; Brindal et al., 2013; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Taib et al., 2012; Wesnes et al., 2003).

Both studies by Mahoney et al. (2005) found an effect of breakfast GL during the mid-postprandial period. Older (9 – 11 years) and younger (6 – 8 years) female children performed better 60 minutes after consuming a LGL breakfast compared to a HGL breakfast. Breakfast GL did not significantly influence the performance of male children. Although no effect of time was reported, Anderson et al. (2020) also reported an interaction between biological sex and breakfast GL. Irrespective of time, task performance was better in females after a HGL drink than LGL drink. The opposite pattern occurred in males, but this was not significant. The reason for these conflicting findings is unclear - participants in Mahoney et al. (2005) and Anderson et al. (2020) were of a similar age and there was a similar difference in GL between the LGL and HGL breakfasts.

One study reported that a HGI breakfast predicted better working memory performance during the late postprandial period (Micha et al., 2011). Two studies reported that a LGL breakfast was associated with better performance during the late postprandial period (Cooper et al., 2012, 2015). Although reaction times were similar 30 minutes post-breakfast, there was a greater improvement in task speed 120 minutes after consuming a LGL breakfast compared to a HGL breakfast (Cooper et al., 2012). On the complex levels of this task, accuracy scores were maintained across the morning following a LGL breakfast but declined following a HGL breakfast. In a later study, Cooper et al. (2015) reported a similar finding, whereby reaction times improved across the morning (from 30 to 120 minutes) after consuming a LGL meal,

regardless of whether participants exercised. However, performance only improved after a HGL meal if participants exercised.

Taib et al. (2012) reported that a LGL breakfast benefitted overall task performance. Relative to baseline, numeric working memory scores declined across the morning in all drink conditions. However, the decline was significantly smaller after consuming an isomaltulose-sweetened drink (lowest GL) compared to a glucose drink (highest GL) or reformulated growing-up milk. As shown in Table 4, the GL of the isomaltulose-sweetened milk and reformulated milk were very similar and so it is unlikely that differences in GL accounted for this finding. The authors also reported that a HGL drink benefitted spatial working memory. Specifically, the overall decline across the morning was significantly smaller after the consumption of glucose compared to all three LGL drinks.

2.3.7.1.3 Semantic memory

One study assessed semantic memory using a verbal fluency task. Micha et al. (2011) reported that a LGI breakfast, irrespective of GL, predicted better performance during the late postprandial period.

2.3.7.1.4 Visuospatial memory

Five studies reported that breakfast GL did not influence visuospatial memory during the early postprandial period (Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Taib et al., 2012; Wesnes et al., 2003), seven during the mid-postprandial period (Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Mahoney et al., 2005; Taib et al., 2012; Wesnes et al., 2003), and six during the late postprandial period (Benton et al., 2007b; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Taib et al., 2012; Wesnes et al., 2003). Young and Benton (2015) were the only authors to report an effect of breakfast GL on visuospatial memory, irrespective of time. However, the beneficial effect of a LGL meal was influenced by the order of meal consumption. There were no differences in performance on the first day of testing. However, on the second day of testing, overall performance was better if a LGL meal was consumed.

2.3.7.2 Speed of attention

Eleven studies measured speed of attention, of which nine reported no effect of breakfast GL during the early postprandial period (Anderson et al., 2020; Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007), mid-postprandial period (Anderson et al., 2020; Brindal et al., 2012; Brindal et al., 2013; Ingwersen, 2011; Ingwersen et al., 2007; Mahoney et al., 2005; Taib et al., 2012), and/or late postprandial period (Anderson et al., 2020; Brindal et

al., 2012; Brindal et al., 2013; Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007; Taib et al., 2012). One study reported that a LGL breakfast benefitted task speed, but only during the late postprandial period. Wesnes et al. (2003) reported a significant decline in performance, relative to baseline, 210 minutes after consuming a HGL drink. However, this decline was reduced by more than half following the consumption of a LGL breakfast.

Two studies reported significant effects of breakfast GL that were not time dependent. Taib et al. (2012) reported that performance declined across the morning. However, the overall decline was significantly greater following the consumption of standard growing-up milk compared to isomaltulose-sweetened growing-up milk. Furthermore, at 180 minutes, there was a non-significant improvement in performance, but only after the consumption of isomaltulose-sweetened milk. Anderson et al. (2020) reported an interaction between breakfast GL and biological sex. Responses were faster overall after the consumption of a LGL drink, compared to a HGL drink, but only in female participants. The opposite pattern emerged for males, but this was non-significant.

2.3.7.3 Accuracy of attention

Thirteen studies measured accuracy of attention. Ten studies reported that breakfast GL did not influence performance during the early postprandial period (Anderson et al., 2020; Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007; Wesnes et al., 2003), mid-postprandial period (Anderson et al., 2020; Brindal et al., 2012; Brindal et al., 2013; Ingwersen, 2011; Ingwersen et al., 2007; Taib et al., 2012; Wesnes et al., 2003; Young & Benton, 2015), and/or late postprandial period (Anderson et al., 2020; Brindal et al., 2012; Brindal et al., 2013; Cooper et al., 2015; Ingwersen, 2011; Taib et al., 2012; Wesnes et al., 2003; Young & Benton, 2015).

During the mid-postprandial period, Mahoney et al. (2005) reported an interaction between age and breakfast GL. Younger children (6 to 8 years old) made more correct responses on an auditory attention task 60 minutes after consuming a LGL breakfast rather than a HGL breakfast. In contrast, no differences in performance were found in older children (9 to 11 years old). Furthermore, breakfast GL did not influence visual attention performance. Ingwersen et al. (2007) also examined the effect of age using the same age groups, however no age effects were observed.

Three studies found a beneficial effect of a LGL breakfast during the late postprandial period. In Cooper et al. (2012), accuracy scores on the more complex trials were similar during the

first test battery (30 minutes). However, during the second test battery (120 minutes), scores were better maintained after consuming a LGL breakfast compared to a HGL breakfast. Similarly, Ingwersen et al. (2007) reported that there was a sharp decline in performance 130 minutes after consuming a HGL breakfast, whereas performance was maintained at this time after consuming a LGL breakfast. Although no effect of breakfast GL was reported using an ANOVA, Benton et al. (2007b) found that the number of lapses of attention (difficult trials only) correlated positively with GL. A lower GL also predicted better sustained attention (difficult trials only).

2.3.7.4 Executive function

2.3.7.4.1 Inhibitory control

Four studies measured inhibitory control, three using the Stroop task (Cooper et al., 2012, 2015; Micha et al., 2011) and one using the go-no-go task (Anderson et al., 2020). Three studies reported no specific effect of breakfast GL during the early postprandial period (Anderson et al., 2020; Cooper et al., 2012, 2015), and one study during the mid-postprandial period and late postprandial period (Anderson et al., 2020). Micha et al. (2011) only measured inhibitory control during the mid-postprandial period and reported that performance was fastest after the consumption of a HGL breakfast with a HGI.

Two studies reported an effect of breakfast GL during the late postprandial period. Cooper et al. (2012) reported similar reaction times during the early postprandial period (30 minutes). However, during the late postprandial period (120 minutes), reaction times significantly improved after the consumption of a HGL meal. In contrast, accuracy scores were better after the consumption of a LGL meal, irrespective of time. In a later study, Cooper et al. (2015) reported an interaction between breakfast GL and exercise. Although GL alone did not influence performance, the combination of a LGL breakfast with exercise resulted in the largest improvement in reaction times during the late postprandial period, but only on the complex trials of the Stroop task. Accuracy scores were not influenced by breakfast GL.

Although Anderson et al. (2020) did not report a specific effect of time, there was an overall effect of breakfast GL that interacted with participants GT status. In those with higher fasting blood glucose levels, faster reaction times were observed following the LGL drink, and the difference in performance between the LGL and HGL drink increased as fasting glucose levels increased. No differences in task accuracy were reported.

2.3.7.4.2. Visual reasoning

One study measured visual reasoning during the mid-postprandial period; no effect of GL was reported (Micha et al., 2011).

2.3.7.5 Speed of information processing

Several studies reported that breakfast GL did not influence speed of information processing during the early (Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Wesnes et al., 2003), mid (Brindal et al., 2012; Brindal et al., 2013; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Taib et al., 2012; Wesnes et al., 2003), and/or late postprandial period (Brindal et al., 2012; Brindal et al., 2013; Cooper et al., 2012, 2015; Ingwersen, 2011; Ingwersen et al., 2007; Lee et al., 2019; Taib et al., 2012; Wesnes et al., 2003). Micha et al. (2011) reported that a HGI breakfast, irrespective of GL, was associated with better speed of information processing during the late postprandial period. Conversely, Young and Benton (2015) reported a beneficial effect of a LGL meal which was influenced by the order of meal consumption. On the first day of testing, there were no differences in performance. However, on the second day of testing, overall performance was better in children who had eaten a LGL breakfast compared to a HGL breakfast.

2.3.7.6 Summary of findings from systematic review of breakfast studies involving children and adolescents

- There was very limited evidence to suggest that breakfast GL influenced cognitive performance within the first hour after consuming breakfast.
- There was some evidence to suggest that a LGL breakfast may protect against a decline in episodic memory and accuracy of attention during the late postprandial period (>120 minutes post-breakfast).
- The relationship between breakfast GL and cognition was influenced by task difficulty, age, and biological sex.
- Inhibitory control may be susceptible to variations in breakfast GL.

2.3.8 Review of non-breakfast studies involving children and adolescents

In the following section, the results of studies that manipulated the GL of nutritional interventions administered after breakfast time in children and adolescents are systematically reviewed.

2.3.8.1 Study characteristics

As summarised in Table 6, all three studies were randomised and used a within-subjects design (Akhavan et al., 2014; Drozdowska et al., 2021; Jansen et al., 2020). In both Jansen et al. (2020) and Drozdowska et al. (2021), participants were blind to the nature of the meals. A standardised breakfast was administered in all studies and participants were instructed to fast for between two to three hours. Akhavan et al. (2014) administered a mid-morning drink sweetened with either glucose, high-fructose corn-syrup, or sucrose. Jansen et al. (2020) and Drozdowska et al. (2021) administered identical meals; GL was manipulated using different types of rice. Jansen et al. (2020) and Drozdowska et al. (2021) administered the same cognitive test battery at one time point during the postprandial period, whilst Akhavan et al. (2014) examined only one cognitive subdomain, namely episodic memory, at multiple times throughout the postprandial period.

2.3.8.2 Memory

2.3.8.2.1 Episodic memory

Using a word list recall task, Akhavan et al. (2014) measured immediate episodic memory 15, 30, 45, and 60 minutes post-drink consumption, whereas delayed episodic memory was only assessed during the mid-postprandial period (90 minutes). The authors reported that differences in GL did not influence episodic memory. However, delayed episodic memory was examined after lunch and therefore effects may have been missed. Furthermore, given that there is evidence that female children are more sensitive to the effects of breakfast GL (Anderson et al., 2020; Brindal et al., 2013; Mahoney et al., 2005), the inclusion of only male children in this study may have contributed to the results

2.3.8.2.2 Working memory

Both Jansen et al. (2020) and Drozdowska et al. (2021) measured working memory using the 2-back task. Jansen et al. (2020) analysed data from only the first visit as order effects were identified. The authors reported that the consumption of a HGL meal was associated with faster reaction times during the early postprandial period (45 minutes) than a LGL meal. However, it is important to note that both meals had a very high GL (LGL = 70 and HGL = 99.5). Drozdowska et al. (2021) tested cognitive performance during the mid-postprandial period (90 minutes). No differences in working memory were observed following the HGL and LGL meals.

2.3.8.3 Attention

Jansen et al. (2020) and Drozdowska et al. (2021) Drozdowska et al. (2021)measured attention using the Trails Part A task during the early and mid-postprandial period, respectively, Neither study reported that differences in GL influenced task performance.

2.3.8.4 Processing speed

Using a simple reaction time task, Jansen et al. (2020) reported that the consumption of a HGL meal compared to a LGL meal was associated with better processing speed accuracy during the early postprandial period (45 minutes). In contrast, Drozdowska et al. (2021) reported that the same meals did not influence processing speed during the mid-postprandial period (90 minutes).

Table 6. Summary of non-breakfast studies involving children and adolescents.

Author (Year)	Participant characteristics	Study design	Nutritional intervention	Cognitive test	Timing of cognitive and blood glucose tests	Results	Comments
Akhavan et al. (2014)	15 healthy male children. Mean age = 12.2 years (SD = 0.4, age range = 9 – 14 years). GT status not assessed.	WS. Randomised. Minimum 1-week washout period. Overnight fast. Standardised breakfast and a 2-hour fast. Drinks consumed between 10am and 12pm.	250 mL drink with: 1. HGL = 54.6 g of glucose (200 kcal, 54.60 GL^2) 3. MGL = 64.9 g of high-fructose cornsyrup-44 (200 kcal, 47.37 GL^2)	WLR task (immediate and delayed episodic memory).	Immediate recall = 15, 30, 45, and 60 minutes. Delayed recall (after lunch) = 90 minutes.	No effect of GL on cognition.	Drinks matched for sweetness, calories, and volume. Did not measure BGLs. Only tested immediate recall during the early PPP.

			2. LGL = 53.3 g of sucrose (200 kcal, 36.24 GL[2])				
Drozdowska et al. (2021)	212 healthy children from one school (87 female, 125 male). Age range = 10 - 12 years. GT status not assessed.	WS. Randomised. Singe-blind. Counterbalanced. Lunchtime intervention. 1-week washout period. Standardised breakfast and a 3-hour fast.	1. HGL = Jasmine rice with ground beef sauce (99.5 GL[1]) 2. LGL = Basmati rice with ground beef sauce (70 GL[1])	Trails part A (attention and processing speed), 2-back task (working memory), and SRT (information processing speed).	Cognition = 90 minutes.	No effect of GL on cognition.	Quantity of meal consumed varied between participants. Measured the glycaemic response to meals using adult participants. Only administered one cognitive test battery.

Jansen et al. (2020)	189 healthy children (84 female, 105 male). Mean age = 11.8 years (SD = 0.7). GT status not assessed.	WS. Randomised. Single-blind. Counterbalanced. Lunchtime intervention. 1-week washout period. Standardised breakfast and a 3-hour fast (quantity not controlled).	1. HGL = Jasmine rice with ground beef sauce (107 GL[1]) 2. LGL = Basmati rice with ground beef sauce (67 GL[1])	Trails part A (attention and processing speed), 2-back task (working memory), and SRT (information processing speed).	Cognition = 45 minutes.	Only included results from the first test period as order effects were identified. 2-back task = consumption of HGL rice resulted in faster RTs compared to MGL rice. SRT task = consumption of the HGL rice resulted in fewer errors compared to the MGL rice.	Quantity of meal consumed varied between participants. Measured the glycaemic response to meals using adult participants. Tested for influence of order effects. Only administered one cognitive test battery.

Note. 1 = GL values reported by study authors and 2 = GL values calculated using published GI tables. WS = within-subjects design, 00 = baseline, GL = glycaemic load, LGL = low GL, HGL = high GL, MGL = medium GL, GT = glucose tolerance, BGLs = blood glucose levels, WLR = word list recall, SRT = simple reaction time.

2.4 Discussion

2.4.1 Breakfast studies involving adults

Studies comparing HGL and LGL breakfasts have produced mixed results. An obvious hypothesis is that certain methodological factors determine the outcome. Therefore, for the first time, this meta-analysis considered a range of possible factors that may influence the response to the glycaemic influence of breakfast.

As summarised in Section 2.3.3.8, there were several lines of evidence to suggest that a LGL breakfast benefits cognitive performance in a time-dependent manner. During the late postprandial period (120 minutes or later), a LGL breakfast was significantly associated with better immediate episodic memory (Figure 2). A similar non-significant trend was also observed for delayed episodic memory during the late postprandial period (150 – 220 minutes; Figure 4). In addition, the beneficial effect of a LGL breakfast on immediate and delayed episodic memory was influenced by participants age (Figure 6) and GT (Figure 3 and 5). However, the sensitivity analysis showed that the removal of most studies, particularly Benton et al. (2003), Young and Benton (2014a), and Sanchez-Aguadero et al. (2020), reduced the effect size of the analyses shown in Figure 2 and Figure 4, highlighting the need for more research in this area to confirm or refute these conclusions.

There was no significant effect of breakfast GL on speed of attention, accuracy of attention, or accuracy of working memory across all three postprandial time windows. These results suggest that the effect of breakfast GL may be subdomain-specific. In line with this, previous reviews have reported that episodic memory is more responsive to breakfast manipulations than other cognitive domains and subdomains (Galioto & Spitznagel, 2016; Hoyland et al., 2008; Smith et al., 2011; Wasyluk et al., 2019). Similarly, episodic memory is also particularly sensitive to the glucose facilitation effect (Riby, 2004; Smith et al., 2011). However, it is important to note that fewer studies assessed working memory than episodic memory in the meta-analysis, and a wider variety of tests were used to measure attention and working memory. These factors may have influenced the findings. The systematic review revealed that differences in breakfast GL can impact other forms of memory, such as semantic and visuospatial memory, as well as speed of information processing and executive functions. However, the evidence was inconsistent, and the majority of studies reported that breakfast GL did not influence task performance. Further research is therefore required to determine whether the effect of breakfast

GL is subdomain-specific or whether this reflects a lack of research and/or methodological differences.

The results of the meta-analysis are consistent with the hypothesis that a LGL breakfast, which provides a steady and continuous supply of glucose to the brain, may be more advantageous for acute cognitive performance than a HGL breakfast (Nilsson et al., 2012; Papanikolaou et al., 2006; Young & Benton, 2014a). It is difficult to assess the validity of this hypothesis because many studies did not measure peripheral glucose levels. Furthermore, in those studies that did, some reported cognitive differences when glucose levels were similar (Benton et al., 2003; Nilsson et al., 2012), and others reported no cognitive differences when glucose levels were markedly different (Kaplan et al., 2000; Lamport et al., 2013a; Sanchez-Aguadero et al., 2020). Although there is a positive correlation between blood glucose and extracellular glucose (Rostami & Bellander, 2011; van de Ven et al., 2012), the concentration of glucose in the brain is approximately 20-30% of that in the blood (Béland-Millar et al., 2017), and there is a time lag of up to 30 minutes between changes in blood glucose and changes in extracellular glucose (Abi-Saab et al., 2002; Gruetter et al., 1998). Cognitive demand can also influence extracellular glucose levels (McNay et al., 2000). Therefore, a failure to observe concurrent cognitive and glycaemic differences does not necessarily disprove this hypothesis. Perhaps the beneficial effect of a LGL relative to HGL breakfast is not directly related to glycaemia, but rather associated aspects of metabolism that appear over time, including changes in cortisol, insulin, glucagon, GLP-1, acetylcholine, glutamate, or serotonin levels (Adolphus et al., 2016; Hoyland et al., 2009).

Previous reviews have suggested that a LGL breakfast may be particularly advantageous to vulnerable groups, including older adults or individuals with poorer GT (Galioto & Spitznagel, 2016; Lamport et al., 2009; Sünram-Lea & Owen, 2017). In contrast, subgroup analyses indicated that a LGL breakfast may exert a greater effect in younger adults or those with better GT. Specifically, a LGL breakfast benefitted immediate episodic memory, during the late postprandial period (120 minutes or later), in the better subgroup but not the poorer GT subgroup. A similar non-significant trend was observed for delayed episodic memory during the late postprandial period. Subgroup analyses also showed that a LGL breakfast benefitted delayed episodic memory, during the mid-postprandial period (62 – 119 minutes), in the younger subgroup but not the older subgroup. The finding that age effects were only observed during the mid-postprandial period is surprising, as all other effects were observed during the late postprandial period.

As the mechanisms underlying the acute cognitive effects of GL are currently unclear, it is difficult to speculate why these subgroup effects occurred. However, it is plausible that such mechanisms are hampered in those with poorer GT or those aged above 35 years old. For example, it has been suggested that the beneficial effect of a LGL breakfast may be due to the generation of a smoother postprandial insulin profile (Benton et al., 2003). Glucose intolerance is associated with impaired insulin action and secretion (Abdul-Ghani et al., 2006) and endothelial dysfunction (Convit, 2005). The transport of insulin and glucose across the BBB, and between intracellular and extracellular fluid in the brain, is thus hindered in glucose intolerant individuals (Lamport et al., 2013a; Young & Benton, 2014a). This may result in a lack of sensitivity to the cognitive effects of GL. The prevalence of glucose intolerance and endothelial dysfunction also increases with age (Matz & Andriantsitohaina, 2003; Shimokata et al., 1991), which may also contribute to age effects.

Consistent with this suggestion, a double-blind, well-controlled study by Young and Benton (2014a) reported that a LGL breakfast benefitted episodic and working memory in middle aged and older adults (45 – 80 years old) with better but not poorer GT. The picture is, however, complicated as a beneficial effect of a LGL breakfast on episodic memory has been demonstrated in older adults with T2DM (Papanikolaou et al., 2006) and IGT (Lamport et al., 2014), and young healthy adults with poorer GT (Nabb & Benton, 2006b). However, it is unclear whether GT interacted with the effects of breakfast GL as Papanikolaou et al. (2006) did not recruit a healthy control group. Furthermore, most participants in Papanikolaou et al. (2006) were treated with metformin or sulphonylureas. These medications improve GT by enhancing insulin secretion and suppressing hepatic glucose production, which may have interacted with the effects of breakfast GL.

Alternatively, the absence of a significant beneficial effect in the older subgroup may be due to the inclusion of participants with a wide range of ages. Specifically, the mean age of the older subgroup ranged from 36.6 years (Lamport et al., 2014) to 65 years (Papanikolaou et al., 2006), whereas the mean age of the younger subgroup ranged from 20.36 years (Nabb & Benton, 2006a) to 28.1 years (Sanchez-Aguadero et al., 2020). It is plausible that the wide age range of the older subgroup introduced variability, which can reduce statistical power and mask significant effects (Jiang et al., 2010; Netz et al., 2019). Indeed, advancing age is associated with increased interindividual variability in baseline nutritional status, GT, and cognitive, physical, and sensory function (Asamane et al., 2020; Ferrucci & Kuchel, 2021; Mungas et al.,

2010; Zulman et al., 2011). Further research aimed at understanding individual differences in the response to GL is clearly warranted.

2.4.2 Breakfast studies involving children and adolescents

Due to a lack of data, and the use of different types of scores, a meta-analysis of the effect of breakfast GL in children and adolescents was not possible. Instead, a systematic review of 16 studies was conducted. Although the cognitive effects of manipulating breakfast GL have been discussed in previous systematic reviews, the influence of the timing of testing was only briefly considered (Adolphus et al., 2016; Álvarez-Bueno et al., 2019; Hoyland et al., 2009). In contrast, the present review systematically examined the cognitive effects of breakfast GL in relation to the timing of testing.

Despite the wealth of studies conducted in children and adolescents, there was no clear and robust effect of breakfast GL on any cognitive domain or subdomain during the early, mid, or late postprandial period. However, there was some evidence to suggest that breakfasts that slowly release glucose may benefit episodic memory and accuracy of attention, particularly during the late postprandial period (120 minutes post-breakfast or later). However, it is important to note that most studies reported no significant differences in episodic memory and accuracy of attention following the consumption of breakfasts differing in GL. No study reported an effect of breakfast GL on accuracy or speed of attention during the early postprandial period, and no study reported that a HGL breakfast positively influenced attention. The effect of breakfast GL on working memory was more heterogeneous, with some studies reporting an advantage of a LGL breakfast (Cooper et al., 2012, 2015; Mahoney et al., 2005; Taib et al., 2012), and other studies reporting an advantage of a HGL breakfast (Anderson et al., 2020; Micha et al., 2011; Taib et al., 2012). Although only four studies measured inhibitory control, significant effects were reported in all studies, which suggests that this cognitive subdomain warrants further investigation.

A recent meta-analysis assessed the effect of breakfast GI, rather than GL, on the cognitive performance of children and adolescents. Álvarez-Bueno et al. (2019) reported that breakfast GI did not influence immediate memory, delayed memory, and attention. However, subgroup analyses revealed that delayed memory scores were significantly higher after a LGI breakfast, compared to HGI breakfast, in children but not adolescents. Álvarez-Bueno et al. (2019) were able to perform a meta-analysis of the effect of breakfast GI because they took a less rigorous

approach than the present meta-analysis. For example, change scores and post-scores were analysed together, subdomains of memory were analysed as one group (e.g., working memory and episodic memory), and the effect of the timing of testing was not examined. It is unclear how these factors influenced their conclusions, however, the findings from the present review indicate that they might be important.

In summary, there was some evidence to suggest that a LGL breakfast exerted a positive effect on episodic memory and accuracy of attention during the late postprandial period. This pattern of results is illustrated in Table 5. However, the quality of evidence was mixed, with most studies showing some concerns of bias. Furthermore, a range of experimental methods were used, giving rise to different methodological limitations. For example, two studies were not randomised, and most studies administered breakfast interventions that were not matched for macronutrient or energy content.

2.4.3 Non-breakfast studies

Most studies have examined the acute effects of breakfast composition on cognition, which presumably reflects the widespread belief that breakfast is the most important meal of the day (Spence, 2017). Of the five non-breakfast studies, three varied the GL of a lunchtime meal (Drozdowska et al., 2021; Jansen et al., 2020; Marchand et al., 2020), one varied the GL of a mid-morning drink (Akhavan et al., 2014), and one varied the GL of an afternoon drink (Keesing et al., 2019). Significant effects were reported in two out of five studies. Contrasting with the results of the meta-analysis, both studies reported that a HGL lunchtime meal benefitted cognitive performance in adults (Marchand et al., 2020) and children (Jansen et al., 2020). However, the difference in performance following the HGL and LGL meals in Marchand et al. (2020) was very small.

For a number of reasons, direct comparisons between breakfast studies and non-breakfast studies may be inappropriate. It is well established that GT fluctuates on a 24-hour cycle. The glycaemic response to identical meals or glucose loads is significantly milder in the morning than in the afternoon and evening (Carroll & Nestel, 1973; Jarrett et al., 1972; Service et al., 1983). This phenomenon is thought to reflect reduced insulin secretion and action during the afternoon and evening than morning (Service et al., 1983). Consequently, the difference in postprandial glucose AUC between LGL and HGL meals is larger during the morning than evening. For example, Wolever and Bolognesi (1996) reported that the difference in glucose

AUC between a LGL and HGL cereal was five times greater at breakfast time than lunchtime. Glycaemic responses are also significantly more variable during the afternoon than morning (Wolever & Bolognesi, 1996). Cortisol also exhibits a circadian rhythm, peaking in the morning and decreasing during the afternoon, which may interact with the effect of GL on cognition (Messier, 2004).

A standardised breakfast or lunch was consumed in all five studies 2 to 3 hours before the experimental meal. However, as blood glucose levels usually return to baseline within 3 to 4 hours, a short fasting interval may mask significant differences in cognition. Consistent with this, Owen et al. (2012) reported that 60 g of glucose improved episodic and working memory following an overnight fast but not following a standardised breakfast and 2-hour fast. Perhaps a longer fast provides more optimal conditions for detecting cognitive differences. The GL and macronutrient composition of the standardised breakfast or lunch is also important, as this can influence the glycaemic response to the subsequent experimental meal. Indeed, Meng et al. (2017) reported that a high protein breakfast, relative to a high carbohydrate breakfast, attenuated the rise in blood glucose levels following a white bread challenge 4-hours later. This suggests that even if the experimental meal is administered when blood glucose levels return to baseline, the nature of the standardised meal needs to be carefully considered. More research into the effects of manipulating the GL of meals or drinks consumed after breakfast time is clearly warranted, especially in children and adolescents who are required to concentrate for long periods of time throughout the school day.

2.4.4 Limitations

The findings are limited by a very low to low certainty of evidence. Studies were highly heterogeneous in terms of participant characteristics, the type of statistical methods employed, pre-test conditions, the composition of breakfast, sample size, and the type of cognitive test administered. The risk of bias assessment indicated that, overall, no study showed a high risk of bias, however 24 out of 33 studies showed some concerns of bias which were mainly related to the randomisation process, blinding of participants and researchers, and study protocol pre-registration. There was also some degree of overlap between the ‘younger’ and ‘older’ subgroups (below or above 35 years of age). For example, Sanchez-Aguadero et al. (2020) sample had a mean age of 28.1 years but an age range of 20 to 40 years. This should be considered when interpreting the results. Subgroup analyses according to GT status were performed by categorising participants as having ‘poorer’ GT if fasting glucose levels were

above 6.1 mmol/L and/or 2-hour glucose levels were above 7 mmol/L. This definition was chosen because it is clinically relevant (Petersen & McGuire, 2005) and did not markedly increase the number of studies excluded from the subgroup analyses. However, these measures reflect different aspects of metabolism (Meyer et al., 2006) hence it is questionable whether they should have been combined. As this area of research evolves, subsequent meta-analyses should consider the moderating effect of postprandial glucose and fasting glucose separately. Lastly, measures of selective attention and sustained attention were analysed together. However, attention is not a unitary construct. Therefore, as the number of studies increase, future research might also consider these aspects of attention separately.

2.4.5 Recommendations for future studies

There are several avenues for future research. More research into the cognitive effects of manipulating the GL of meals or drinks after breakfast time would be beneficial. Future work could also place a greater emphasis on understanding the neurobiological mechanisms underlying the effect of breakfast GL on acute cognition. For example, functional Magnetic Resonance Imaging has not yet been applied to this area of research. However, it has been used to explore the neural underpinnings of the glucose facilitation effect (Peters et al., 2020), as well as the effect of GL on appetite and craving (Lennerz et al., 2013). Similarly, various biomarkers that are related to acute cognitive performance and/or postprandial glycaemia could be measured, such as heart rate variability, insulin, glucagon, GLP-1, free fatty acids, or cortisol (Dybjer et al., 2020; Nilsson et al., 2008; Saito et al., 2018). Several studies have reported that the gut microbiome plays a key role in postprandial glycaemia (Berry et al., 2020; Mendes-Soares et al., 2019; Zeevi et al., 2015), and as such may influence the cognitive response to variations in breakfast GL. Lastly, very few studies have specifically targeted adolescents, who may respond differently to children.

2.4.6 Conclusions

In conclusion, the meta-analysis revealed that the consumption of a LGL breakfast, rather than a HGL breakfast, was associated with better episodic memory during the late postprandial period in adults. Subgroup analyses indicated that the relationship between breakfast GL and episodic memory was influenced by GT and age. A review of studies involving children and adolescents also suggested that a LGL breakfast may benefit episodic memory and attention during the late postprandial period. Although there are many reports of a significant influence

of breakfast GL, these are not consistent. As such, it would be premature to suggest that public health guidelines recommend consuming a LGL breakfast to improve acute cognitive performance. More comparable studies are needed in order to establish the critical variables that lead to a beneficial response. Such findings would have far reaching implications for public health policy and school breakfast programmes. The present review found that the nature of the task used, the timing of testing, population age, and pre-existing GT are relevant. No doubt there are other factors that should be considered, which will emerge as the field progresses.

Chapter 3

The acute effects of a pre-bed drink varying in glycaemic load on sleep, sleep-dependent memory, and nocturnal glucose metabolism.

3.1 Introduction

As discussed in Chapter 2, numerous studies have examined the effect of breakfast GL on postprandial cognition in children, adolescents, and adults. A meta-analysis of studies involving adults revealed that the consumption of a LGL breakfast, in comparison to a HGL breakfast, was associated with significantly better immediate episodic memory during the late postprandial period (>120 minutes post-breakfast consumption). It is widely accepted that the consolidation of episodic and procedural memories is facilitated by sleep (Section 3.1.3.1). However, no studies have examined whether the consumption of meals or drinks differing in GL shortly before bedtime influences sleep-dependent memory consolidation. In this chapter, the evidence for a relationship between sleep and memory is discussed, followed by an overview of the effect of carbohydrate intake on sleep architecture.

3.1.1 Sleep architecture

Sleep is defined as a reversible state of reduced consciousness and altered responsiveness to external stimuli (Harrington & Lee-Chiong, 2012). According to the American Academy of Sleep Medicine (AASM) (Berry et al., 2012), sleep consists of two phases: REM sleep and non-REM (NREM) sleep. NREM sleep is further divided into stage N1, N2, and N3. Within a 6 to 8 hour sleep window, the human body cycles through these stages four to six times **(Patel et al., 2022)**. REM sleep begins approximately 90 minutes after sleep onset. Each sleep stage is associated with specific brain wave patterns, eye movements, and muscle tone, which can be distinguished using polysomnography (PSG). PSG is the gold-standard technique for measuring sleep architecture and sleep continuity variables, such as total sleep time, WASO, and SOL. Electroencephalography (EEG), electromyography (EMG), electrooculography (EOG), and electrocardiography (ECG) are used to measure brain wave patterns, muscle tone, eye movements, and heart rate, respectively.

In adults, stage N1 accounts for 5% of total sleep time, N2 accounts for 50%, N3 accounts for 20%, and REM sleep accounts for 25%. Stage N1, or light sleep, is characterised by low-amplitude mixed-frequency activity. A higher percentage of N1 sleep is indicative of fragmented sleep (Shrivastava et al., 2014). Stage N2 is associated with low-amplitude mixed-

frequency activity, sleep spindles, and K-complexes. Sleep spindles (10-16 Hz) are short bursts of neural activity, lasting at least 0.5 seconds, generated by oscillations in thalamocortical networks (Shrivastava et al., 2014). K-complexes are sharp delta waves that last for approximately one second. Although K-complexes are generated across the cortex, they are mostly observed in the frontal and pre-frontal cortices (Gandhi & Emmady, 2022). Stage N3 is characterised by low frequency, high amplitude delta waves (0.5-4 Hz), hippocampal sharp waves, neocortical slow oscillations, and thalamocortical sleep spindles (Léger et al., 2018). N3 sleep dominates the first half of the night, progressively reducing in duration and frequency thereafter. The duration of both REM sleep and N2 sleep increases throughout the night (Shrivastava et al., 2014). REM sleep consists of two distinct microstates – phasic REM sleep and tonic REM sleep. Phasic REM sleep is characterised by hippocampal theta oscillations, bursts of REMs, irregular muscle switches, and sympathetic activity, whereas tonic REM sleep is characterised by low muscle tone (Najar & da Mota Gomes, 2022).

3.1.2 Neurobiology of sleep

According to the two-process theory of sleep regulation (Borbély, 1982), the timing and structure of sleep is controlled by an interaction between two processes – a homeostatic process (S) and circadian process (C). The homeostatic drive for sleep, termed sleep pressure, increases during waking and decreases during sleep. Adenosine is a biochemical marker of sleep pressure, accumulating in the basal forebrain during waking and declining during sleep (Borbély et al., 2016). Process C dictates the daily rhythm of sleep and wakefulness. It is regulated by the central circadian clock located in the suprachiasmatic nucleus of the hypothalamus. Core body temperature and melatonin are examples of biomarkers of process C (Borbély et al., 2016). Core body temperature begins to rise at approximately 4am, peaks during the evening, and declines thereafter (Lack & Lushington, 1996). The secretion of melatonin, on the other hand, increases after the onset of darkness and peaks between 2-4am (Cardinali & Pévet, 1998).

The sleep-wake cycle is regulated by groups of neurons located across different areas of the brain. Wakefulness is controlled by the ascending arousal system (Schwartz & Roth, 2008). From the brainstem, cholinergic, glutamatergic, and monoaminergic neurons (serotonin, noradrenaline, dopamine, and histamine) innervate the thalamus, lateral hypothalamic area, basal forebrain, and/or cortex (Monti et al., 2022). Cholinergic and glutamatergic neurons also fire during REM sleep, highlighting their role in cortical activation (Lee et al., 2005). Apart

from dopaminergic neurons, monoaminergic neurons are generally maximally active during wake, less active during NREM sleep, and silent during REM sleep (Monti, 2010). For example, most serotonergic neurons are located in the raphe nucleus of the brainstem. Relative to wake, activity in the raphe nucleus is reduced during NREM sleep and suppressed during REM sleep (Monti, 2010). Furthermore, optogenetic stimulation of serotonergic neurons during NREM sleep induces wakefulness (Kato et al., 2022). Neurons containing gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, also promote arousal within this system by reducing the activity of inhibitory cortical neurons. The lateral hypothalamic area contains orexin neurons which project to all regions of the ascending arousal system (Monti, 2010). Orexin neurons are active during wakefulness and silent during sleep (Mieda et al., 2013). Excitation of orexin neurons in rats increases the amount of time spent awake and decreases the duration of NREM and REM sleep, whilst inhibition of orexin neurons has the opposite effect (Sakurai, 2005). A defect in the release of orexins, or an absence of neurons expressing orexins, causes narcolepsy (Sakurai, 2013).

Sleep occurs when activity in the ascending arousal system is inhibited. Sleep-active neurons within the ventrolateral preoptic area (VLPO) begin to fire during drowsiness, are active during REM sleep, and reach peak activity during NREM sleep, especially N3 sleep (Saper, 2013). Most of these neurons contain GABA and the inhibitory neuropeptide galanin; both of which inhibit the activity of neurons in the ascending arousal system (Monti et al., 2022). Most VLPO sleep-promoting neurons are inhibited by acetylcholine, serotonin, and noradrenaline, but not histamine (Gallopin et al., 2000). REM sleep is generated by cholinergic REM-on neurons in the upper pons and adjacent portions of the midbrain (Monti et al., 2022). More recently, it was discovered that neurons within the lateral hypothalamic area play a role in REM sleep. Neurons producing melanin-concentrating hormone (MCH), an inhibitory sleep-promoting neuropeptide, are inactive during wake and active during sleep, especially REM sleep (Blanco-Centurion et al., 2019; Hassani et al., 2009). Stimulation of MCH neurons during NREM sleep in rats increased the number of NREM-to-REM transitions and the duration of REM sleep, suggesting that MCH neurons play a role in the induction and maintenance of REM sleep (Jego et al., 2013). In humans, Blouin et al. (2013) showed that MCH levels in the amygdala were significantly higher during sleep than wake and peaked during sleep onset, suggesting that MHC neurons may also play a role in sleep induction. MCH neurons are intermixed with orexin neurons in the lateral hypothalamic area; both groups of neurons target the same regions and are mutually inhibitory (Konadhode et al., 2013).

The transition between NREM and REM sleep is controlled by a "flip-flop" switch involving two groups of mutually inhibitory neurons in the upper pons (Saper, 2013). GABAergic REM-off neurons located in the ventrolateral periaqueductal gray matter and adjacent lateral pontine tegmentum fire during NREM sleep, which inhibits REM sleep. Noradrenergic and serotonergic neurons also inhibit REM sleep by exciting REM-off neurons and inhibiting REM-on neurons. During REM sleep, GABAergic REM-on neurons in the sublaterodorsal region inhibit the activity of REM-off neurons. A subset of cholinergic neurons in the brainstem also promote REM sleep by exciting REM-on neurons and inhibiting REM-off neurons (Saper, 2013).

3.1.3 The function of sleep

It is widely agreed that sleep does not serve a single function but rather many physiological, biochemical, and psychological functions (Zielinski et al., 2016). Some of the proposed functions of sleep include energy conservation, learning and memory, thermoregulation, metabolic waste removal, and tissue repair (Assefa et al., 2015; Zielinski et al., 2016). The importance of sleep for memory consolidation is discussed in more detail in the next section.

3.1.3.1 Sleep-dependent memory consolidation

Studies have repeatedly shown that sleep deprivation prior to learning can significantly disrupt hippocampal function, resulting in a reduced ability to encode new memories (Drummond et al., 2000; Kaida et al., 2015; Walker, 2008; Yoo et al., 2007). There is also consistent evidence that sleep facilitates the consolidation of new fragile memories by integrating them into pre-existing networks (Rasch & Born, 2013). Procedural memory performance is enhanced when encoding is followed by sleep compared to an equal length period of wake (Gui et al., 2017; Schmid et al., 2020). For example, using a finger tapping task, Walker et al. (2002) reported a 20% improvement in motor speed following a night of sleep versus wake. Enhancements in performance were observed whether participants slept immediately after learning or up to 12 hours later. The magnitude of motor learning was also positively associated with the percentage of N2 sleep late in the night. Studies have reported similar beneficial effects for episodic memory (Backhaus et al., 2008; Gais et al., 2006; Gais et al., 2002; Lahl et al., 2008; Seehagen et al., 2015), dating as far back as 1924 (Jenkins & Dallenbach, 1924). The beneficial effect of sleep on procedural and episodic memory consolidation has also been observed following daytime naps lasting between 6 to 90 minutes (Farhadian et al., 2021).

Although it is widely accepted that sleep benefits episodic memory consolidation, there is debate regarding whether sleep selectively strengthens emotional episodic memories over neutral episodic memories. Some studies have reported that positive and negative material was preferentially consolidated over neutral material following a period of sleep (Hu et al., 2006; Payne et al., 2008; Reid et al., 2022), whereas other studies reported no differences in retention (Atienza & Cantero, 2008; Gilson et al., 2015; Lehmann et al., 2016). A meta-analysis of 31 studies by Lipinska et al. (2019) revealed that sleep did not selectively enhance the recall of emotional material over neutral material. However, subgroup analyses highlighted several influential methodological factors. The difference in recall for emotional versus neutral material, following an interval of sleep, was greater in studies that used a free recall task compared to a recognition task. Furthermore, an emotional valence effect was observed in studies that utilised pre/post-sleep change scores but not studies that utilised post-sleep scores. Gender also influenced the results, with larger emotional valence effects found in studies that only recruited male participants. Taken together, these findings suggest that the likelihood of observing an emotional valence effect is influenced by biological sex, the type of task administered, and the method of calculating performance scores.

3.1.3.1.1 Sleep stages and sleep-dependent memory consolidation

The dual-process theory postulates that different stages of sleep support the consolidation of different types of memory. Most evidence to support the dual-process hypothesis comes from studies employing a split-night paradigm. Sleep across the first half of the night, which mostly consists of N3 sleep, is compared to sleep across the second half of the night, which is rich in REM sleep (Reid et al., 2022). The amount of N2 sleep during the first and second half of the night is usually similar (Walker, 2008). Studies have typically shown that early sleep benefits non-emotional episodic memory, whereas late sleep benefits emotional episodic memory and procedural memory (Barrett & Ekstrand, 1972; Fowler et al., 1973; Tucker et al., 2006). For example, Plihal and Born (1997, 1999) compared the effects of early sleep and late sleep on non-emotional episodic and procedural memory consolidation. Early sleep improved episodic performance (paired-associate word task and spatial rotation task), but not procedural performance (mirror tracing task and word stem priming). The opposite effect was reported for late, REM-rich sleep. Wagner et al. (2001) compared the retention of emotional and neutral material following 3 hours of early sleep, late sleep, or wake. Sleep selectively enhanced the retention of emotional material relative to neutral material, but this effect was only observed

during late REM-rich sleep. This finding has been replicated by other studies (Groch et al., 2013; Schaefer et al., 2020; Wagner et al., 2001) .

Further support for the dual process theory comes from studies that pharmacologically suppressed different stages of sleep. In comparison to wakefulness, N3 sleep is characterised by reduced cholinergic activity, whereas REM sleep is characterised by similar or increased levels of cholinergic activity (Diekelmann & Born, 2010). Suppression of REM sleep by blocking cholinergic receptors prevented overnight gains in procedural memory but not non-emotional episodic memories (Ackermann & Rasch, 2014). Conversely, increasing cholinergic activity during N3 sleep blocked overnight gains in non-emotional episodic memory but not procedural memory (Gais & Born, 2004). Other studies have reported positive associations between the duration of N3 sleep and overnight improvements in non-emotional episodic memory (Wilhelm et al., 2008; Zhang & Gruber, 2019), as well as the duration of REM sleep and overnight improvements in emotional memory (Nishida et al., 2009; Payne et al., 2012) and procedural memory (Plihal & Born, 1997, 1999). An increase in the density and number of REMs and the duration of REM sleep has also been reported post-procedural learning (Smith et al., 2004).

However, a number of findings oppose the dual process theory. There is evidence that REM-rich sleep can enhance aspects of non-emotional episodic memory (Fogel et al., 2007; Tilley & Empson, 1978), and that N3-rich sleep can enhance procedural memory (Aeschbach et al., 2008; Huber et al., 2006) and emotional memory (Cairney et al., 2014). Furthermore, despite suppressing REM sleep, selective noradrenaline re-uptake inhibitors enhanced performance on a finger tapping task which was associated with an increased duration of N2 sleep and number of sleep spindles (Rasch et al., 2009). Studies have also reported a positive association between the duration of N2 sleep and retention of episodic material (Clemens et al., 2005; Clemens et al., 2006; Gais et al., 2002; Ruch et al., 2012). These findings suggests that although certain stages of sleep may provide more optimal conditions for the consolidation of certain types of memories, there is not a strict dichotomy (Farhadian et al., 2021).

3.1.4 Carbohydrate and sleep

3.1.4.1 Carbohydrate and sleep architecture and continuity

Despite the importance of sleep for normal daily functioning, it is estimated that one in four people in the United Kingdom do not sleep for the recommended length of time (Kocevska et

al., 2021). Furthermore, approximately 30% of the general population experience symptoms of insomnia, including difficulties with falling and staying asleep and excessive daytime sleepiness (Roth, 2007). The increasing prevalence of sleep problems represents a major public health issue, as poor sleep is a risk factor for obesity, abnormal glucose metabolism, endocrine dysfunction, dementia, and cardiovascular disease (Ferrie et al., 2011). For example, the risk of developing T2DM is increased by 84% in individuals with difficulties maintaining sleep and 28% in individuals who have less than 5 hours of sleep per night (Cappuccio et al., 2010). Therefore, the identification of modifiable lifestyle factors that improve sleep is essential.

One influential factor is diet (Peuhkuri et al., 2012). The impact of diet on measures of sleep architecture and continuity has been investigated using a range of whole foods and food products, including cow's milk (Valtonen et al., 2005), Horlicks (Southwell et al., 1972), chamomile tea (Sánchez-Ortuño et al., 2009), valerian root (Sánchez-Ortuño et al., 2009), tart cherries (Garrido et al., 2010), and kiwifruit (Lin et al., 2011). Studies have also manipulated the macronutrient composition of diet, most of which have focused on carbohydrate intake. For example, Kwan et al. (1986) reported that the consumption of a low carbohydrate diet for seven days increased REM latency relative to participant's habitual diet. In a study by Lindseth et al. (2013), participants consumed a high protein, high carbohydrate, high fat, or control diet for four days. Actigraphy data showed that the consumption of a high carbohydrate diet was associated with a shorter sleep onset latency (SOL) relative to a control diet, whereas a high protein diet was associated with fewer wake episodes relative to a control diet. There is also evidence that the amount of carbohydrate consumed shortly before bedtime affects sleep architecture. For example, Yajima et al. (2014) provided male participants with a high carbohydrate or high fat meal, matched for protein content, 4-hours before bedtime. The authors reported that less N3 sleep occurred during the first sleep cycle after the high carbohydrate meal compared to the high fat meal.

Two recent meta-analyses synthesised the results of studies that manipulated the amount of carbohydrate consumed across several days or shortly before bedtime. The results of studies included in both meta-analyses are summarised in Table 7. A meta-analysis of six studies by Benton et al. (2022) reported that consuming a higher percentage of energy as carbohydrate was associated with a shorter duration of REM sleep and a higher duration of N3 sleep. Furthermore, a lower intake of carbohydrate was associated with a shorter SOL and a trend towards better sleep efficiency. Similarly, a meta-analysis of 11 studies by Vlahoyiannis et al. (2021) reported that the consumption of meals lower in carbohydrate increased the duration of

N3 sleep and decreased the duration of REM sleep. These findings clearly indicate that the effect of carbohydrate on sleep is not homogenous, rather the effect differs depending upon the stage of sleep. The consumption of different amounts of carbohydrate will inevitably produce different postprandial glycaemic response. However, as most studies included in Benton et al. (2022) and Vlahoyiannis et al. (2021) manipulated the carbohydrate content of meals by altering their fat or protein content, the findings cannot be directly attributed to the glycaemic nature of the meals. Furthermore, it is unknown whether larger effects were observed in studies that manipulated carbohydrate intake shortly before bedtime or over a longer period of time.

Studies that have administered meals matched for macronutrient and energy content provide insight into whether sleep is affected by the glycaemic nature of meals (Table 7). Using a sample of healthy males, Afaghi et al. (2007) varied the GL of meals by administering Jasmine rice (HGL) or Mahatma rice (LGL) 4-hours before bedtime. SOL was approximately eight minutes shorter following the consumption of the HGL meal compared to LGL meal. Vlahoyiannis et al. (2018) administered the same meals as Afaghi et al. (2007) 2-hours before bedtime. The HGL meal was associated with a longer total sleep time, better sleep efficiency score, and shorter SOL than the LGL meal. Herrera (2010) recruited a sample of sleep-initiation insomniacs. Participants consumed a HGL or LGL meal 3-hours before habitual bedtime. Participants reported feeling more rested after the HGL meal, especially females, but no differences in objective measures of sleep were found. Given that sleep architecture is influenced by the quantity of carbohydrate consumed before bedtime, it is surprising that no study reported an effect of GL on sleep architecture. However, to date, only two studies of this kind have recruited healthy adults (Afaghi et al., 2007; Vlahoyiannis et al., 2018) hence more well-controlled studies are needed for conclusions to be made.

To date, no studies have administered drinks matched for macronutrient and energy content. Jalilolghadr et al. (2011) gave children a LGL drink (full fat milk with honey) or a HGL drink (low fat milk with glucose) one hour before bedtime. The drinks contained different amounts of carbohydrate, protein, and fat. The HGL drink was associated with a higher number of total arousal indices and NREM arousal indices than the LGL drink, which is indicative of poorer sleep quality, but only during the first half of the night. An alternative low glycaemic disaccharide which has not yet been used in this area of research is isomaltulose. It is made from sucrose via the enzymatic rearrangement of the alpha-1,2-linkage between glucose and fructose to an alpha-1,6-linkage. Due to its glycosidic bond, isomaltulose is more slowly hydrolysed by enzymes and hence produces a lower glycaemic response than sucrose (Holub

et al., 2010). One novel suggestion is to directly compare the effects of glucose and isomaltulose, a paradigm which was used by several of the studies reviewed in Chapter 2. There are large differences in the GI of isomaltulose (GI = 32) and glucose (GI = 100), which may produce large differences in sleep.

Although no studies have investigated whether isomaltulose influences sleep, studies have examined whether isomaltulose influences daytime levels of energy and fatigue. Young and Benton (2015) reported no differences in ratings of energy and tiredness following the consumption of breakfasts sweetened using glucose, sucrose, or isomaltulose. In contrast, Deng et al. (2021) reported that participants felt significantly more energetic 60 minutes after the consumption of a breakfast drink containing isomaltulose compared to sucrose. No differences were observed after 30 and 90 minutes. Similarly, Yamamoto et al. (2023) reported that the consumption of an isomaltulose-sweetened drink during the afternoon (2pm), compared to a glucose-sweetened drink, was associated with lower ratings of physical fatigue following a demanding cognitive test battery. These findings suggest that the consumption of meals or drinks lower in GL may be associated with more energy and less physical fatigue during the daytime. However, the effect of isomaltulose on energy and fatigue levels may differ when ratings are obtained post-sleep.

Table 7. Summary of studies examining the effects of carbohydrate on sleep.

Author (year)	Study characteristics	Measurement of sleep	Time of meal consumption	Nutritional intervention	Results
Afaghi et al. (2007)	12 males, age range = 18-25 years, WS design, randomised, 1-week washout period.	PSG. Sleepiness VAS (30 minutes and 1-, 2-, 3-, and 4-hours post-meal).	4-hours before bedtime.	Isocaloric and macronutrient matched meals (90.6% CHO, 1.5% fat, 7.9% PRO, 764 kcal): 1. LGL/LGI = 81.3 GL, 50 GI[1] 2. HGL/LGI = 175 GL, 109 GI[1]	SOL = lower after the HGL meal than LGL meal. Sleepiness VAS = participants reported feeling sleepier after the HGL meal than LGL meal.
Afaghi et al. (2008)	14 males, age range = 18-35 years, WS design, non-randomised, tested on consecutive days.	PSG.	4-hours before bedtime.	Isocaloric (1090 kcal) meals consumed four hours before bedtime: 1. Very low CHO = <1% CHO, 61% fat, 38% PRO[3] 2. High CHO = 72% CHO, 12% fat, 16% PRO[3]	Sleep efficiency = better sleep efficiency score after the low CHO meal. Combined N1 and N2 score = higher after the low CHO meal. REM sleep % = higher after the high CHO meal. N3 sleep % and duration = higher after the low CHO meal.

Daniel et al. (2019)	9 male high-performance athletes, WS design, randomised, tested on consecutive days.	Actigraphy. Sleepiness VAS (1-hour after evening meal and shortly after wake onset) ESS (shortly after wake onset).	Evening meal consumed 4-hours before bedtime and snack 1.5 hours before bedtime.	1. LGL evening meal = 924 kcal, 56.2% CHO, 23.2% fat, 20.6% PRO, 65 GL, 49.5 GI and snack = 1083 kcal, 59.2% CHO, 28.6% fat, 12.2% PRO, 76 GL, 47.9 GI[1] 2, HGL evening meal = 833 kcal, 62.8% CHO, 19.9% fat, 17.4% PRO, 97 GL, 74.9 GI and snack = 1058 kcal, 64.1% CHO, 25.4% fat, 10.5% PRO, 120 GL, 71.8 GI[1]	Composition of evening meal/snack did not influence any measure of sleep.
Herrera (2010)	4 males and 4 females with a diagnosis of insomnia, WS design, randomised.	PSG. Sleepiness VAS (1, 2, and 3 hours after meal consumption). Sleep diary (shortly after wake onset).	3-hours before bedtime.	Isocaloric meals (500 kcal): 1. LGL = 65% CHO, 16% fat, 18% PRO, 38 GL, 51 GI[1] 2. HGL = 66% CHO, 16% fat, 17% PRO, 59 GL, 79 GI[1]	Sleep diary = participants felt more rested after the HGL meal, especially females.

Jalilolghadr et al. (2011)	4 males and 4 females, age range = 8-12 years, WS design, randomised, tested on 3 consecutive nights.	PSG.	1-hour before bedtime.	1. LGL = 37.3% CHO, 44.2% fat, 18.5% PRO, 277 kcal, 7.4 GL, 66 GI[1] 2. HGL = 75.6% CHO, 2.3% fat, 22.1% PRO, 238 kcal, 52.8 GL, 134 GI[1]	NREM arousal indices and total arousal indices = higher after the HGL drink than LGL drink, but only during the first half of the night.
Kwan et al. (1986)	6 females, age range = 20-23 years, WS design, non-randomised.	PSG.	Each diet was consumed for 7 days.	1. High fat = 9% CHO, 71% fat, 20% PRO, 1929 kcal[3] 2. Habitual diet = 49% CHO, 38% fat, 13% PRO, 2066 kcal[3]	REM latency = longer after the high fat diet than habitual diet.
Lindseth et al. (2013)	44 participants, mean age = 20.6 years, WS design, randomised, counterbalanced, 2-week washout period.	Actigraphy. PSQI (post-diet).	Each diet was consumed for 4 days.	1. High PRO = 22% CHO, 22% fat, 56% PRO[3] 2. High fat = 22% CHO, 56% fat, 22% PRO[3] 3. High CHO = 56% CHO, 22% fat, 22% PRO[3] 4. Control = 50% CHO, 35% fat, 15% PRO[3]	WASO = shorter after high PRO diet than control diet. SOL = shorter after high CHO diet than control diet.
Lindseth and Murray (2016)	36 participants, mean age = 20.9 years, WS design, randomised,	Actigraphy. PSQI (post-diet).	Each diet was consumed for 4 days.	1. High PRO = 40% CHO, 15% fat, 45% PRO[3]	WASO = shorter after high CHO diet than all other diets.

	counterbalanced, 2-week washout period.			2. High fat = 25% CHO, 65% fat, 10% PRO[3] 3. High CHO = 80% CHO, 10% fat, 10% PRO[3] 4. Control = 50% CHO, 35% fat, 15% PRO[3]	PSQI = high fat diet associated with better sleep quality than all other diets.
Phillips et al. (1975)	8 young males, mixed design (after consuming the control diet, participants were randomised to the high fat or high CHO diet), 2-week washout period.	PSG.	Each diet was consumed for 4 days. The control diet was consumed for the first 2 days, followed by either the high fat or high CHO diet.	1. High fat = 13% CHO, 77% fat, 10% PRO, 2995 kcal[3] 2. High CHO = 80% CHO, 10% fat, 10% PRO, 2997 kcal[3] 3. Control = 47% CHO, 43% fat, 10% PRO[3]	N1 sleep duration = lower after both the high fat and high CHO diet than the control diet. N3 sleep duration = lower after the high CHO diet, and higher after the high fat diet, than the control diet. REM sleep duration = higher after the high CHO diet, in particular, and high fat diet than the control diet.
Porter and Horne (1981)	6 young males, WS design, randomised, counterbalanced, 3-day washout period.	PSG.	45-minutes before bedtime.	1. Low CHO = 47% CHO, 47% fat, 6% PRO, 401 kcal[3] 2. High CHO = 73% CHO, 23% fat, 4% PRO, 714 kcal[3]	N1 sleep duration = lower after the high CHO meal.

					N3 sleep duration = lower after the high CHO meal. REM sleep duration = greater after the high CHO meal, but only during the first half of the night.
Vlahoyiannis et al. (2018)	10 males, mean age = 23.2 years, WS design, double-blind, randomised, counterbalanced, 7-day washout period.	PSG.	2-hours before bedtime.	Isocaloric and macronutrient matched meals (90.6% CHO, 1.5% fat, 7.9% PRO, 764 kcal): 1. LGL/LGI = 81.3 GL, 50 GI[1] 2. HGL/LGI = 175 GL, 109 GI[1] Identical to Afaghi et al. (2007).	Total sleep time = longer after the HGL meal. Sleep efficiency = higher after the HGL meal. SOL = higher after the LGL meal. WASO = longer after the LGL meal.
Yajima et al. (2014)	10 males, mean age = 24.6 years, WS design, counterbalanced, 5-18 day washout period.	PSG.	4-hours before bedtime.	1. High fat = 12% CHO, 78% fat, 10% PRO, 770 kcal[3] 2. High CHO = 80% CHO, 10% fat, 10% PRO, 798 kcal[3]	N3 sleep = less N3 sleep during the first sleep cycle after the high CHO meal.

Note. 1 = GI/GL reported in study, 2 = GI/GL estimated using published GI tables, and 3 = unable to calculate GI or GL due to insufficient information. SOL = sleep onset latency, WASO = wake after sleep onset, REM = rapid eye movement, PSG = polysomnography, LGL = low

glycaemic load, HGL = high glycaemic load, PRO = protein, CHO = carbohydrate, GL = glycaemic load, WS = within-subjects, VAS = visual analogue scale, PSQI = Pittsburgh Sleep Quality Index.

3.1.4.2 Carbohydrate and sleep-dependent memory consolidation

Despite evidence that certain stages of sleep support the consolidation of certain types of memory (Barrett & Ekstrand, 1972; Fowler et al., 1973; Tucker et al., 2006), and the architecture of sleep is affected by the amount of carbohydrate consumed before bedtime (Benton et al., 2022; Vlahoyiannis et al., 2021), no study has explored whether carbohydrate consumption influences sleep-dependent memory consolidation. To date, only one study has investigated the effect of diet on sleep-dependent memory consolidation. Herzog et al. (2012) examined the impact of daytime caloric intake on procedural and episodic memory consolidation following seven hours of sleep or total sleep deprivation. Participants completed a memory encoding session at 8am (day 1) and a retrieval session at 10.30am (day 2). Three meals and drinks were consumed throughout the first day, providing 50% (low calorie condition) or 150% (high calorie condition) of each participants estimated total energy expenditure (low calorie condition). Daytime caloric intake did not influence sleep-dependent episodic and procedural memory consolidation. However, a high daytime caloric intake prior to total sleep deprivation enhanced procedural memory consolidation to the extent that it was comparable to performance levels following sleep. The long interval between learning and sleep may have contributed to the findings, as sleep exerts a stronger effect on memory consolidation when it occurs shortly after learning (Holz et al., 2012; Talamini et al., 2008). Another study experimentally induced hypoglycaemia using an hyperinsulinaemic clamp (2.2 mmol/L) in healthy and type 1 diabetic participants during the first hour of sleep, when most N3 sleep occurs. The authors reported that this reduced sleep-dependent episodic memory consolidation (Jauch-Chara et al., 2007).

As discussed in Chapter 1, numerous studies have reported that the consumption of glucose can enhance the consolidation of memories during the day, especially non-emotional episodic memories. Although recall is typically better for emotional stimuli than neutral stimuli, there is limited evidence that the glucose facilitation effect exerts a stronger effect on emotional stimuli than neutral stimuli (Brandt et al., 2010; Brandt et al., 2006; Smith et al., 2011). In Chapter 2, a meta-analysis of the effect of breakfast GL on postprandial cognition revealed that the consumption of a LGL breakfast was significantly associated with better immediate episodic memory in adults during the late postprandial period. Only one study included in the systematic review in Chapter 2 directly compared the effects of isomaltulose and glucose on memory in adults. Young and Benton (2014a) reported that the consumption of an isomaltulose-sweetened breakfast (LGL) was associated with better episodic memory in those

with better GT, whereas a glucose-sweetened breakfast (HGL) was associated with better episodic memory in those with poorer GT. However, several studies have compared the effects of isomaltulose and sucrose on episodic memory (Deng et al., 2021; Dye et al., 2010; Keesing et al., 2019; Marchand et al., 2020; Young & Benton, 2014a). The only authors to report a significant difference in episodic memory performance were Young and Benton (2014a). In those with better GT, which did not fall below baseline during the postprandial period, episodic memory was better after the LGL breakfast compared to the sucrose-sweetened breakfast (MGL). In those with better GT, which fell below baseline during the postprandial period, both the LGL and MGL breakfasts were associated with better episodic memory compared to the HGL breakfast. Therefore, an exploration of whether pre-bedtime GL influences sleep-dependent memory consolidation is warranted.

3.1.4.3 Mechanisms underlying the effect of carbohydrate on sleep

The mechanisms underlying the effects of carbohydrate on sleep are poorly understood. Tryptophan, an essential long chain neutral amino acid (LNAA), has received the most attention. Tryptophan is required for the synthesis of serotonin and melatonin. The main determinant of brain tryptophan is not the level of tryptophan in the blood but rather the ratio of tryptophan to other LNAAs (Fernstrom & Wurtman, 1972). After the consumption of a high carbohydrate or HGL meal, insulin stimulates the selective uptake of all LNAAs other than tryptophan, facilitating its entry into the brain. It is argued that as more tryptophan enters the brain, the rate of serotonin and melatonin synthesis is increased, which has consequences for sleep. As tryptophan is the least abundant amino acid found in protein, the consumption of protein decreases the ratio of tryptophan to other LNAAs in the blood hence reducing its entry into the brain. However, for a number of reasons, it is questionable whether increasing the synthesis of serotonin will categorically improve sleep. Indeed, the activity of serotonergic neurons in the raphe nucleus is reduced during NREM sleep and suppressed during REM sleep (Monti, 2010). Wakefulness is induced by optogenetic stimulation of serotonergic neurons during NREM sleep (Kato et al., 2022), and depletion of brain serotonin had no effect on SWS (Ross et al., 1976). Based on these findings, Monti (2010) concluded that serotonin promotes wake rather than sleep. Furthermore, an analysis of 30 studies by Benton and Donohoe (1999) indicated that in order to produce a favourable tryptophan to other LNAAs ratio, protein must provide less than 10% of calories in a meal. As the studies included in Benton et al. (2022) provided meals that contained between 4 to 26% of energy as protein, this suggests that the effects of carbohydrate on sleep may not be mediated by changes in tryptophan.

Alternatively, it was recently hypothesised that the effects of carbohydrate on sleep may be due to changes in blood glucose levels (Benton et al., 2022). There is a positive correlation between extracellular and blood glucose levels (Rostami & Bellander, 2011; van de Ven et al., 2012). Though the concentration of glucose in the brain is 20-30% of that in the blood (Béland-Millar et al., 2017), changes in blood glucose levels cause rapid changes in brain glucose levels (Abi-Saab et al., 2002; Gruetter et al., 1998). The lateral hypothalamic area contains a large number of glucose-sensing neurons which respond to a rise in extracellular glucose concentrations by increasing (glucose-excited neurons) or decreasing (glucose-inhibited neurons) their firing rate within seconds or minutes (Burdakov & Adamantidis, 2020). Approximately 80% of orexin neurons are glucose inhibited (Burdakov & Adamantidis, 2020). Increasing extracellular glucose levels suppressed the activity of orexin neurons in a dose-dependent manner (Burdakov et al., 2005). Importantly, the concentrations of extracellular glucose were physiologically relevant, which suggests that the firing rate of orexin neurons changes in response to normal fluctuations in peripheral glucose levels (Burdakov et al., 2005). Cai et al. (1999) also reported that insulin-induced low plasma glucose levels increased the concentration of extracellular prepro-orexin, a precursor of orexins.

Sleep-promoting neurons in the VLPO are glucose-excited (Burdakov & Adamantidis, 2020). Varin et al. (2015) reported that local infusion of glucose into the VLPO of mice dose-dependently increased the firing rate of sleep-promoting neurons, prolonged the duration of N3 sleep, and reduced the latency of the first episode of N3 sleep. The authors suggested that increasing brain glucose levels may contribute to the onset and maintenance of N3 sleep by exciting sleep-promoting neurons. MCH neurons are also glucose-excited (Burdakov & Adamantidis, 2020). Burdakov et al. (2005) reported that MCH neurons were dose-dependently excited by physiologically relevant increases in extracellular glucose levels. The effect of glucose on the activity of MCH neurons and sleep architecture has not yet been directly studied. However, optogenetic stimulation of MCH neurons in rats increased total sleep time and reduced SOL and the length of wake bouts (Konadhode et al., 2013), whilst central MCH injections increased REM sleep by 200% and N3 sleep by 70% (Peyron et al., 2009). It is therefore plausible that changes in blood glucose levels arising from the consumption of drinks differing in GL may influence the activity of glucose-sensing neurons implicated in the initiation and maintenance of sleep and wakefulness. The consumption of a HGL drink produces a rapid rise and fall in glucose levels, which may promote wakefulness via stimulation of orexin neurons. In contrast, the consumption of a LGL drink shortly before sleep will

produce a smaller and steadier rise and fall in blood glucose levels, which may stimulate orexin neurons to a lesser extent (Benton et al., 2022). This is a hypothesis that remains to be tested.

3.1.5 Summary

In summary, numerous studies have shown that certain sleep architecture and continuity variables are influenced by the consumption of meals differing in carbohydrate quantity and/or quality. Compared to a high carbohydrate meal, the consumption of a low carbohydrate meal has been associated with more N3 sleep and less REM sleep (Benton et al., 2022; Vlahoyiannis et al., 2021). Although changes in N3 sleep and REM sleep have not been reported in studies that administered isocaloric, macronutrient matched meals (Afaghi et al., 2007; Vlahoyiannis et al., 2018), different effects may occur if the nutritional intervention is administered closer to sleep. There is also clear evidence that sleep enhances the consolidation of procedural and episodic memories (Backhaus et al., 2008; Gais et al., 2006; Gais et al., 2002; Lahl et al., 2008; Nishida et al., 2009; Seehagen et al., 2015; Walker et al., 2002). Furthermore, certain stages of sleep appear to play a key role in the consolidation of certain types of memories (Plihal & Born, 1997, 1999; Reid et al., 2022; Wagner et al., 2001). However, no studies have examined whether carbohydrate-induced changes in sleep architecture affects sleep-dependent memory consolidation.

3.1.6 Aims of sleep study

The purpose of this study was to compare the effects of consuming a HGL drink (50 g glucose) and LGL drink (50 g isomaltulose) fifteen minutes before bedtime in twenty healthy young male adults. Primary outcome measures included PSG-defined N3 sleep and REM sleep percentage and nocturnal interstitial glucose levels. Secondary outcome measures included subjective measures of sleep quality and sleep-dependent memory consolidation. Exploratory outcome measures included PSG-defined SOL, WASO, sleep efficiency, and sleep architecture during the first and second half of the night.

Primary hypotheses:

1. The HGL drink compared to the LGL drink will be associated with a larger and faster rise and fall in glucose levels during the first half of the night.
2. The HGL drink compared to the LGL drink will be associated with less N3 sleep.
3. The HGL drink compared to the LGL drink will be associated with more REM sleep.

Exploratory hypothesis:

Given the discrepancies in the literature, and the very high GLs used in previous research that are not comparable to the present research (Afaghi et al., 2007; Vlahoyiannis et al., 2018), it was not possible draw on that literature to specify hypotheses for SOL, WASO, and sleep efficiency hence these variables were considered exploratory. As there is evidence that carbohydrate intake differentially influences sleep during the first and second half of the night (Jalilolghadr et al., 2011; Porter & Horne, 1981), the following exploratory hypothesis was tested:

1. The consumption of drinks differing in GL will differentially influence sleep architecture during the first and second half of the night.

3.2 Methods

3.2.1 Participants

This study was registered with ClinicalTrials.gov (NCT05591573). Twenty healthy male participants took part in the study (mean age = 24.2 years, SD = 5.25, age range = 19 to 33 years). Only male participants were recruited as the menstrual cycle influences sleep, metabolism, and sleep-dependent memory consolidation (Baker & Driver, 2007; Genzel et al., 2012). Seventeen participants had a BMI and body fat percentage within the normal range. The remaining three participants were classified as overweight according to these measures. The following inclusion criteria were applied: non-smoker, a BMI between 18 to 30, a Pittsburgh Sleep Quality Index (PSQI; Appendix 7) (Buysse et al., 1989) sleep efficiency score above 85%, a normal habitual sleep schedule (i.e., bedtime usually commenced between 10 to 12pm) and sleep duration (i.e., 6.5 to 9 hours of sleep per night), and a normal Depression Anxiety Stress Scale-21 (DASS-21; Appendix 8) (Henry & Crawford, 2005) score (depression subscale = 0 to 4, stress subscale = 0 to 7, and anxiety subscale = 0 to 3). Participants were excluded from the study if they had a physical or psychiatric disorder (e.g., diabetes, gastrointestinal disease, insomnia, epilepsy, or anxiety disorder), a diagnosis of dyslexia, took prescribed medication that influenced sleep or metabolism, worked night shifts, used recreational drugs within the past six months, regularly consumed alcohol (>3 units of alcohol per day) or caffeine (>300 mg per day), or regularly engaged in vigorous exercise (>3 hours per week). Participants were also excluded if they had a food allergy or intolerance or engaged in nocturnal eating, as assessed using the Meal Patterns Questionnaire (Alfonsson et al., 2016) (Appendix 9). The study was approved by Swansea Universities Psychology Ethics Committee. Written informed

consent was obtained before taking part in the study (Appendix 10 and 11). Participants were paid £200 after attending the final session.

3.2.2 Design

A double-blind, within-subjects design was used, whereby participants received a pre-bedtime drink containing either glucose (HGL) or isomaltulose (LGL) on visit 2. After a one-week washout period, the alternate drink was consumed. Participants received water on the familiarisation night (visit 1). Drinks were administered in a counterbalanced and randomised order, using a computer-generated randomisation list.

3.2.3 Nutritional intervention

The standardised evening meal consisted of instant mashed potato (40 g with 200 ml boiled water), carrots (30 g), broad beans (50 g), garden peas (40 g), tinned vegetable soup (200 g), jellybeans (35 g), and a slice of toasted brown bread. The carrots, broad beans, and garden peas were added to the vegetable soup to make the meal easier to consume. The evening meal provided 1542.8 kJ, 72.07 g carbohydrate, 12.75 g protein, and 4.38 g fat (GI = 404, GL = 45.83). The test drinks were supplied by BENEO GmbH (Mannheim, Germany). The HGL drink contained 50 g glucose (GI = 100, GL = 50) and the LGL drink contained 50 g isomaltulose, commercially known as Palatinose™ (GI = 32, GL = 16). Glucose and isomaltulose were packed in opaque pre-labelled sachets. The drinks were prepared by mixing one sachet with 300 ml of water. Drinks were fruit-flavoured and matched for taste, appearance, and odour.

3.2.4 Polysomnography

All participants underwent three nights of PSG. Sleep was recorded using a Trackit™ Mk2 PSG recorder (Lifelines Ltd, Hants, UK) at Swansea Universities Sleep Laboratory. A standard 10-20 system was followed for EEG electrode placement. The following EEG montage was used: FPz (ground), Cz (reference), C3, C4, F3, and F4. Two mastoid electrodes, A1 and A2, were also set-up. Gold cup electrodes were attached using adhesive gel and tape. Two chin EMG, two ECG, and two EOG (below the left outer canthus and above the right outer canthus) were attached using disposable adhesive electrodes. Sleepware G3 software (Phillips Respironics Inc.) was used to score each sleep record. Thirty second epochs were scored

manually under blind conditions and in accordance with the AASM (Berry et al., 2012). Data from the first night was not scored.

The following sleep architecture variables were extracted: N1, N2, N3, and REM sleep as a percentage of total sleep time, and wake percentage. The following sleep continuity variables were extracted: total sleep time (the total number of PSG defined sleep in minutes), WASO (wake time after sleep onset in minutes), SOL (onset of N1 sleep from lights off in minutes), arousal index (number of arousals per hour), and sleep efficiency (total sleep time divided by time in bed x 100). As there is evidence that carbohydrate intake differentially influences sleep during the first and second half of the night (Jalilolghadr et al., 2011; Porter & Horne, 1981), the following variables were also calculated for each half of the night: N1, N2, N3, and REM sleep as a percentage of total sleep time, and wake percentage. The first half of the night was defined as the first 4 hours of sleep from sleep onset. The second half of the night reflected the remaining time spent asleep. As waketime was self-selected, the length of the second half of the night varied.

3.2.5 Subjective measures of sleep quality

3.2.5.1 Leeds Sleep Evaluation Questionnaire (LSEQ)

The LSEQ (Parrott & Hindmarch, 1978) was used to measure subjective sleep quality (Appendix 12). The questionnaire was administered 20 minutes after lights on to control for sleep inertia. The questionnaire contains ten 100mm visual analogue scales (VAS) corresponding to four domains of sleep: ‘ease of getting to sleep’, ‘quality of sleep’, ‘ease of waking from sleep’, and ‘behaviour following sleep’. Each item is anchored by opposite states – for example, “More difficult than usual” and “Easier than usual”. Higher scores reflect a more positive evaluation of sleep. The LSEQ (Parrott & Hindmarch, 1978) has previously been used to measure subjective changes in sleep quality following nutritional interventions (Cornu et al., 2010; Stevens et al., 2017).

3.2.5.2 Epworth Sleepiness Scale (ESS)

A modified version of the ESS (Johns, 1991) was used to assesses subjective daytime sleepiness throughout the day after sleeping in the laboratory (Appendix 13). The scale is comprised of eight hypothetical situations which are rated on a scale from 0 (no chance of dozing off) to 3 (high chance of dozing off). The situations included: sitting and reading, watching TV, sitting inactive in a public place, being a passenger in a motor vehicle for an hour

or more, lying down in the afternoon, sitting and talking to someone, sitting quietly after lunch (no alcohol), and stopping for a few minutes in traffic. A total score is calculated by summing the scores for each situation; the maximum score is 24. Higher scores reflect higher levels of daytime sleepiness.

3.2.6 Memory consolidation

3.2.6.1 Procedural memory

Procedural memory was assessed using a finger tapping task which was similar to that used by Walker et al. (2002). The task was created using Gorilla Experiment Builder (Gorilla sc). Using their non-dominant hand, participants placed their fingers on the keys '1', '2', '3', and '4' so that one finger corresponded to one key. Participants were instructed to repeatedly type a 5-digit sequence presented on-screen as quickly and as accurately as possible for 30 seconds, followed by a 30 second break. The sequence remained on-screen until each break to minimise working memory demands. A black asterisk appeared on-screen after a key was pressed. The learning phase (evening) consisted of 12 trials, whereas the recall phase (morning) consisted of four trials. Three identical versions of the task were created using different sequences. Version one (3-2-4-1-3) was always administered during the familiarisation session, as this was the only version that provided participants with immediate on-screen feedback ('correct' or 'incorrect'). Version two (2-3-1-4-2) and version three (4-1-3-2-4) were administered during the second or third session in a randomised and counterbalanced order.

The mean number of correctly typed sequences during the last three trials of the learning phase (i.e., trial 10, 11, and 12) and the last three trials of the recall phase (i.e., trial 2, 3, and 4) were calculated, termed 'mean' scores. In addition, the mean number of correctly typed sequences during the best three trials of both the learning phase and recall phase were calculated, termed 'best' scores. To assess the impact of GL on nocturnal memory consolidation, change scores were calculated by subtracting learning phase scores from recall phase scores. Negative change scores indicated that fewer sequences were typed in the morning than the evening.

3.2.6.2 Episodic memory

Episodic memory was assessed using a story recall task presented in Qualtrics. Three neutral, three negative, and three positive stories were taken from a set of 12 stories that had previously been validated in an unpublished pilot study (Appendix 14). Three sets of stories were created; each set contained a neutral story, positive story, and negative story. Participants viewed the

same set of stories during visit 1, 2, and 3, but the order of presentation within each visit was counterbalanced across participants. During the learning phase, participants were given three minutes to memorise as many details as possible from the first story. Participants either read the story or listened to the story, depending on personal preference. After three minutes, participants were asked to rate the story using the following scales: incomprehensible-comprehensible, uninteresting-interesting, difficult-easy, neutral-emotional, unarousing-startling, unimportant-important, abstract-concrete, serious-amusing, boring-arousing, unfamiliar-familiar, negative-positive, and unrelatable-relatable. Participants were then instructed to freely recall the story using an on-screen text box; no time limit was set. The same procedure was followed for the second and third story. During the recall phase, participants were given unlimited time to freely recall the stories in the same order that they were presented in the learning phase.

All nine stories contained 11 sentence and a total word count between 161 and 163. Stories were scored manually, and only nouns, adjectives, and verbs were scored. One point was assigned for each correctly recalled scored word. A change of tense was accepted (e.g., 'work' to 'worked), as well as contractions (e.g., 'do not' to 'don't') and synonyms (e.g., 'elated' to 'happy'). Three scores were calculated: total score (ranging from 87 to 98 words), total buffer score (ranging from 11 to 20 words), and total content score (ranging from 69 to 83 words). The total buffer score was calculated using the number of scored words recalled from the first and last sentence, to control for primacy and recency effects. The total content score was calculated using the number of scored words recalled from the main body of the story. Each score was divided by the maximum number of scored words possible and multiplied by 100. To assess the impact of GL on nocturnal memory consolidation, change scores were calculated by subtracting learning phase scores from recall phase scores (e.g., total number of scored buffer words during the recall phase minus total number of scored buffer words during the learning phase). Negative change scores meant that fewer words were recalled during the recall phase i.e., more words were forgotten overnight.

3.2.7 Continuous glucose monitoring

A Dexcom G6 (Dexcom, Inc., San Diego, CA, USA) continuous glucose monitor was used to measure interstitial glucose levels every five minutes. Data were transmitted via Bluetooth to a receiver. The device uses a subcutaneous glucose oxidase-based sensor, which was placed on the back of the upper arm, on each participant's non-dominant side. This location produces the

smallest difference between capillary and interstitial glucose levels (Castorino et al., 2020). The mean time lag between Dexcom G6 interstitial glucose levels and capillary glucose levels is approximately 3.6 minutes (Garg et al., 2022). The receiver was blinded so that participants did not receive any real time feedback on their glucose levels.

3.2.8 Procedure

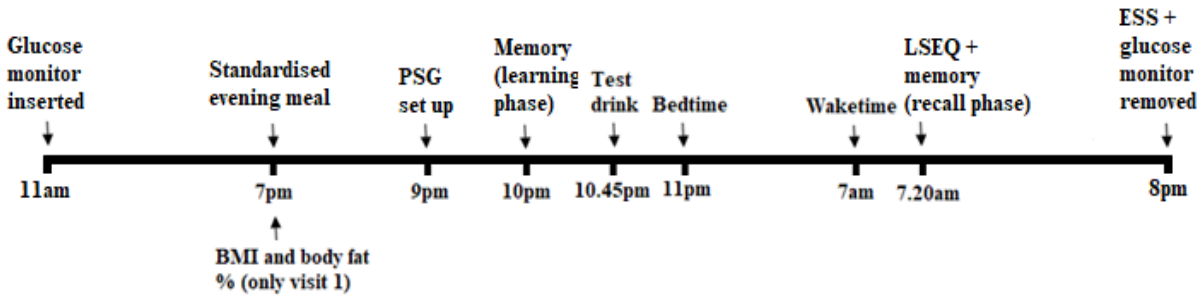


Figure 12. Sleep study procedure. *Note.* Times are approximate. PSG = polysomnography, BMI = body mass index, LSEQ = Leeds Sleep Evaluation Questionnaire, ESS = Epworth Sleepiness Scale.

The procedure followed during each test session is depicted in Figure 12. Participants attended the sleep laboratory on three occasions, one week apart. The purpose of the first visit was to minimise the first night effect by familiarising participants with the study requirements and novel laboratory conditions. The same procedure was followed across all three nights, however written informed consent and anthropometric data (height, weight, BMI, and body fat percentage) were obtained during visit one. Participants were instructed to consume similar meals and drinks, including caffeine, on the day of each sleep study and begin fasting from 2pm (water permitted). Participants were also instructed to refrain from napping prior to each session and abstain from vigorous exercise and alcohol on the day of testing until 8pm the following day. Participants were informed that if they did not sleep normally the night before each session, the sleep study would be rescheduled. A continuous glucose monitor was inserted at approximately 11am on the morning of each session and removed at 8pm the next day. At 7pm, participants arrived at the sleep laboratory and adherence to the study protocol was verbally checked. A standardised evening meal was consumed within 15 minutes. Water was consumed ad libitum throughout each session. Participants were prepared for PSG recording at 9pm. At 10pm, the finger tapping task and story recall task were administered in a randomised and counterbalanced order. The tasks took approximately 30 to 45 minutes to

complete. After finishing both tasks, participants were asked to consume either water (visit 1) or one of two test drinks (visit 2 and 3). Participants were left to go to sleep at approximately 11pm; bedtime was consistent for each participant. Participants were allowed to wake freely, but no later than 8.15am, so that each participant's waketime resembled their habitual waketime as closely as possible. The PSG set-up was removed immediately after awakening. The LSEQ (Parrott & Hindmarch, 1978) was administered approximately 20 minutes later. The recall phase of both memory tasks was then completed in the same order as during the evening. Breakfast was provided upon request. At 8pm, the ESS (Johns, 1991) was completed and the continuous glucose monitor removed. Participants were debriefed after finishing the study (Appendix 15).

3.2.9 Statistical analysis

Statistical analyses were performed using IBM SPSS statistics for Windows, Version 28 (IBM, Corp., Armonk, NY, USA). All data were analysed using an ANOVA, with Drink (HGL and LGL) entered as a within-subjects factor. Changes in postprandial interstitial glucose levels were analysed using a two-way ANOVA, with Time as a within-subjects factor (Drink X Time [baseline, 30, 60, 90, 120, and 150 minutes]). Changes in nocturnal interstitial glucose levels were also analysed using a two-way ANOVA (Drink X Time [sleep onset, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 390 minutes]). Changes in sleep architecture, sleep continuity, subjective sleep quality, and procedural memory were examined using a two-way mixed ANOVA, with Order as a between-subjects factor (Drink X Order [HGL first or LGL first). To determine whether the HGL and LGL drinks differentially influenced sleep architecture during the first and second half of the night, the following three-way mixed ANOVA was performed: Drink X Order X Time (first and second half of night). Lastly, to determine whether the drinks influenced episodic memory, a three-way mixed ANOVA was performed, with Valence as a within-subjects factor (Drink X Order X Valence [positive, negative, and neutral]). Significant interactions were followed up by appropriate post hoc t-tests. A Bonferroni correction was applied to all post hoc tests to control for multiple comparisons. Given that small sample sizes can inflate the type 2 error rate, Bayesian statistics were also used to establish whether there is evidence of absence or absence of evidence (Keysers et al., 2020). Bayesian statistics were performed post hoc using JASP, Version 0.17.1, and reported in Appendix 16. A Bayes factor between 1 and 3 is considered anecdotal evidence,

3 and 10 is considered moderate evidence, and greater than 10 is considered strong evidence (van Doorn et al., 2021).

A Greenhouse-Geisser correction was performed when appropriate. Outliers were identified using Cook's distance. In order to avoid considerably reducing the sample size, a less conservative threshold of 0.2 was used. Cases with a Cook's distance above 0.2 were removed from the analysis and the data were reanalysed. Outliers were retained if their removal did not influence the results. Normality was assessed using a Shapiro-Wilks test. Some data violated this assumption. However, for the following reasons, a mixed ANOVA was still used – 1) there is no non-parametric alternative to a mixed ANOVA, 2) mixed ANOVAs are robust against normality violations, and 3) only a small proportion of the data were not normally distributed.

3.3 Results

For brevity, the results of analyses involving the following outcome measures are reported in Appendix 16: N1 sleep percentage, N2 sleep percentage, wake percentage, total sleep time, and arousal indices.

3.3.1 Primary analyses

3.3.1.1 Postprandial and nocturnal interstitial glucose levels

3.3.1.1.1 Glycaemic response to the high and low glycaemic load drinks

Data were not obtained from two participants due to a technical error. The interstitial glycaemic responses to the experimental drinks are shown in Figure 13. Mauchly's Test of Sphericity indicated that both the within-subjects factor Time ($\chi2(14) = 43.774$, $p = 0.001$) and Drink X Time interaction ($\chi2(14) = 23.951$, $p = 0.049$) violated the assumption of sphericity, therefore Greenhouse-Geisser corrections were applied where appropriate. The main effect of Drink was non-significant ($F(1,17) = 0.313$, $p = 0.58$, $np^2 = .018$). However, the Drink X Time interaction was significant ($F(2.950,50.155) = 11.652$, $p = 0.001$, $np^2 = .407$). Bonferroni corrected post hoc t-tests ($\alpha = 0.008$). indicated that the HGL drink was associated with significantly higher glucose levels at 30 minutes ($p = 0.001$) and lower glucose levels at 150 minutes ($p = 0.001$) compared to the LGL drink. Glucose levels were also higher after the LGL drink than HGL drink at 120 minutes ($p = 0.013$), but this was no longer significant after applying a Bonferroni correction.

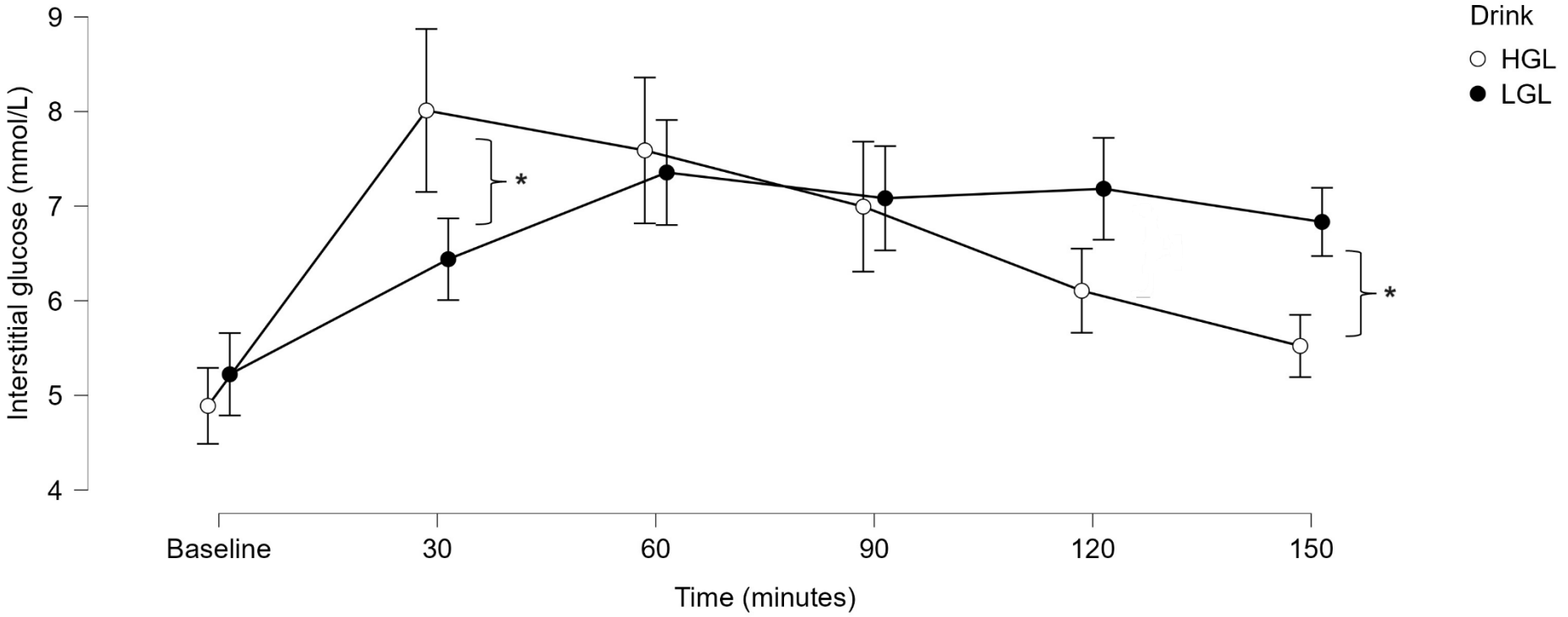


Figure 13. Glycaemic response to the high and low glycaemic load drinks. The Drink X Time interaction was significant (F(2.950,50.155) = 11.652, p = 0.001, np^2 = .407), Bonferroni corrected post hoc t-tests revealed that the HGL drink was associated with significantly higher glucose levels at 30 minutes (* p = 0.001) and lower glucose levels at 150 minutes (* p = 0.001) compared to the LGL drink. Glucose levels were also higher after the LGL drink at 120 minutes, but this was no longer significant after applying a Bonferroni correction (p = 0.013). *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 6 ANOVA, with Drink (HGL and LGL) and Time (baseline and 30, 60, 90, 120, and 150 minutes) as within-subjects factors (n = 18). Baseline blood glucose levels were obtained approximately 10 minutes before drink consumption.

3.3.1.1.2 Nocturnal interstitial glucose levels

Data were not obtained from two participants due to a technical error. Mean nocturnal interstitial glucose levels are shown in Figure 14. Mauchly's Test of Sphericity indicated that both the within-subjects factor Time ($\chi 2(90) = 166.784$, $p = 0.001$) and Drink X Time interaction ($\chi 2(90) = 151.106$, $p = 0.001$) were significant, therefore Greenhouse-Geisser corrections were applied. The main effect of Drink was non-significant ($F(1,17) = 1.112$, $p = 0.31$, $np^2 = .061$). The Drink X Time interaction was significant ($F(4.512,76.705) = 2.500$, $p = 0.04$, $np^2 = .128$). After applying a Bonferroni correction for 14 tests ($\alpha = 0.0035$), post hoc t-tests revealed that glucose levels were significantly higher 120 minutes after sleep onset following the LGL drink than HGL drink ($p = 0.001$). The LGL drink was also associated with higher glucose levels 90 minutes ($p = 0.01$) and 150 minutes ($p = 0.043$) after sleep onset, but these tests were no longer significant after applying a Bonferroni correction.

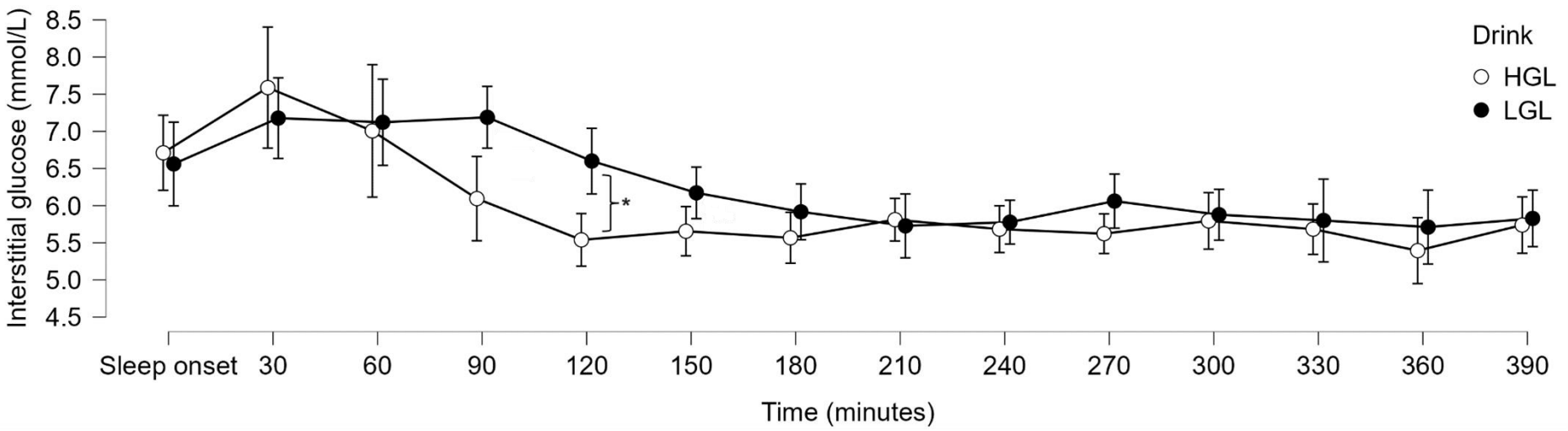


Figure 14. Nocturnal interstitial glucose levels after the high and low glycaemic load drinks. The Drink X Time interaction was significant ($F(4.512,76.705) = 2.500$, $p = 0.04$, $np^2 = .128$). Bonferroni corrected post hoc t-tests revealed that glucose levels were significantly higher 120 minutes after sleep onset following the LGL drink than HGL drink (* $p = 0.001$). Glucose levels were also higher 90 minutes ($p = 0.01$) and 150 minutes ($p = 0.043$) after sleep onset following the LGL drinks, but these were no longer significant after applying a Bonferroni correction. *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 14 ANOVA, with Drink (HGL and LGL) and Time (sleep onset, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 390 minutes) as within-subjects factors ($n = 18$).

3.3.1.2 Polysomnographic parameters

Sleep continuity and sleep architecture variables following the HGL and LGL drinks are displayed in Table 8.

Table 8. Polysomnographic parameters following the high and low glycaemic load drinks.

	HGL drink	LGL drink	N
Sleep continuity			
Total sleep time (mins)	456.80 (29.63)	461.23 (25.28)	20
Sleep efficiency (%)	93.08 (4.15)	93.39 (3.43)	20
WASO (mins)	21.03 (11.2)	22.71 (11.58)	19
SOL (mins)	9.85 (8.18)	8.97 (6.64)	19
Arousal index	5.78 (2.37)	5.19 (1.78)	18
Sleep architecture			
N1 (%)	10.29 (7.88)	10.58 (7.31)	20
N2 (%)	53 (9.07)	53.6 (8.95)	20
N3 (%)	26.27 (5.45)	27.62 (6.89)	18
REM (%)	10.3 (6.53)	8.58 (3.32)	20
Wake (%)	6.92 (4.13)	6.89 (3.14)	20
Sleep architecture during the first half of the night			
N1 (%)	12.12 (8.80)	10.28 (7.96)	20
N2 (%)	45.72 (8.63)	50.32 (13.57)	18
N3 (%)	38.39 (10.26)	35.63 (14.46)	20
REM (%)	5.48 (5.76)	5.58 (3.96)	19
Wake (%)	7.68 (4.84)	5.33 (2.14)	17
Sleep architecture during the second half of the night			
N1 (%)	8.69 (9.92)	10.96 (10.97)	20
N2 (%)	64.13 (9.08)	58.83 (10.39)	18
N3 (%)	14.72 (5.79)	18.47 (11.24)	20
REM (%)	13.38 (6.90)	11.36 (5.5)	19
Wake (%)	4.38 (2.58)*	6.51 (3.38)*	17

Note. Data are mean values (SD). WASO = wake after sleep onset, SOL = sleep onset latency, REM = rapid eye movement. * $p = 0.011$.

3.3.1.2.1 N3 sleep

Three outliers were removed from the analysis. The main effect of Drink was non-significant ($F(1,15) = 1.149$, $p = 0.301$, $np^2 = .071$). There was a significant Drink X Order interaction ($F(1,15) = 5.595$, $p = 0.032$, $np^2 = .272$). As shown in Figure 15, post hoc t-tests indicated that the LGL drink was associated with a higher N3 percentage than the HGL drink, but only when the HGL drink was consumed first ($p = 0.032$). However, this was no longer significant after applying a Bonferroni correction for four tests ($\alpha = 0.012$). The percentage of N3 sleep across the whole night did not differ between drink conditions when the LGL drink was consumed first ($p = 0.361$).

As there was an order effect, data from the first and second experimental night were analysed separately using an independent t test. Participants removed from the interaction above were also removed from these analyses. Using data from the first experimental night, the main effect of Drink was non-significant ($t(15) = -1.349$, $p = 0.199$). However, given that the study was not designed (and therefore powered) for a between subject's analysis Cohen's d was used to establish whether there was a meaningful effect size. Mean N3 sleep percentage was higher following the LGL drink (mean = 27.50, SD = 6.41) than HGL drink (mean = 23.98, SD = 4.20), with a medium effect size (Cohen's $d = 0.63$). Using data from the second experimental night, the main effect of Drink was also non-significant ($t(15) = -.178$, $p = 0.862$). There was a negligible difference in the mean N3 sleep percentage between the LGL drink (mean = 29.28, SD = 4.99) and HGL drink (mean = 28.71, SD = 7.66), and a small effect size (Cohen's $d = 0.09$).

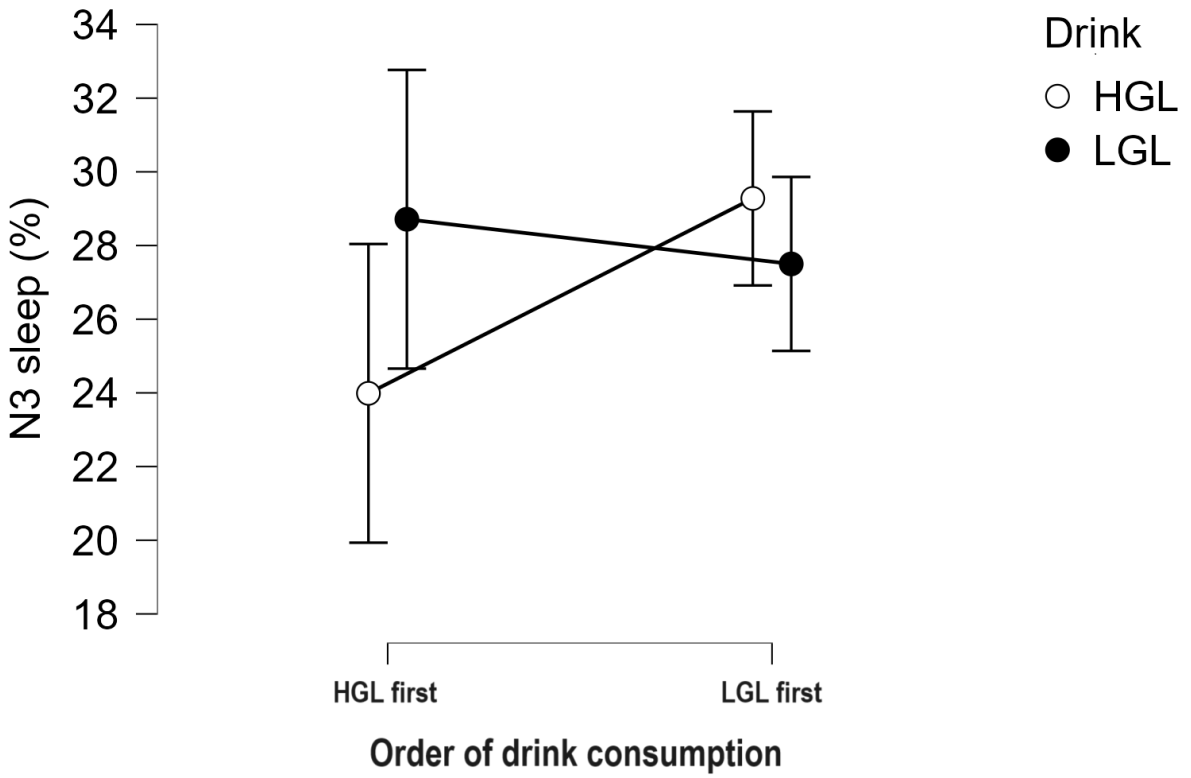


Figure 15. Percentage of N3 sleep according to order of drink consumption. There was a significant Drink X Order interaction ($F(1,15) = 5.595$, $p = 0.032$, $np^2 = .272$), whereby the LGL drink was associated with a higher percentage of N3 sleep, compared to the HGL drink, but only when the HGL drink was consumed first ($p = 0.032$). However, this was no longer significant after applying a Bonferroni correction for four tests ($\alpha = 0.012$). *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 2 ANOVA, with Drink (HGL and LGL) as a within-subjects factor and Order (HGL first or LGL first) as a between-subjects factors ($n = 17$).

3.3.1.2.2 REM sleep

Two outliers were identified but retained in the analysis as they did not change the result. Both the interaction Drink X Order ($F(1,18) = 0.003$, $p = 0.96$, $np^2 = .000$) and main effect of Drink ($F(1,18) = 1.539$, $p = 0.23$, $np^2 = .079$) were non-significant.

3.3.2 Secondary analyses

3.3.2.1 Subjective measures of sleep

Subjective measures of sleep quality after the HGL and LGL drink are shown in Table 9.

Table 9. Subjective measures of sleep quality.

	HGL drink	**LGL drink**
LSEQ (n = 19)		
Getting to sleep	15.21 (6.02)	15.26 (5.83)
Quality of sleep	8.53 (4.25)	7.58 (4.15)
Ease of waking from sleep	11.89 (3.49)	12.00 (3.13)
Behaviour following sleep	14.00 (3.61)	13.84 (4.98)
ESS (n = 20)		
Daytime sleepiness score	4.20 (3.85)	4.9 (4.20)

Note. Data are presented as means (SD). LSEQ = Leeds Sleep Evaluation Questionnaire, ESS = Epworth Daytime Sleepiness Scale. Higher LSEQ scores are indicative of better sleep quality. Higher ESS scores are indicative of increased daytime sleepiness.

3.3.2.1.1 Leeds Sleep Evaluation Questionnaire

Data were not obtained from one participant due a technical error. Outliers were identified in all analyses; removal of outliers did not significantly change the results. Separate ANOVAs were performed for each subscale of the LSEQ. For the 'getting to sleep subscale', both the Drink X Order interaction ($F(1,17) = 0.718$, $p = 0.408$, $\eta p^2 = .041$) and main effect of Drink ($F(1,17) = 0.000$, $p = 0.986$, $\eta p^2 = .000$) were non-significant. For the 'quality of sleep' subscale, the Drink X Order interaction ($F(1,17) = 0.063$, $p = 0.805$, $\eta p^2 = .004$) and main effect of Drink ($F(1,17) = 0.856$, $p = 0.368$, $\eta p^2 = .048$) were non-significant. For the 'ease of waking from sleep' subscale, the Drink X Order interaction was non-significant ($F(1,17) = 0.120$, $p = 0.733$, $\eta p^2 = .007$), as well as the main effect of Drink ($F(1,17) = 0.010$, $p = 0.922$, $\eta p^2 = .001$). Lastly, the Drink X Order interaction ($F(1,17) = 0.216$, $p = 0.648$, $\eta p^2 = .013$) and main effect

of Drink (F(1,17) = 0.018, p = 0.896, ηp^2 = .001) were non-significant for the 'behaviour following sleep' subscale.

3.3.2.1.2 Epworth Daytime Sleepiness Scale

One outlier was identified. Removal of this outlier did not influence the results. Both the Drink X Order interaction (F(1,18) = 1.823, p = 0.19, ηp^2 = .092) and main effect of Drink were non-significant (F(1,18) = 1.103, p = 0.31, ηp^2 = .058).

3.3.2.2 Sleep-dependent memory consolidation

3.3.2.2.1 Episodic memory

The mean overnight change in memory for positive, negative, and neutral stories is shown in Table 10. Preliminary checks showed that performance did not differ during the learning phase between drink conditions (all p = NS; Appendix 16). Furthermore, preliminary checks indicated that fewer words were recalled in the morning than evening for all types of stories and scores (all p = 0.05, Appendix 16). Story ratings can also be found in Appendix 16.

Table 10. Overnight change in performance on the story recall task.

	HGL drink	**LGL drink**
Change in total number of words recalled (n = 18)		
Positive	-8.78 (5.36)	-9.39 (12.49)
Negative	-5.17 (6.71)	-5.72 (7.51)
Neutral	-5.94 (5.87)	-3.17 (10.41)
Change in total number of content words recalled[1] (n = 20)		
Positive	-10.09 (10.85)	-9.07 (12.68)
Negative	-5.2 (8.08)	-5.90 (9.35)
Neutral	-6.4 (6.85)	-5.65 (20.01)
Change in total number of buffer words recalled[2] (n = 18)		
Positive	-18.83 (19.27)	-12.89 (16.16)
Negative	-6.33 (10.09)	-5.44 (11.91)
Neutral	-3.39 (13.28)	-4.89 (10.84)

Note. Data are presented as means (SD). Overnight retention was calculated by subtracting learning phase scores from recall phase scores. Negative retention scores indicate that fewer words were recalled in the morning than evening. 1 = number of words recalled from the main body of the stories and 2 = number of words recalled from the first and last sentence of the stories.

3.3.2.2.1.1 Total number of words forgotten

Two outliers were identified and removed from the analysis. The main effect of Drink ($F(1,16) = 0.321$, $p = 0.58$, $\eta p^2 = 0.02$) and Drink X Order X Valence interaction ($F(2,32) = 1.095$, $p = 0.35$, $\eta p^2 = 0.064$) were non-significant. The main effect of Valence just missed significance ($F(2,32) = 3.121$, $p = 0.06$, $\eta p^2 = .163$). As shown in Figure 16, more words were forgotten overnight from the positive stories than neutral stories ($p = 0.022$). However, this was no longer significant after applying a Bonferroni correction for three tests ($\alpha = 0.016$). No other differences in overnight retention were found.

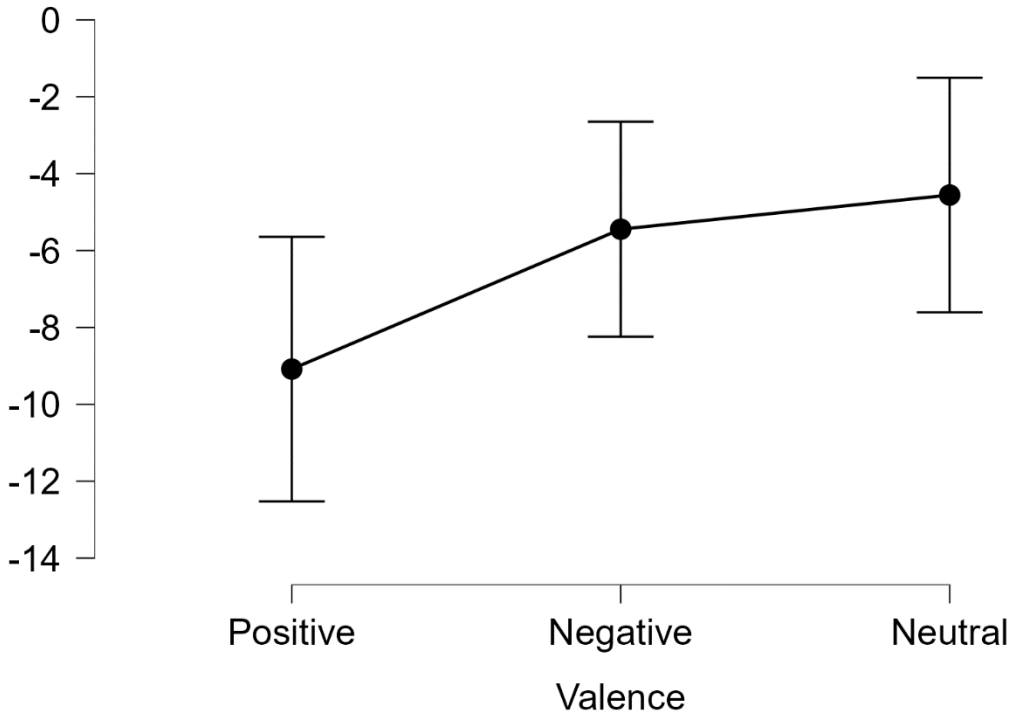


Figure 16. Overnight change in the total number of words recalled for each type of story. The main effect of Valence just missed significance ($F(2,32) = 3.121$, $p = 0.06$, $\eta p^2 = .163$). Post hoc t-tests revealed that overnight retention was poorer for positive stories than neutral stories ($p = 0.022$), but this was no longer significant after applying a Bonferroni correction. *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 3 X 2 mixed ANOVA, with Drink (HGL and LGL) and Valence (positive, negative, and neutral) as within-subjects factors and Order (HGL first or LGL first) as a between-subjects factors ($n = 18$).

3.3.2.2.1.2 Total number of content words forgotten

Five outliers were identified but kept in the analysis. Both the main effect of Valence ($F(2,36) = 1.448$, $p = 0.249$, $\eta p^2 = .074$) and main effect of Drink ($F(1,18) = 0.028$, $p = 0.869$, $\eta p^2 = .002$) were non-significant. The Valence X Drink X Order interaction was also non-significant ($F(2,36) = 1.803$, $p = 0.179$, $\eta p^2 = .091$).

3.3.2.2.1.3 Total number of buffer words forgotten

Two outliers were identified and removed from the analysis as they influenced the results. A Greenhouse-Geisser correction was applied to all analyses involving the variable Valence ($\chi 2(2) = 6.592$, $p = 0.04$). The main effect of Drink ($F(1,16) = 0.612$, $p = 0.445$, $\eta p^2 = 0.037$) and Drink X Valence X Order interaction ($F(1.699,27.183) = 2.595$, $p = 0.100$, $\eta p^2 = .140$) were non-significant. The main effect of Valence was significant ($F(1.475,23.606) = 7.260$, $p = 0.007$, $\eta p^2 = .312$) and is illustrated in Figure 17. Bonferroni corrected post hoc t-tests ($\alpha = 0.016$) revealed that significantly more words were forgotten overnight from the positive stories than negative stories ($p = 0.008$) and neutral stories ($p = 0.011$).

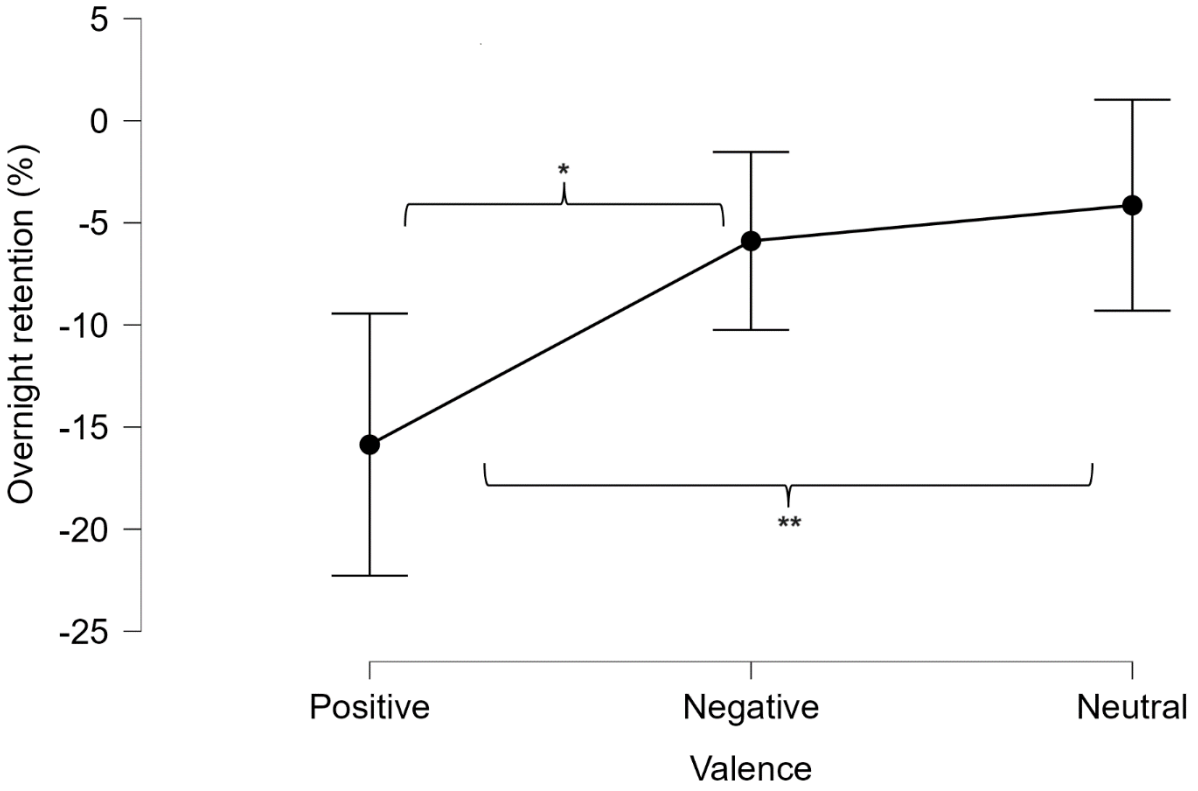


Figure 17. Overnight change in the total number of buffer words recalled for each type of story. The main effect of Valence was significant ($F(1.475,23.606) = 7.260$, $p = 0.007$, $\eta p^2 = .312$). After applying a Bonferroni correction, post hoc t-tests showed that significantly more words were forgotten overnight from the positive stories than negative stories (* $p = 0.008$) and neutral stories (** $p = 0.011$). *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 3 X 2 mixed ANOVA, with Drink (HGL and LGL) and Valence (positive, negative, and neutral) as within-subjects factors and Order (HGL first or LGL first) as a between-subjects factors (n = 18).

3.3.2.2.2 Procedural memory

The mean overnight change in procedural memory is shown in Table 11. Preliminary checks indicated that performance did not differ during the learning phase between drink conditions (all p = NS; Appendix 16). Preliminary checks also indicated that mean scores, but not best scores, were significantly better in the morning than evening (p = 0.001, Appendix 16).

Table 11. Overnight change in performance on the finger tapping task.

	HGL drink	LGL drink
Change in mean performance[1] (n = 18)	2.13 (2.79)	1.93 (2.79)
Change in best performance[2] (n = 18)	0.89 (1.97)	0.72 (2.26)

Note. Data are presented as means (SD). Overnight retention was calculated by subtracting learning phase scores from recall phase scores. Positive retention scores indicate an overnight improvement in procedural memory. 1 = last three trials and 2 = best three trials.

3.3.2.2.2.1 Mean scores

Data were not obtained from two participants due to a technical error. Two outliers were identified but retained in the analysis as they did not influence the results. The interaction Drink X Order was not significant ($F(1,16) = 0.062$, $p = 0.807$, $\eta p^2 = .004$), as well as the main effect of Drink ($F(1,16) = 0.059$, $p = 0.811$, $\eta p^2 = .004$).

3.3.2.2.2.2 Best scores

Data were not obtained from two participants due to a technical error. One outlier was identified but retained in the analysis. Both the Drink X Order interaction ($F(1,16) = 0.304$, $p = 0.589$, $\eta p2 = .019$) and main effect of Drink ($F(1,16) = 0.143$, $p = 0.710$, $\eta p^2 = 0.009$) were non-significant.

3.3.3 Exploratory analyses

3.3.3.1 Sleep onset latency

Two outliers were removed from the SOL analysis. The main effect of Drink was non-significant ($F(1,16) = 0.099$, $p = 0.76$, $np^2 = .006$). The interaction Drink X Order just missed significance ($F(1,16) = 4.305$, $p = 0.054$, $np^2 = .212$). Bonferroni corrected post hoc t-tests failed to reveal any significant effects. However, there was a trend towards a longer SOL after the LGL drink compared to HGL drink, but only when the LGL drink was consumed first (p = 0.09). Follow-up tests were also not significant when the HGL drink was consumed first (p= 0.964).

Given the trending Drink X Order interaction, data from the first and second experimental night were analysed separately using a one-way ANOVA. Two outliers were removed from the analyses. The effect of Drink was non-significant ($t(16) = 0.473$, $p = 0.321$). Mean values indicated that SOL was longer after the LGL drink (mean = 11.31, SD = 7.95) than HGL drink (mean = 9.77, SD = 5.80). The effect size was small (Cohen's d = 0.21). Using data from the second experimental visit, the main effect of Drink was also non-significant ($t(16) = 0.232$, $p = 0.410$). There was a negligible differences in SOL between the LGL drink (mean = 7.32, SD = 5.14) than HGL drink (mean = 6.83, SD = 3.66), and a small effect size (Cohen's d = 0.12).

3.3.3.2 Sleep efficiency

Outliers were identified but retained in the analysis. The Drink X Order interaction was non-significant ($F(1,18) = 0.026$, $p = 0.87$, $np^2 = .001$), as well as the main effect of Drink ($F(1,18) = 0.099$, $p = 0.76$, $np^2 = .005$).

3.3.3.3 Wake-after-sleep-onset

Two outliers were removed from the WASO analysis. The main effect of Drink was non-significant ($F(1,16) = 0.430$, $p = 0.52$, $np^2 = .025$). The Drink X Order interaction just missed significance, ($F(1,16) = 3.685$, $p = 0.073$, $np^2 = .187$). As shown in Figure 18, when the HGL drink was consumed first, there was a longer WASO after the LGL drink than HGL drink ($p = 0.026$), although this did not survive the Bonferroni correction which was set at $\alpha = 0.012$ (for four tests). When the LGL drink was consumed first, follow-up tests were not significant ($p = 0.368$).

The order effect was explored using an independent t test. Two outliers were removed from the analyses. The main effect of Drink was non-significant ($t(16) = -1.065$, $p = 0.303$). Mean WASO was higher after the LGL drink (mean = 19.5, SD = 8.83) than HDL drink (mean = 15.43, SD = 7.35), with a small effect size (Cohen's d = 0.49). For the second experimental night, the main effect of Drink was also non-significant ($t(16) = -.363$, $p = 0.721$). There was a negligible difference in mean WASO between the LGL drink (mean = 24.52, SD = 12.52) and HGL drink (mean = 22.67, SD = 9.01), with a small effect size (Cohen's d = 0.17).

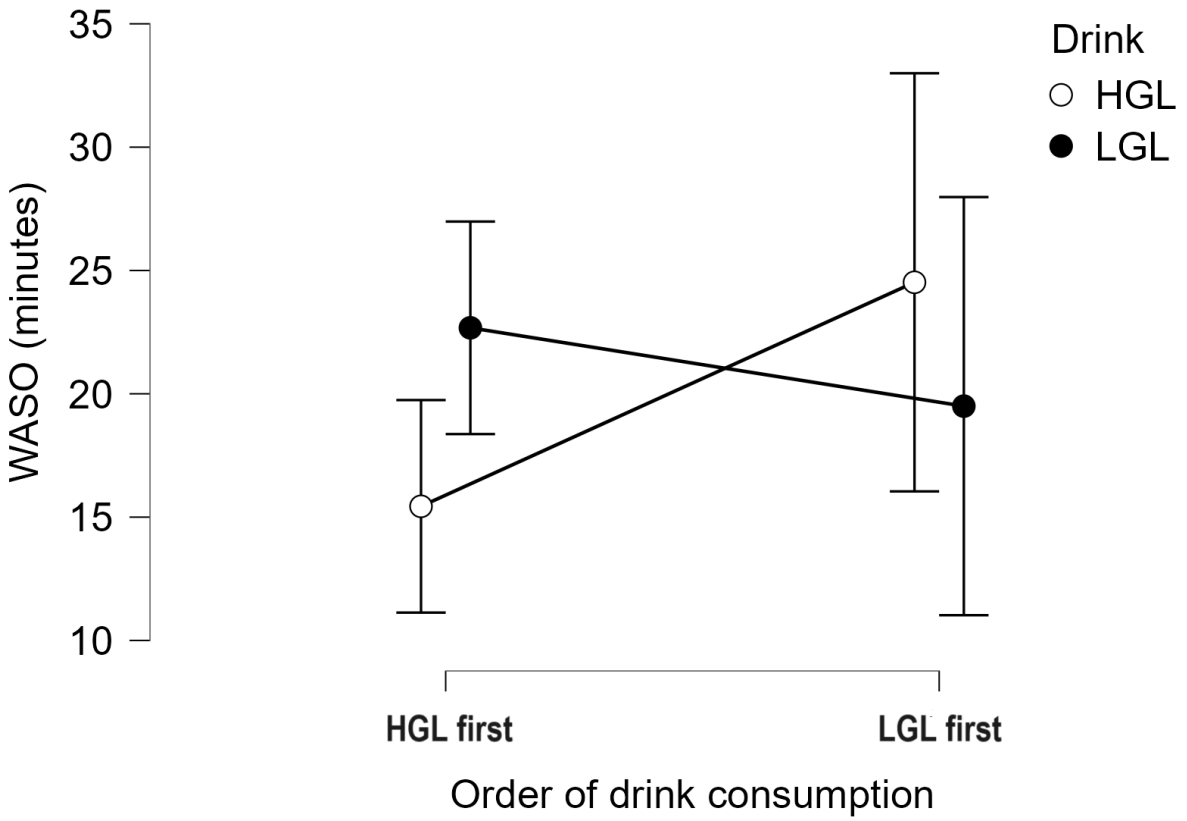


Figure 18. Wake after sleep onset according to order of drink consumption. The Drink X Order interaction just missed significance ($F(1,16) = 3.685$, $p = 0.073$, $np^2 = .187$). When the HGL drink was consumed first, there was a longer WASO after the LGL drink than HGL drink ($p = 0.026$). However, this was no longer significant after applying a Bonferroni correction for four tests. *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 2 ANOVA, with Drink (HGL and LGL) as a within-subjects factor and Order (HGL first or LGL first) as a between-subjects factors (n = 18).

3.3.3.4 Sleep architecture during the first and second half of the night

For brevity, the results of analyses involving the following outcome measures are reported in Appendix 16: N1 sleep percentage, N2 sleep percentage, and wake percentage.

3.3.3.4.1 N3 sleep percentage

Three outliers were identified but kept in the analysis. The interaction Drink X Order X Time was non-significant ($F(1,18) = .565$, $p = 0.462$, $np^2 = .030$). The main effect of Drink was non-significant ($F(1,18) = 0.124$, $p = 0.729$, $np^2 = .007$). The main effect of Time was significant ($F(1,18) = 37.187$, $p = 0.001$, $np^2 = .674$), whereby a higher percentage of N3 sleep occurred during the first half of the night (mean = 37.01, SD = 12.45) compared to the second half of the night (mean = 16.59, SD = 7.33).

3.3.3.4.2 REM sleep percentage

One outlier was identified and removed from the analysis. The main effect of Drink was non-significant ($F(1,17) = 0.566$, $p = 0.462$, $np^2 = .032$). However, the Drink X Order X Time interaction was significant ($F(1,17) = 4.647$, $p = 0.046$, $np^2 = .215$). All effects are illustrated in Figure 19. With a Bonferroni correction for eight comparisons, $\alpha = 0.006$ was considered significant. In those who consumed the HGL drink first, the HGL drink was associated with a significantly lower percentage of REM sleep during the first half of the night than second half of the night ($p = 0.001$). Furthermore, in those who consumed the HGL drink first, there was a non-significant trend towards a higher percentage of REM sleep during the second half of the night after the HGL drink than LGL drink ($p = 0.058$), but this did not survive Bonferroni correction. In those who consumed the LGL drink first, a significantly lower percentage of REM sleep occurred during the first half of the night than second half of the night after the LGL drink ($p = 0.001$). The same pattern emerged for the HGL drink, but this did not remain significant after applying a Bonferroni correction ($p = 0.025$). The main effect of Time was also significant ($F(1,17) = 60.406$, $p = 0.001$, $np^2 = .780$), whereby more REM sleep occurred during the second half of the night (mean = 12.38, SD = 4.10) than the first (mean = 5.53, SD = 4.10).

Given the significant Drink X Order X Time interaction, data from the first and second experimental night were reanalysed separately using a two-way ANOVA. One outlier was removed from the analysis. During the first experimental night, the interaction Drink X Time was non-significant ($F(1,17) = 0.122$, $p = 0.731$, $np^2 = .007$). During the first half of the night, mean REM percentage was slightly higher after the HGL drink (mean = 5.56, SD = 6.11) than

LGL drink (mean = 3.70, SD = 2.63), with a small effect size (Cohen's d = 0.39). During the second half of the night, mean REM percentage was also slightly higher after the HGL drink (mean = 15.63, SD = 7.57) than LGL drink (mean = 12.57, SD = 6.64), with a small effect size (Cohen's d = 0.43). During the second experimental night, the interaction Drink X Time was also non-significant ($F(1,17) = 0.997$, $p = 0.332$, $np^2 = .055$). Mean REM percentage was slightly higher after the HGL drink (mean = 7.28, SD = 4.30) than LGL drink (mean = 5.40, SD = 5.71) during the first half of the night, with a small effect size (Cohen's d = 0.38). No difference in mean REM sleep percentage were observed between the HGL drink (mean = 10.28, SD = 4.29) and LGL drink (mean = 10.88, SD = 5.41), with a small effect size (Cohen's d = -0.12).

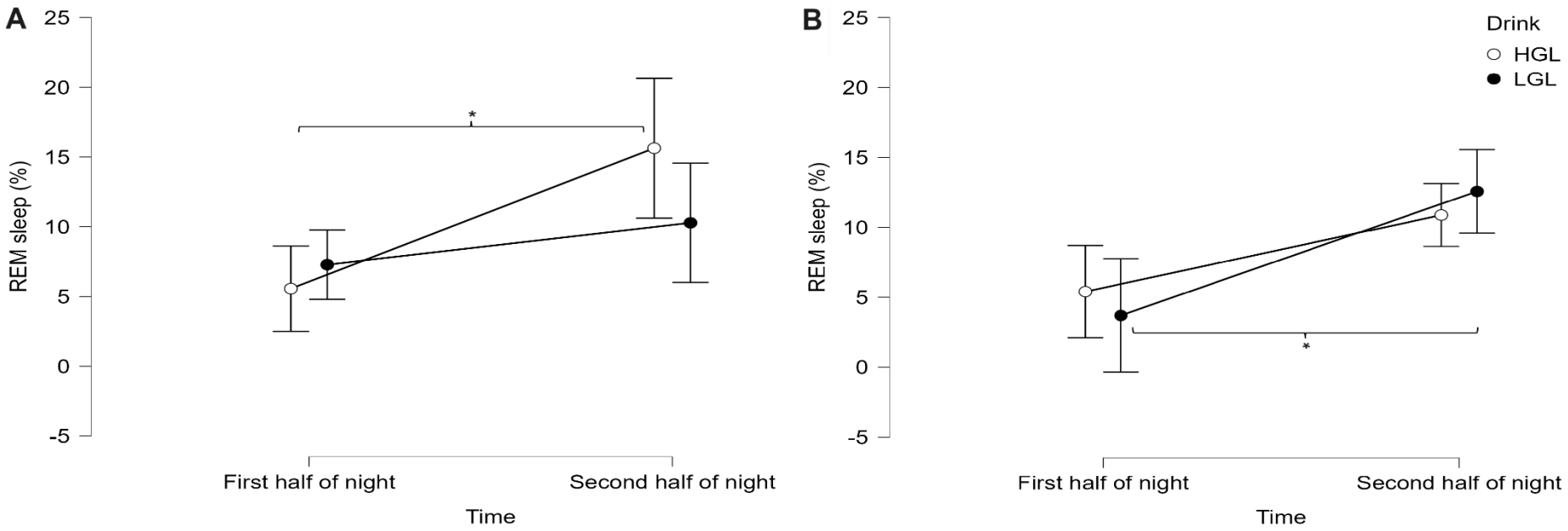


Figure 19. Percentage of REM sleep in those who consumed the high glycaemic drink (A) or low glycaemic drink (B) first. The Drink X Order X Time interaction was significant ($F(1,17) = 4.647$, $p = 0.046$, $np^2 = .215$). When the HGL drink was consumed first, the HGL drink was associated with a significantly higher percentage of REM sleep during the second half of the night compared to the first half of the night (* $p = 0.001$). When the LGL drink was consumed first, the LGL drink was also associated with a significantly higher percentage of REM sleep during the second half of the night compared to the first half of the night (* $p = 0.001$). A similar pattern emerged for the HGL drink in those who consumed the LGL drink first, but this was no longer significant after applying a Bonferroni correction. There was also a non-significant trend towards a higher percentage of REM sleep during the second half of the night after the HGL drink than LGL drink, but only in those who consumed the HGL drink first ($p = 0.058$). *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 2 X 3 ANOVA, with Drink (HGL and LGL) and Time (first and second half of night) within-subjects factors2, and Order (HGL or LGL first) as between-subjects factors ($n = 19$).

3.3.4 Summary of findings from sleep study

- REM sleep percentage, procedural and episodic memory consolidation, subjective sleep quality, subjective daytime sleepiness, SOL, and sleep efficiency did not significantly differ between drink conditions.
- Postprandial glucose levels: the HGL drink was associated with significantly higher glucose levels 30 minutes post-consumption and significantly lower glucose levels 150 minutes post-consumption compared to the LGL drink (Figure 13).
- Nocturnal glucose: the HGL drink was associated with significantly lower glucose levels 120 minutes after sleep onset compared to the LGL drink (Figure 14).
- N3 sleep: the LGL drink was associated with a higher percentage of N3 sleep across the whole night than the HGL drink, but only when the HGL drink was consumed first. This was no longer significant after applying a Bonferroni correction (Figure 15). The Bayesian analysis showed anecdotal evidence in favour of the alternative hypothesis (BF+0 = 2.27; Appendix 16). A medium (Cohen's d = 0.63) and small (Cohen's d = 0.09) effect size was found between the LGL and HGL drink when data from the first and second experimental night were analysed, respectively.
- WASO: the LGL drink was associated with a longer WASO than the HGL drink, but only when the HGL drink was consumed first. However, this was no longer significant after applying a Bonferroni correction (Figure 18). The Bayesian analysis showed moderate evidence in favour of the alternative hypothesis (BF+0 = 3.09; Appendix 16). Small effect sizes were found between the drinks when data from the first (Cohen's d = 0.49) and second (Cohen's d = 0.17) experimental night were analysed separately.
- REM sleep (split-night): there was a non-significant trend towards a higher percentage of REM sleep during the second half of the night after the HGL drink than LGL drink, but only when the HGL drink was consumed first (p = 0.058; Figure 19). The Bayesian analysis showed anecdotal evidence in favour of the alternative hypothesis (BF+0 = 1.23; Appendix 16). Small effect sizes were found between the HGL and LGL drink when data from the first and second experimental night were analysed separately, with the largest effect size occurring during the second half of the night on the first experimental night (Cohen's d = 0.43).
- Wake (split-night): the LGL drink was associated with a significantly higher percentage of wake than the HGL drink during the second half of the night (Appendix 16).

3.4 Discussion

3.4.1 Interstitial glucose levels

It was hypothesised that the HGL drink would be associated with a larger and faster rise and fall in glucose levels during the first half of the night compared to the LGL drink. There was mixed support for this hypothesis. The analysis showed that the HGL drink was associated with significantly lower glucose levels 120 minutes after sleep onset compared to the LGL drink (Figure 14). The LGL drink was associated with higher glucose levels 90- and 150-minutes after sleep onset, but the differences did not survive Bonferroni correction. The goal of this study was to elicit large and significant differences in nocturnal glucose using isomaltulose and glucose. However, these findings suggest that the novel paradigm used in the present study was only somewhat successful. The glycaemic response to identical meals and drinks is milder during the morning than evening and evening than night (Carroll & Nestel, 1973; Gibbs et al., 2014; Knutsson et al., 2002). Furthermore, the difference in GI and postprandial glycaemia between a HGI and LGI meal is smaller during the evening than morning (Gibbs et al., 2010; Gibbs et al., 2014). Therefore, the circadian rhythm in glucose metabolism may have diminished the anticipated large differences in nocturnal glucose levels between drinks. Future research could determine whether larger differences in glycaemia are elicited by administering a higher dose of glucose or by utilizing the second meal effect (Wolever et al., 1988).

3.4.2 Sleep architecture

This study compared the effects of consuming a HGL and LGL drink fifteen minutes before bedtime on sleep architecture. Consistent with past studies that administered isocaloric, macronutrient-matched nutritional interventions (Afaghi et al., 2007; Herrera, 2010; Vlahoyiannis et al., 2018), differences in GL did not influence the percentage of N1 sleep, N2 sleep, and time spent awake across the whole night (Appendix 16). It was hypothesised that a significantly higher percentage of N3 sleep would occur after the LGL drink than HGL drink. The present study found that, when the HGL drink was consumed first, the LGL drink was associated with a higher percentage of N3 sleep than the HGL drink (Figure 15). This corresponded to a difference of approximately 22 minutes in N3 sleep duration between the LGL drink and HGL drink. However, the difference was no longer significant after applying a Bonferroni correction, which could be due to insufficient power. Nonetheless, it is important to note that this finding is consistent with the results of two recent meta-analyses, whereby the consumption of a lower amount of carbohydrate, which inevitably produced a smaller rise in

blood glucose levels, was associated with more N3 sleep (Benton et al., 2022; Vlahoyiannis et al., 2021). Although the Bonferroni correction reduces the risk of type 1 errors, it does so at the expense of type 2 errors (Perneger, 1998). To account for this, Bayesian statistics were used to differentiate absence of evidence from evidence of absence (van Doorn et al., 2021). The Bayesian analysis showed only anecdotal evidence in favour of the alternative hypothesis (BF+0 = 2.27; Appendix 16). Therefore, further research is needed before firm conclusions are drawn.

It was also hypothesised that the HGL drink would be associated with a significantly higher percentage of REM sleep across the whole night than the LGL drink. The present study found no evidence to support this hypothesis, which is in line with past research (Afaghi et al., 2007; Herrera, 2010; Vlahoyiannis et al., 2018), However, the exploratory split-night analysis provided some tentative evidence to support this hypothesis. In those who consumed the HGL drink first, the HGL drink was associated with a significantly higher percentage of REM sleep during the second half of the night than the first. Similarly, in those who consumed the LGL drink first, the LGL drink was associated with a significantly higher percentage of REM sleep during the second half of the night than the first. A similar pattern occurred after the HGL drink, but this was no longer significant after applying a Bonferroni correction. These findings are consistent with the normal architecture of sleep, whereby REM-sleep dominates during the second half of the night (Shrivastava et al., 2014)**.** During the second half of the night, there was a non-significant trend towards a higher percentage of REM sleep after the HGL drink than LGL drink, but only when the HGL drink was consumed first. This equated to a difference of 12 minutes (5%) in REM sleep duration. Although this finding reflected a non-significant trend, the meta-analyses by Benton et al. (2022) and Vlahoyiannis et al. (2021) also reported the consumption of a higher amount of carbohydrate, which inevitably elicited a larger glycaemic response, was associated with significantly more REM sleep. Therefore, it is possible that the non-significant difference in REM sleep between drink conditions was due to the study being underpowered. However, the Bayesian analysis indicated only anecdotal evidence in favour of the alternative hypothesis (BF+0 = 1.23; Appendix 16) hence further research is needed.

Also worth considering is that there is also a biological plausibility for carbohydrate-induced changes in N3 sleep and REM sleep. Studies have shown that sleep-promoting neurons in the VLPO and lateral hypothalamic area are dose-dependently excited in response to increasing glucose levels within the physiological range (Burdakov et al., 2005). Varin et al. (2015)

showed that local infusion of glucose into the VLPO increased the duration of N3 sleep and reduced the latency of the first episode of N3 sleep. No studies of this nature have been conducted on MCH neurons located in the lateral hypothalamic area. However, intracerebroventricular MCH injections dose-dependent increased REM sleep by 200% and N3 sleep by 70% (Verret et al., 2003), and infusion with an MCH receptor antagonist significantly reduced the duration of REM sleep (Ahnaou et al., 2008). Various hormones are also released in response to changes in blood glucose levels, such as insulin, cortisol, cholecystokinin, adrenaline, and growth hormone, and administration of these hormones can influence the duration of N3 and REM sleep (Friess et al., 2004; Kapás et al., 1988; Kapás et al., 1991; Schmid et al., 2020). For example, plasma growth hormone levels are highest during N3 sleep (Davidson et al., 1991). Growth hormone injections have been shown to increase the amount of N3 sleep in men (Van Cauter & Plat, 1996). The release of growth hormone can be inhibited by the consumption of a glucose load (Hage et al., 2019) and a high carbohydrate diet for 10 days (Merimee et al., 1976), potentially having consequences for N3 sleep. Despite these promising mechanisms the present data do not permit firm conclusions to be drawn so more data are required.

To the best of the authors knowledge, this is the first study of this kind that examined whether order of drink consumption influenced the effect of GL on sleep, making the findings difficult to interpret. It is unclear why order effects occurred as the order of drink consumption was randomised and there was a one-week washout period between both experimental nights. Both order effects occurred in those who consumed glucose first. Data from the first and second experimental night were analysed separately to explore this further; no significant differences were found between drink conditions. However, as the study was not designed and therefore powered to perform a between-subjects analysis, Cohen's d was used to assess the magnitude of the difference between drinks. With regards to the percentage of N3 sleep, there was a medium effect size (Cohen's d = 0.63) between the LGL drink and HGL drink on the first experimental night, and a small effect size (Cohen's d = 0.09) on the second experimental night. Similarly, the largest effect size in REM sleep percentage between drink conditions occurred during the second half of the night on the first experimental night (Cohen's d = 0.43). It is possible that a residual first night effect occurred, which is characterised by atypical sleep architecture and continuity. The first night effect is thought to reflect an increased state of vigilance and stress caused by the PSG equipment and unfamiliar sleeping environment. Although the inclusion of an acclimatisation night enables participants to adapt to the sleep

laboratory, residual disturbances in sleep architecture after the first night have been reported (Le Bon et al., 2001; Toussaint et al., 1995).

3.4.3 Sleep continuity

The consumption of drinks differing in GL shortly before bedtime did not influence sleep efficiency, total sleep time, and arousal index. Unexpectedly, WASO was longer after the LGL drink than HGL drink in those who consumed the HGL drink first, but the difference did not survive Bonferroni correction (Figure 18). The split-night analysis also showed that the percentage of wake during the second half of the night was significantly higher after the LGL drink than HGL drink (Appendix 16). Consistent with this finding, Vlahoyiannis et al. (2018) reported that the consumption of a LGL meal two hours before bedtime was associated with a significantly longer WASO than a HGL meal. Furthermore, a Bayesian analysis of WASO (BF_{+0} = 3.09) and wake percentage during the second half of the night (BF_{+0} = 5.01) showed moderate evidence in favour of the alternative hypothesis (Appendix 16), suggesting that future research could prove valuable.

In contrast with previous research (Afaghi et al., 2007; Vlahoyiannis et al., 2018), SOL did not significantly differ between drink conditions. Afaghi et al. (2007) reported that SOL was eight minutes longer after the consumption of a LGL meal, relative to a HGL meal, four hours before bedtime. Similarly, Vlahoyiannis et al. (2018) reported that SOL was approximately 19 minutes longer after the consumption of a LGL meal two hours before bedtime. The inconsistent findings may be attributed to methodological differences. Firstly, Vlahoyiannis et al. (2018) and Afaghi et al. (2007) administered meals two and four hours before bedtime, respectively, whereas the present study administered drinks 15 minutes before bedtime. Secondly, both meals administered in Afaghi et al. (2007) and Vlahoyiannis et al. (2018) were high GL (HGL meal = 175, LGL meal = 81). Although the mechanisms underlying the effect of GL on sleep are currently unknown, it is plausible that these mechanisms may be influenced by differences in the timing of meal consumption and GL of meals/drink.

3.4.4 Sleep-dependent memory consolidation

To the best of the authors knowledge, this is the first study to examine the influence of pre-bedtime diet on sleep-dependent memory consolidation. There was no differential effect of the HGL and LGL drinks on episodic (emotional and non-emotional) and procedural memory

consolidation. Consistent with these results, Herzog et al. (2012) also reported that differences in daytime energy intake did not influence sleep-dependent procedural and non-emotional episodic memory.

Previous research has shown that the duration of N3 sleep is associated with overnight improvements in episodic memory (Wilhelm et al., 2008; Zhang & Gruber, 2019). There is also a positive association between the duration of REM sleep and N2 sleep and the consolidation of both emotional and procedural memories (Clemens et al., 2005; Clemens et al., 2006; Nishida et al., 2009; Payne et al., 2012; Plihal & Born, 1997, 1999). Therefore, the magnitude of the change in N3 sleep and REM sleep may have been too small to influence memory consolidation. Indeed, the difference in REM sleep percentage between drink conditions reflected a non-significant trend, whilst the difference in the N3 sleep percentage was no longer significant after applying a Bonferroni correction. Larger increases in the duration of N3 sleep or REM sleep may be required for changes in sleep-dependent memory consolidation to occur. Alternatively, increasing the duration of a specific stage of sleep may not be sufficient. Rather, microfeatures of sleep may need to be enhanced. For example, increasing slow oscillatory activity via transcranial Direct Current Stimulation during early sleep enhanced the retention of non-emotional episodic memories (Marshall et al., 2004). Importantly, transcranial Direct Current Stimulation did not influence the percentage of N3 sleep. Kaestner et al. (2013) compared the effects of two hypnotic drugs – zolpidem and sodium oxybate - on sleep and emotional memory. Only zolpidem was associated with enhanced retention of negative and highly arousing stimuli relative to the placebo. The beneficial effect of zolpidem on memory was attributed to the increased sleep spindle density during N2 sleep, rather than changes in the duration of specific stages of sleep. A potential avenue for future research is to examine whether diet influences microfeatures of sleep and, in turn, memory consolidation.

In contrast with previous research (Bueno-Lopez et al., 2021; Gais et al., 2007; Marshall et al., 2004), episodic memory did not improve after a night of sleep (Appendix 16). Furthermore, an unexpected emotional valence effect also occurred, whereby significantly more buffer words were forgotten overnight from the positive stories than both negative and neutral stories. There was also no difference in the number of words remembered overnight between the negative and neutral stories. This finding is somewhat surprising as both the negative and positive stories were rated as significantly more arousing, startling, and interesting than the neutral stories, factors known to influence the magnitude of the emotional valence effect (Gilson et al., 2015;

McGaugh, 2018). These ratings may reflect demand characteristics as the stories were clearly distinguishable in terms of valence (Ferentzi et al., 2022). Images, rather than stories, are typically used to measure sleep-dependent memory consolidation (Reid et al., 2022). Images are generally better remembered and elicit higher levels of arousal than words (Bayer & Schacht, 2014; Houwer & Hermans, 1994; Quinlan et al., 2010; Winkielman & Gogolushko, 2018). Future research may therefore benefit from administering image-based memory tasks rather the narrative-based memory tasks.

3.4.5 Subjective measures of sleep quality

The LSEQ (Parrott & Hindmarch, 1978) was used to assess subjective sleep quality approximately 20 minutes after awakening, whilst the ESS (Johns, 1991) was administered at 8pm the evening after each visit to measure daytime sleepiness. Results showed that differences in the GL of a pre-bedtime drink did not influence subjective sleep quality and daytime sleepiness. The effect of pre-bedtime diet on subjective measures of sleep has rarely been examined. Daniel et al. (2019) reported that the consumption of an evening meal and snack differing in GI did not influence daytime sleepiness which was measured immediately after awakening. Herrera (2010) reported that the consumption of a HGL meal was associated with increased levels of sleepiness 60 minutes after meal consumption. Afaghi et al. (2007) reported that subjective ratings of sleepiness were greater at bedtime after a HGL meal than LGL meal. These findings suggest that the timing of assessment may be important. In the present study, the ESS (Johns, 1991) was administered in the evening to determine whether differences in pre-bedtime GL influenced sleepiness levels throughout the subsequent day. Napping was only prohibited on the day of each visit. Therefore, if participants napped after leaving the laboratory, which was not recorded, any differences in daytime sleepiness levels may have been mitigated. In addition, large discrepancies between subjective and objective measures of sleep quality are frequently reported (Campanini et al., 2017; Klier & Wagner, 2022).

3.4.6 Limitations

The present study has several limitations that warrant discussion. The data were collected in an artificial sleep laboratory and therefore different effects may have occurred at home. In addition, although “lights off” occurred at a similar time for each participant on all three nights, it is unknown whether this time was similar to their habitual bedtime. As such, spuriously short or long SOLs may have occurred. Drinks were consumed approximately fifteen minutes before

bedtime, which disrupted some participants sleep as they needed to use the toilet facilities during the night. Although it is possible that a short duration between drink consumption and bedtime contributed to the percentage of wake during the night, it does not explain why the percentage of wake during the second half of the night differed significantly between drink conditions. The study was also underpowered, and this issue was compounded by the removal of outliers.

3.4.7 Recommendations for future research

The present study examined the effect of consuming drinks differing in GL fifteen minutes before bedtime. If the glycaemic nature of drinks is important, then it is likely that variations in the length of time between meal/drink consumption and bedtime will produce different results. Manipulating the timing of meal/drink consumption in relation to the stage of circadian rhythm may also produce different effects. In addition, given the second meal effect, future research could assess whether different effects occur when a LGL evening meal is consumed rather than a HGL evening meal. Females were excluded from the present study due to the impact of the menstrual cycle on metabolism, sleep, and sleep-dependent memory consolidation (Baker & Driver, 2007). Therefore, studies could explore whether the menstrual cycle also influences the effect of GL on sleep and memory. Future research would also benefit from making comparisons between pre-intervention, habitual sleep (e.g., using sleep diaries or actigraphy watches) and post-intervention sleep. Studies could examine whether the consumption of drinks differing in GL benefits sleep in clinical populations, which have largely been overlooked. Lastly, given that the consumption of a HGL breakfast only improved working memory in participants with poorer memory at baseline (Dye et al., 2010), future research could explore whether the effect of pre-bedtime nutrition on sleep-dependent memory consolidation is dependent upon baseline performance.

3.4.8 Conclusion

In conclusion, the findings suggest that more research is needed to determine whether certain stages of sleep may be affected by the consumption of drinks differing in GL shortly before bedtime. Here, the LGL drink was associated with a higher percentage of N3 sleep when the HGL drink was consumed first, but this did not survive Bonferroni correction (Figure 15). There was also a non-significant trend towards more REM sleep during the second half of the night after the HGL drink, but only in those who consumed the HGL drink first (Figure 19). It

is important for these findings to be interpreted within a context. The study was underpowered, outliers were removed from both analyses, and the systematic application of a Bonferroni correction may have artificially inflated the type 2 error rate. There is also biological plausibility for an effect of GL on N3 sleep and REM sleep, and the Bayesian analyses provided anecdotal and strong evidence in favour of an effect, respectively. However, it is clear that more research is needed for firm conclusions to be made. There was tentative evidence that measures of sleep fragmentation (wake percentage and WASO) were affected by the drinks. However, these finding should be interpreted with caution given their novelty. In contrast, sleep-dependent memory consolidation and subjective measures of sleep were not influenced by the experimental drinks. The implications of increasing the amount of time spent in a specific stage of sleep are difficult to assess, as there are negative metabolic consequences to reducing both N3 sleep and REM sleep (Gonnissen et al., 2013; Van Cauter et al., 2008). However, if replicated, pre-bedtime diet could be targeted in individuals deficient in N3 sleep or REM sleep.

Chapter 4

The chronic effects of cinnamon, turmeric, and curcumin supplementation on glycaemic control, cognition, lipids, inflammation, and mood.

4.1 Introduction

The prevalence of diabetes is expected to increase from 415 million to 642 million people by 2040, with T2DM accounting for 90% of diagnoses (Zheng et al., 2018). It is also estimated that more than 470 million people will have prediabetes by 2030 (Tabák et al., 2012). Individuals with T2DM and IGT are at an increased risk of Alzheimer's disease, cardiovascular disease, vascular dementia, and liver disease (El-Serag et al., 2004; Ford et al., 2010; Profenno et al., 2010; Rönnemaa et al., 2008). Therefore, there is an urgent need to identify safe and effective modifiable lifestyle strategies that facilitate optimal blood glucose levels. Bioactive polyphenolic compounds, which were introduced in Chapter 1, possess a wide range of beneficial health properties, such as anti-diabetic, anti-hyperlipidaemic, and anti-inflammatory effects (Costa et al., 2017; Kim et al., 2016; Sun et al., 2020). In the last two decades, numerous studies have examined the effects of cinnamon and turmeric on glycaemic control in those with T2DM, in particular, and IGT, whereas healthy populations remain relatively under researched.

As discussed in Section 1.5.2, cognitive impairments have been observed in individuals with T2DM and elevated blood glucose levels within the normal range (Awad et al., 2002; Craft et al., 1994; Messier et al., 2003; Palta et al., 2014; Vanhanen et al., 1998). Improvements in glycaemic control have led to improvements in cognition in patients with T2DM and IGT (Gradman et al., 1993; Luchsinger et al., 2011; Naor et al., 1997; Watson et al., 2006). Therefore, if supplementation with cinnamon and turmeric enhanced glycaemic control in healthy middle-aged and older adults, then improvements in cognition may also occur. This would have important implications for the prevention of cognitive decline (Seddon et al., 2019). Similarly, given the association between poorer GT and mood (Sommerfield et al., 2004; Young & Benton, 2014a, 2014b), improvements in mood may also ensue. In this chapter, the beneficial health effects of cinnamon and turmeric in healthy and clinical populations are reviewed, as well as the impact of these spices on cognition, mood, anthropometric measures, thirst, and hunger.

4.1.1 Cinnamon

Cinnamon is extracted from the inner bark of the *Cinnamomum* species. It is one of the oldest spices used in traditional Chinese and Ayurvedic medicine (Davis & Yokoyama, 2011). Although over 250 species have been identified, the majority of research has focused on *Cinnamomum cassia* due to its affordability (Medagama, 2015). In type 2 diabetics, chronic supplementation (ranging from 120 mg to 3 g per day for 1 to 4 months) with cinnamon lowered levels of fasting glucose, 2-hour postprandial glucose, HbA1c, and homeostatic model assessment for insulin resistance (HOMA-IR) (Akilen et al., 2010; Crawford, 2009; Lu et al., 2012; Mang et al., 2006; Mirmiranpour et al., 2020; Radhia et al., 2010; Sahib, 2016; Vafa et al., 2012). However, opposing findings have been reported (Blevins et al., 2007; Hasanzade et al., 2013; Suppapitiporn & Kanpaksi, 2006). Studies involving prediabetic patients have also produced mixed findings. For example, Wickenberg et al. (2014) reported that supplementation with 12 g of cinnamon per day for 12 weeks had no effect on HbA1c and fasting glucose. In contrast, fasting glucose and postprandial glucose (2-hours post-OGTT) improved after individuals with IGT consumed 500 mg of cinnamon per day for eight weeks (Anderson et al., 2016). Similarly, supplementing 1.5 g of cinnamon per day for twelve weeks improved fasting glucose, 2-hour glucose post-OGTT, and glucose AUC post-OGTT (Romeo et al., 2020). Discrepancies may be due to differences in the type of cinnamon used, strength of dosage, severity of diabetes/IGT, and presence of comorbidities. For example, larger effects tend to occur in those with poorer GT at baseline (Kirkham et al., 2009; Liu et al., 2015; Mang et al., 2006).

Few studies have explored the potential glucose-lowering effects of cinnamon in healthy populations (Table 12). Kizilaslan and Erdem (2019) reported that the consumption of 3 g of cinnamon *cassia* per day for 40 days lowered glucose levels post-breakfast, whereas the consumption of 6 g lowered both fasting and postprandial glucose levels. However, no changes in HbA1c levels were reported. For improvements in HbA1c to occur, it is recommended that cinnamon should be ingested for a minimum of two to three months as the life span of red blood cells is approximately 120 days (Medagama, 2015). In Solomon and Blannin (2009), participants ingested 3 g of cinnamon per day for two weeks. An OGTT was performed pre- and post-intervention. Cinnamon supplementation significantly reduced insulin AUC post-OGTT and 30-minute glucose post-OGTT. No changes in fasting glucose levels were reported. Conversely, Ranasinghe et al. (2017) reported that three months of Ceylon cinnamon

supplementation, which increased at monthly intervals (85 mg, 250 mg, and 500 mg), did not reduce fasting blood glucose levels. Similarly, Tang et al. (2008) reported no improvements in fasting glucose levels after one month of supplementation with 3 g of cinnamon *cassia* per day. These findings suggest that the effects of cinnamon in healthy adults may differ depending on the type of cinnamon administered, measure of glycaemia, length of intervention, and strength of dosage.

Cinnamon contains a range of polyphenols, such as flavonoids (e.g., cinnamaldehyde) and phenolic acids (e.g., dihydroxy-hydrocinnamic acid and eugenol), that act on different levels of the insulin-signalling pathway (Kim et al., 2016; Santos & da Silva, 2018). Indeed, out of 49 spices and herbs, cinnamon possessed the strongest insulin mimetic effect (Broadhurst et al., 2000). Cinnamon polyphenols increase glucose uptake by stimulating insulin secretion and upregulating the translocation and expression of GLUT 4 (Shen et al., 2014). Cinnamon enhances insulin sensitivity by inhibiting tyrosine phosphatase and increasing insulin receptor phosphorylation (Eijaz et al., 2014; Imparl-Radosevich et al., 1998). Cinnamaldehyde can repair pancreatic β-cells (Li et al., 2013) and increase glycogenesis by inhibiting glycogen synthase kinase 3β activity and activating glycogen synthase activity (Jarvill-Taylor et al., 2001). Cinnamon polyphenols have also been shown to reduce postprandial glycaemia by influencing the rate of carbohydrate digestion and absorption. For example, Adisakwattana et al. (2011) showed that eugenol inhibited α-glucosidase and pancreatic α-amylase activity, whilst Liu et al. (2023) found that a phenolic cinnamon extract inhibited glucose transport in the small intestine. In humans, the addition of cinnamon *cassia* to a high carbohydrate meal also delayed the rate of gastric emptying (Hlebowicz et al., 2007) and increased the secretion of GLP-1 (Hlebowicz et al., 2009).

Changes in lipid metabolism and inflammation may also lead to improvements in glycaemic control, and vice versa. Indeed, elevated triglyceride levels can induce inflammation, leading to insulin resistance and β-cell dysfunction (Haffner, 2003; Wu & Ballantyne, 2017). With regards to lipid profiles, a meta-analysis of 10 randomised controlled trials in type 2 diabetics revealed that cinnamon supplementation (0.12 to 6 g per day for 4 to 18 weeks) significantly reduced levels of total cholesterol, LDL-cholesterol, and triglycerides, and increased levels of HDL-cholesterol (Allen et al., 2013). However, inconsistent effects have been reported in prediabetic and healthy populations (Table 12). Anderson et al. (2016) reported that total cholesterol and LDL-cholesterol levels were reduced in prediabetic patients after two months of cinnamon supplementation (500 mg per day), whereas Wickenberg et al. (2014) reported no

improvements in lipid profiles after 12 weeks of cinnamon supplementation (12 g per day). In healthy adults, Tang et al. (2008) reported that four weeks of supplementation with 3 g of cinnamon did not improve lipid profiles. Conversely, Ranasinghe et al. (2017) reported a significant reduction in total cholesterol levels and LDL-cholesterol levels after three months of cinnamon supplementation. Improvements in biomarkers of inflammation, such as c-reactive protein (CRP) and malondialdehyde, have been reported following chronic supplementation with cinnamon in individuals with T2DM or IGT (Zhu et al., 2020). To the best of the authors knowledge, only one study has examined the chronic effects of cinnamon in healthy participants. Mashhadi et al. (2013) reported that six weeks of supplementation with 3 g of cinnamon resulted in a significant reduction in interleukin-6 levels in female athletes. However, it is important to note that baseline interleukin-6 levels in the cinnamon group were within the clinical range.

In *vivo* and in *vitro* studies have highlighted several mechanisms of action underlying the anti-hyperlipidaemic and anti-inflammatory effects of cinnamon. For example, cinnamate can reduce cholesterol synthesis by inhibiting hepatic β-hydroxy-β-methylglutaryl-Coenzyme A reductase activity, which is the same pathway that statins target (Abeysekera et al., 2022; Lee et al., 2003). Cinnamon polyphenols can also decrease the digestion of fat into free fatty acids and glycerol by inhibiting the activity of pancreatic lipase activity, and the absorption of cholesterol by inhibiting the activity of pancreatic cholesterol esterase (Abeysekera et al., 2022; Silva et al., 2022). With regards to inflammation, both cinnamaldehyde and eugenol inhibited the secretion of pro-inflammatory cytokines and increased the activity of antioxidant enzymes (Mateen et al., 2019). Taken together, animal studies provide strong support for the anti-hyperlipidaemic, anti-diabetic, and anti-inflammatory effects of cinnamon, and these effects have been substantiated by randomised controlled trials in type 2 diabetics. However, the potential health effects of cinnamon in healthy populations requires further clarification.

Table 12. Summary of studies examining the effects of cinnamon on glucose levels, lipid profiles, or inflammation in healthy populations.

Author (year)	Study characteristics	Nutritional intervention	Outcome measures	Results
Kizilaslan and Erdem (2019)	41 adults, mean age = 37.95 years, BS design, group allocation depended on participants daily cinnamon consumption (non-randomised).	40-day intervention using ground cinnamon *cassia* which was mixed with apples and milk: 1. 1 g/day 2. 3 g/day 3. 6 g/day	Fasting glucose, postprandial glucose (2-hours post-breakfast), HbA1c, and BMI. Data collected at baseline and 20- and 40-day follow-up.	Fasting glucose = declined from baseline in the 6 g/day group after 40 days but not 20 days. Postprandial glucose = declined from baseline in all 3 groups after 40 days but not 20 days.
Mashhadi et al. (2013)	49 healthy athletes, median age = 17.58 years (age range = 13-25 years), BS design, randomised, double-blind.	6-week intervention: 1. 3 g/day ginger 2. 3 g/day cinnamon 3. Placebo	Interleukin-6 levels. Data collected at baseline and 6-week follow-up.	Interleukin-6 levels = declined from baseline to the follow-up visit in both active groups. Larger decline in both active groups compared to the placebo group.
Solomon and Blannin (2009)	8 males, mean age = 25.1 years, WS design, 2-week washout period, single-blind.	14-day intervention using cinnamon *cassia* capsules: 1. 3 g/day 2. Placebo	Fasting glucose and OGTT profiles. Data collected at baseline and after 1, 14, 16, 18, and 20 days.	30-minute glucose and insulin levels = lower after 14 days of consuming the active supplement than placebo supplement.

				Insulin responses to OGTT = AUC lower after 14 days of consuming the active supplement compared to baseline. Insulin sensitivity = improved after 14 days of consuming the active supplement compared to baseline.
Ranasinghe et al. (2017)	28 adults, mean age = 38.8 years, BS design, non-randomised.	1-month intervention using cinnamon *zeylanicum* capsules. Dosage increased at monthly intervals: 1. 85 mg/day 2. 250 mg/day 3. 500 mg/day	Fasting glucose, lipid profiles, weight, waist and hip circumference, and BMI. Data collected at baseline and 1-, 2-, and 3-months follow-up.	Total cholesterol = decline after 3 months of supplementation compared to baseline. LDL-cholesterol = decline after 3 months of supplementation compared to baseline. Hip circumference = decline after 1 and 3 months of supplementation compared to baseline.
Tang et al. (2008)	11 adults, mean age = 27.6 years, WS design, randomised.	1-month intervention using cinnamon *cassia* or turmeric capsules (results reported in Table 13): 1. 3 g/day of cinnamon 2. 2.8 g/day of turmeric	Fasting glucose, total cholesterol, and triacylglycerol levels.	No significant changes in any outcome measure.

	Data collected at baseline and 1 month follow-up.

BS = between-subjects, WS = within-subjects, HbA1c = haemoglobin A1C, HOMA-IR = homeostatic model assessment for insulin resistance, BMI = body mass index, LDL = low density lipoprotein, OGTT = oral glucose tolerance test,

4.1.2 Turmeric

Turmeric (*Curcuma longa)* is a member of the ginger family that has traditionally been used for flavouring, colouring, and medicinal purposes in Asia for over 2500 years (Wickenberg et al., 2010). Approximately 2 to 6% of turmeric is made up of polyphenolic curcuminoids which possess anti-diabetic, anti-hyperlipidaemic, and anti-inflammatory properties (Singletary, 2020). The three main curcuminoids are bisdemethoxycurcumin (3 to 6%), demethoxycurcumin (17%), and curcumin (77%). Most research has focused on curcumin as it is the most bioactive and abundant curcuminoid (Singletary, 2020). Turmeric also contains essential oils (3 to 7%), such as α-turmerone and *ar*-turmerone, which have received less scientific interest but possess similar biological properties to curcuminoids (Zhang & Kitts, 2021). For example, in *vivo* and in *vitro* studies have shown that both curcuminoids and *ar*-turmerone inhibited the activity of α-glucosidase and pancreatic α-amylase, with bisdemethoxycurcumin exerting the strongest effect on α-glucosidase (Kalaycıoğlu et al., 2017). Curcuminoids can also reduce blood glucose levels by stimulating the secretion of GLP-1, increasing cellular glucose uptake and glycogenesis, and decreasing glycogenolysis and gluconeogenesis (Fujiwara et al., 2008). Curcumin has been shown to reduce lipogenesis and adipogenesis and modulate the activity of enzymes involved in lipid homeostasis such as hepatic *β*-hydroxy-*β*-methylglutaryl-Coenzyme A reductase activity and fatty acid synthase (Jang et al., 2008). Additionally, curcumin may lower triglyceride and cholesterol levels by mitigating lipogenic gene expression (Kang & Chen, 2009).

A meta-analysis of randomised controlled trials involving patients with metabolic diseases revealed that supplementation with turmeric or curcuminoids significantly reduced fasting blood glucose levels, HbA1c levels, and HOMA-IR levels (Yuan et al., 2022). Beneficial effects on postprandial glycaemia, lipid profiles, and inflammation have also been reported in patients with IGT or T2DM (Adab et al., 2013; Adibian et al., 2019; Na et al., 2013; Neta et al., 2021). The effects of turmeric supplementation in healthy adults are less consistent (Table 13). To the best of the authors knowledge, no study has reported an improvement in CRP levels or measures of glycaemic control following turmeric or curcumin supplementation in healthy adults (Cox et al., 2015; Cox et al., 2020; Nieman et al., 2012; Oza, 2017; Tang et al., 2008). Unexpectedly, Cox et al. (2020) reported that fasting glucose levels were higher in the active group (400 mg/day of Longvida™ curcumin) than placebo group at the 3-month follow-up visit, whilst DiSilvestro et al. (2012) reported that myeloperoxidase levels increased in the

active group (80 mg/day of Longvida™ curcumin) from baseline to the 1-month follow-up visit. Several studies have, however, reported improvements in lipid profiles. For example, one week of supplementation with 500 mg of curcuminoids decreased total cholesterol and triglyceride levels (Pungcharoenkul & Thongnopnua, 2011), whilst one week of supplementation with 500 mg of curcumin decreased total cholesterol levels and increased HDL-cholesterol levels (Soni & Kutian, 1992). Four weeks of supplementation with Longvida™ curcumin improved triglyceride levels (DiSilvestro et al., 2012) and LDL-cholesterol and total cholesterol levels (Cox et al., 2015). Differences in the type of supplement administered (e.g., powdered turmeric or isolated curcumin), bioavailability of curcumin, strength of dosage, duration of intervention, and baseline characteristics may account for the inconsistent findings (Karandish et al., 2021).

Table 13. Summary of studies examining the effects of turmeric/curcumin on glucose levels, lipid profiles, or inflammation in healthy populations.

Author (year)	Study characteristics	Nutritional intervention	Outcome measures	Results
Cox et al. (2015)	60 adults, mean age = 68.5 years, BS design, randomised, double-blind.	Acute (1- and 3-hours post-consumption), chronic (1 month), and acute-on-chronic (1 and 3 hours post-consumption after 1 month of supplementation) using capsules: 1. 400 mg/day of Longvida™ curcumin 2. Placebo	Fasting glucose, lipid profiles, and inflammatory markers (CRP, interleukin 1β, interleukin 6, and tumour necrosis factor α). Data collected at baseline and 1 month follow-up.	Total cholesterol and LDL-cholesterol = lower at the 1-month follow-up in the active group.
Cox et al. (2020)	85 adults, mean age = 68.6 years, BS design, randomised, double-blind.	3-month intervention using capsules: 1. 400 mg/day of Longvida™ curcumin 2. Placebo	Fasting glucose, lipid profiles, and inflammatory markers (CRP, interleukin 1β, interleukin 6, protein carbonyls, and tumour necrosis factor α).	Fasting glucose = higher in the active group at the 3-month follow-up.

			Data collected at baseline and 1 and 3 month follow-up.	
DiSilvestro et al. (2012)	38 adults, mean age = 48.05 years, BS design.	1-month intervention using capsules: 1. 80 mg/day of Longvida™ curcumin 2. Placebo	Lipid profiles and inflammatory markers (CRP, ceruloplasmin, and myeloperoxidase). Data collected at baseline and 1 month follow-up.	Triglycerides = declined from baseline to follow-up, but only in the active group. Myeloperoxidase = increased from baseline to follow-up, but only in the active group (suggested to reflect strengthened cellular immune function rather than an inflammatory response).
Esmaily et al. (2015)	30 obese adults, mean age = 38.33, WS design, randomised, 2-week washout-period	1-month intervention using capsules: 1. 1 g/day curcumin 2. Placebo	BMI and weight. Data collected at baseline and at the 4-, 6-, and 10-week follow-up visits.	No significant changes in BMI or weight.
Nieman et al. (2012)	61 obese/overweight females, mean age = 56.7 years, WS design, randomised, double-blind.	1-month intervention using capsules: 1. 1 g/day red pepper spice 2. 2.8 g/day turmeric 3. Placebo	Fasting glucose, inflammatory markers (7 inflammatory cytokines and CRP), weight, and body fat percentage.	No significant changes in any outcome measure.

			Data collected at baseline and at each 1-month follow-up.	
Oza (2017)	8 female adults, mean age = 24.8 years, WS design, randomised, double-blind, 5-week washout-period.	3-week intervention using capsules: 1. 500 mg/day of turmeric 2. Placebo	Fasting glucose and insulin, and 2-hour glycaemic responses to a high carbohydrate breakfast. Data collected at baseline and 3-week follow-up.	No significant changes in any outcome measure.
Pungcharoenkul and Thongnopnua (2011)	24 adults, mean age = 29.3 years, BS design, randomised, double-blind.	1-week intervention using capsules: 1. 500 mg/day of curcuminoids 2. 6 g/day of curcuminoids 3. 200 IU/day of vitamin E	Lipid profiles Data collected at baseline and 1-week follow-up.	Total cholesterol and triglycerides = declined from baseline to 1-week follow-up in those who consumed 500 mg/day. Smaller, but significant, decline in those who consumed 6 g/day.
Soni and Kutian (1992)	10 adults, age range = 24-45 years, non-randomised, no placebo condition.	1-week intervention using capsules: 1. 500 mg/day of curcumin	Lipid profiles and weight. Data collected at baseline and 1-week follow-up.	HDL-cholesterol = increased from baseline to 1-week follow-up. Total cholesterol = decreased from baseline to 1-week follow-up.

Tang et al. (2008)	11 healthy participants, mean age = 27.6 years, WS design, randomised.	1-month intervention, using turmeric or cinnamon *cassia* capsules (results reported in Table 12): 1. 3 g/day of cinnamon 2. 2.8 g/day of turmeric	Fasting glucose, total cholesterol, and triacylglycerol levels. Data collected at baseline and 1 month follow-up.	No significant changes in any outcome measure.

BS = between-subjects design, WS = within-subjects design, CRP = c-reactive protein, LDL = low density lipoprotein,

4.1.3 Cognition and mood

As previously stated, improvements in glycaemic control following chronic supplementation with cinnamon and turmeric could lead to improvements in cognition and mood. However, cinnamon and turmeric possess many other biological properties that may also enhance cognition and mood. In *vivo* and in *vitro* studies have reported that curcumin promotes neurogenesis and neuronal plasticity (Ma et al., 2022; Tiwari et al., 2014) and reduces amyloid and tau aggregation (Mutsuga et al., 2012). The latter finding has been replicated in healthy adults following 18 months of curcumin supplementation (Small et al., 2018). Cinnamon and turmeric can reduce biomarkers of inflammation and oxidative stress, both of which are related to the pathogenesis of dementia and mood disorders (Small et al., 2018; Zhu et al., 2020). Cinnamaldehyde has been shown to protect against endothelial dysfunction under hyperglycaemic and hyperlipidaemic conditions (Dong et al., 2014; Wang et al., 2015), whereas curcumin can improve cerebral blood flow (Awasthi et al., 2010).

To the best of the authors knowledge, no studies have examined the chronic effects of cinnamon supplementation on cognition or mood. In contrast, improvements have been reported following both acute and chronic supplementation with turmeric/curcumin (Table 14). For example, Lee et al. (2014) reported that the addition of turmeric, but not cinnamon, to a high carbohydrate breakfast improved postprandial working memory in prediabetic older adults, especially in those with the highest level of insulin resistance and body fat. Esmaily et al. (2015) reported that one month of curcumin supplementation (1 g) improved anxiety in obese adults. An 18-month randomised controlled trial by Small et al. (2018) reported that Theracurcumin™ (180 mg) improved verbal memory, attention, and depression scores in adults without dementia, and reduced amyloid and tau accumulation in the amygdala and hippocampus. In cognitively intact older adults, Cox et al. (2015) also reported that Longvida™ curcumin (400 mg) improved postprandial working memory and attention, whilst four weeks of supplementation lowered levels of fatigue and improved working memory. A follow-up study by the same authors reported that various aspects of mood were improved after one month of ingesting Longvida™ curcumin, whilst spatial and working memory improved after three months (Cox et al., 2020). Conversely, a 12-month randomised controlled trial involving healthy older adults found that curcumin supplementation did not improve cognition (Rainey-Smith et al., 2016). However, there was a significant decline in cognition in the placebo group, suggesting that curcumin may preserve cognitive function over time. A large percentage of

participants withdrew from the study due to gastrointestinal complaints, which may have contributed to the non-significant findings. Together, the evidence suggests that turmeric/curcumin offers a promising strategy for improving cognition and mood in healthy and prediabetic adults.

Table 14. Summary of studies examining the acute and chronic effects of turmeric or cinnamon on cognition or mood.

Author (year)	Study characteristics	Nutritional intervention	Outcome measures	Results
Cox et al. (2015)	60 healthy adults, mean age = 68.5 years, BS design, randomised, double-blind.	1-month intervention using capsules: 1. 400 mg/day of Longvida™ curcumin 2. Placebo Also examined acute effects (1- and 3-hours post-consumption) and acute-on-chronic effects (1- and 3-hours post-consumption after 1 month of supplementation).	Cognition = word list recall (episodic memory), picture recognition (visual memory), serial subtractions task (working memory), arrow flankers task and digit vigilance task (attention), and rapid visual information processing task and reaction time task (information processing speed). Mood = general mood (DASS-21), general fatigue (CFS), and state mood/fatigue (VAS – before and after cognitive test battery). Data collected at baseline and 1 month follow-up.	Working memory = better postprandial scores (1 hour) and post-intervention scores (chronic) in the active group on the easiest level of the task. Attention (digit vigilance task) = better postprandial scores (1 hour) in the active group. General fatigue = larger decline from baseline to follow-up in the active group. State fatigue = declined from baseline to follow-up in the active group but increased in the placebo group.

Cox et al. (2020)	85 healthy adults, mean age = 68.6 years, BS design, randomised, double-blind.	3-month intervention using capsules: 1. 400 mg/day of Longvida™ curcumin 2. Placebo	Cognition = serial subtractions task (working memory), arrow flanker task and DATT (attention), and vMWM task (spatial learning/memory). Mood = general mood (POMS, PSS, and GHQ-28), general fatigue (CFS), and state mood/fatigue (VAS – before and after cognitive test battery). Data collected at baseline and 1- and 3-month follow-up.	POMS = fatigue/inertia ratings were lower at both follow-up visits in the active group, whilst tension/anxiety, confusion/bewilderment, and anger/hostility ratings were lower at the 1-month follow-up. Spatial learning/memory = better performance at the 3 month follow-up in the active group. Working memory = better performance on the hardest level of the serial subtractions task at the 3-month follow-up in the active group.
Esmaily et al. (2015)	30 obese adults, mean age = 38.33 years, WS design, randomised, 2-week washout-period.	1-month intervention using capsules: 1. 1 g/day curcumin 2. Placebo	Mood = symptoms of anxiety (BAI) and depression (BDI).	Anxiety = lower scores at final follow-up visit after consuming the active supplement than placebo supplement.

			Data collected at baseline and 4-, 6-, and 10-week follow-up visits.	
Lee et al. (2014)	48 adults with IGT, mean age = 73.2 years, BS design, randomised, double-blind.	Acute intervention. One of four capsules consumed in conjunction with a standardised breakfast: 1. 1 g/day turmeric 2. 2 g/day cinnamon *cassia* 3. 1 g/day turmeric and 2 g/day cinnamon *cassia* 4. Placebo	Cognition = n-back task (working memory). Data collected at baseline and 6 hours post-breakfast.	Working memory = larger improvement from pre- to post-breakfast after the consumption of turmeric compared to the placebo.
Rainey-Smith et al. (2016)	96 healthy adults, mean age = 66 years, BS design, randomised, double-blind.	12-month intervention using capsules: 1. 1500 mg/day Biocurcumax™ 2. Placebo	Cognition = MoCA (general cognitive function), episodic memory (RAVLT), verbal fluency (semantic memory), WAIS-R (psychomotor speed), CogState battery (working memory, executive function, and visual memory).	General cognitive function scores = declined in the placebo group after 6 months but not the active group.

			General mood (DASS). Data collected at baseline and 6- and 12-month follow-up.	
Santos-Parker et al. (2018)	39 healthy adults, mean age = 62.2 years, BS design, randomised, double-blind.	3-month intervention using capsules: 1. 2000 mg/day of Longvida™ curcumin 2. Placebo	Cognition = NIH Toolbox-Cognition Battery (working memory, attention, executive function, episodic memory, and processing speed) Data collected at baseline and 3-month follow-up.	No significant changes in any outcome measure.
Small et al. (2018)	40 healthy adults, mean age = 63.1 years, BS design, randomised, double-blind.	18-month intervention using capsules: 1. 180 mg/day Theracurcumin™ 2. Placebo	Cognition = Buschke SRT (episodic memory), BVMT-R (visual memory), and Trails Part A (attention)	Episodic memory and attention = significantly improved from baseline to 18 months in the active group but not the placebo group. Depression scores = significantly improved from baseline to 18 months in the active group only.

	Mood = symptoms of depression (BDI). Data collected at baseline and 6- and 18-month follow-up.	Amyloid and tau accumulation in the amygdala and hippocampus also significantly declined in the active group.

BS = between-subjects, WS = within-subjects, DATT = Divided Attention Tracking Task, NASA-TLX = NASA Task Load Index, VAS = visual analogue scales, PSQI = Pittsburgh Sleep Quality Index, GHQ = General Health Questionnaire, PSS = Perceived Stress Scale, POMS = Profile of Mood States, CFS = Chalder Fatigue Scale, BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, WAIS-R = Wechsler Adult Intelligence Scale revised, RAVLT = Rey Auditory Verbal Learning Test, MoCA = Montreal Cognitive Assessment, vMWM = virtual Morris Water Maze, BVMT-R = Brief Visual Memory Test-Revised, SRT = Selective Reminding Test,

4.1.4 Sensations of hunger and thirst

Significant reductions in BMI and body fat percentage have been observed following chronic supplementation with cinnamon and turmeric/curcumin (Mousavi et al., 2020; Qin et al., 2010; Yazdanpanah et al., 2020). However, opposing findings have been reported (Esmaily et al., 2015; Kizilaslan & Erdem, 2019; Nieman et al., 2012; Ranasinghe et al., 2017; Soni & Kutian, 1992). Though speculative, changes in BMI and body fat percentage over time may reflect changes in subjective sensations of appetite and thirst. For example, Zanzer et al. (2017) administered drinks containing individual spices, including turmeric or cinnamon, prior to a high glycaemic breakfast. Ratings of appetite were taken several times throughout the postprandial period. Both cinnamon and turmeric lowered ratings of 'prospective consumption' throughout the morning, whereas only turmeric lowered ratings of 'desire to eat'. The turmeric drink also significantly increased plasma peptide tyrosine tyrosine, which was not measured after cinnamon intake. Peptide tyrosine tyrosine is a gut hormone that has been shown to reduce energy intake and hunger sensations when administered intravenously to humans (De Silva & Bloom, 2012). Haldar et al. (2018) reported that the consumption of a curry containing a mixture of spices, including both cinnamon and turmeric, was associated with a reduction in postprandial appetite compared to a control meal. Conversely, Hlebowicz et al. (2009) reported that the addition of cinnamon to a carbohydrate challenge increased GLP-1 concentrations, which also has appetite suppressing effects, but had no impact on self-reported hunger. Markey et al. (2011) and Chezem et al. (2013) also reported that cinnamon ingestion did not influence self-reported ratings of hunger and thirst and ad libitum food intake. However, no studies have examined the chronic, combined effect of cinnamon and turmeric on sensations of hunger and thirst, which may yield larger effects.

4.1.5 Summary

The chronic effects of cinnamon and turmeric on indices of GT, including fasting glucose, OGTT profiles, and HbA1c percentage, have frequently been investigated in type 2 diabetics. Similarly, numerous studies have examined the effects of cinnamon and turmeric on lipid and CRP levels in those with T2DM. However, few studies have been conducted in healthy populations and the findings are inconsistent. Studies examining the acute and chronic effects of turmeric/curcumin on cognition and mood have produced promising results in healthy individuals, whereas the chronic effects of cinnamon on these measures have not yet been

examined. Previous literature has also shown that cinnamon and turmeric/curcumin can improve anthropometric measures, including BMI and body fat percentage. Acute studies have also demonstrated positive effects of cinnamon and turmeric on appetite-related hormones, whereas inconsistent effects have been demonstrated using self-report measures of appetite and thirst. To date, most studies have administered cinnamon and turmeric in isolation. Whilst it is important to understand their individual effects, particularly from a mechanistic perspective, spices are usually consumed in combination in everyday life. Multiple pathways may be targeted by co-ingesting cinnamon and turmeric/curcumin, and synergistic or additive beneficial effects may ensue. For example, co-administration of turmeric and black seeds for four weeks improved fasting blood glucose and LGL cholesterol, whereas consuming black seeds and turmeric alone did not (Amin et al., 2015). Studies have also generally administered turmeric or curcumin in isolation. However, co-ingesting turmeric and curcumin enhances the bioavailability of curcumin (Nasef et al., 2019) and provides a broader spectrum of bioactive compounds (de Melo et al., 2018).

4.1.6 Aims of polyphenol study

The aim of this study was to investigate the combined effect of supplementing with cinnamon and turmeric/curcumin for three months in apparently healthy middle-aged and older adults. Primary outcome measures included indices of GT (fasting glucose, OGTT profiles, and HbA1c) and cognition (working memory, episodic memory, attention, and psychomotor speed). Secondary outcome measures included lipid profiles (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides), CRP levels, self-reported mood, hunger, and thirst, BMI, and body fat percentage.

Primary hypotheses:

1. The active group will display larger improvements in measures of GT (fasting glucose, OGTT profiles, and HbA1c) than the placebo group.
2. The active group will display larger improvements in cognitive performance than the placebo group.

Secondary hypothesis:

Due to a lack of prior literature, there were no hypotheses for the following secondary outcome measures: CRP levels, BMI, body fat percentage, and self-reported mood, hunger, and thirst.

However, there was sufficient prior research to formulate the following hypothesis for lipid profiles:

1. The active group will display larger improvements in lipid profiles than the placebo group.

Post-hoc exploratory analysis:

Due to the unexpected heterogeneity in baseline indices of GT between participants, the following post-hoc exploratory analysis was performed:

1. The effect of supplementation on indices of GT will be influenced by individual differences in GT at baseline.

4.2 Methods

4.2.1 Participants

Thirty participants were initially recruited. However, two participants were excluded from the study because their baseline triglyceride levels were extremely high. This resulted in a total sample size of 28 (mean age = 64.14 years, SD = 7.8, and age range = 51 to 79 years). An equal number of males and females took part in the study. Participants were recruited using posters and online advertisements. Exclusion criteria included the following: current smoker, a diagnosis of type 1 or 2 diabetes or use of medication to control blood glucose levels, chronic liver or kidney disease, gastrointestinal disease, cardiovascular disease, or a history of neuropsychological disease. Participants had normal, or corrected-to-normal, hearing and eyesight. Seven participants were taking medication for asthma, two for blood pressure, six for cholesterol, two for allergies, one for pain relief, and one for hormone replacement therapy. Baseline BMI scores indicated that eight participants were underweight, 15 participants were normal weight, and five participants were overweight. Ethical approval was granted by the Psychology Ethics Committee at Swansea University. Written informed consent was obtained from all participants prior to testing (Appendix 17 and 18). Participants were paid £200 for taking part in the study.

4.2.2 Design

A between-subjects, randomised, double-blind, and placebo-controlled design was used. Participants attended the Psychology laboratory on four separate occasions, with

approximately 30 days between each session. Participants were randomly assigned to the placebo group (n = 15) or active group (n = 13) using a computer-generated randomisation list.

4.2.3 Nutritional intervention

Both the active and placebo group were instructed to take four tablets per day for three months - two tablets with breakfast and two with an evening meal. The active supplements were provided by NeoLife International and are commercially available in the USA under the name NeoLife Botanical Balance. Four active supplements contained 1 g of cinnamon (Cinnamomum *cassia* bark extract), 200 mg of curcumin (curcuma longa L extract), 200 mg of turmeric (curcuma longa L extract), 40 µg of chromium, and 50 mg of alpha-lipoic acid. Four placebo supplements contained 100 mg of stearic acid, 27 mg of tricalcium phosphate, 288 mg of rice flour, 109 mg of oat fibre, 86 mg of barley flour, 52 mg of Arabic gum, 40 mg of apple pectin, 40 mg of carrageenan, 43 mg of soya fibre, 16 mg of orange fibre, and 2.8 mg of apple fibre. The placebo supplements were identical in size, colour, and shape to the active supplements. Participants received a 4-week supply of supplements during the first, second, and third visit. Supplement bottles were identical and labelled with a contact number if needed. Compliance was measured by asking participants at the beginning of each session if they had adhered to the instructions. Supplements were consumed the night before visit 2, 3, and 4 hence it may be assumed that any changes reflected chronic consumption as opposed to acute consumption.

4.2.4 Cognitive test battery

At the time that this study was designed, few studies had examined the effects of turmeric/curcumin on cognition, and no studies had examined the effects of cinnamon on cognition. As there was no evidence that the effects of turmeric/curcumin on cognition were domain-specific, an inclusive approach was taken when designing the cognitive test battery. Turmeric/curcumin had previously been shown to improve working memory (Cox et al., 2015; Lee et al., 2014), episodic memory (Small et al., 2018), and attention (Cox et al., 2015; Small et al., 2018) hence these cognitive domains were assessed in the present study. Working memory was assessed using the n-back task, which was used by Lee et al. (2014), and the letter-number sequencing task. These tasks were chosen as they are less influenced by mathematical skill than the serial subtraction task which was used by Cox et al. (2015). The cognitive tasks administered in the present study have also been shown to be sensitive to the effects of

nutrition, including breakfast composition (Cooper et al., 2012; Ginieis et al., 2018; Nabb & Benton, 2006a, 2006b).

4.2.4.1 Episodic memory

Immediate and delayed episodic memory was measured using a word list recall task (Appendix 19). Four lists of 30 words were matched for the number of syllables, image ability, and frequency with which they occur in English. As participants completed the memory task twice during each visit, the word lists were split so that the same two lists were viewed on visit 1 and 3, and the other two lists on visit 2 and 4. This meant that there was a two-month gap between viewing the same word list. During the immediate recall task, participants viewed one word on-screen for three seconds, directly followed by the next word. Immediately after viewing the list of words, participants were given five minutes to write down as many words as possible in any order. Delayed episodic memory was assessed 30 minutes later. The total number of words correctly recalled during the immediate and delayed memory tasks were recorded.

4.2.4.2 Working memory

The n-back task consisted of three levels (0-back, 1-back, and 2-back). Participants completed two blocks per level. Within each block, participants viewed a sequence of letters (e.g., A, F, K, P) which were presented on-screen, individually, for 1.5 seconds. A total of 47 letters were presented within each block, of which six were targets. On the 0-back level, participants were instructed to press the space bar when they saw the letter 'A'. On the 1-back level, participants pressed the space bar when the current letter matched the letter that preceded it. On the 2-back level, participants pressed the space bar when the current letter matched the letter that appeared two trials prior. Participants were instructed to respond as quickly, and accurately, as possible. Stimuli were continuously presented on-screen until the block ended. Breaks were permitted between each block if required. Using only correct trials, the total number of responses and mean reaction times per level were calculated.

The letter-number sequencing task is a subset of the Wechsler Adult Intelligence Scale (Wechsler, 1997). In this task, participants were presented with a series of random letters and numbers (e.g., L, K, 1, 7) via headphones. Immediately after hearing the list, participants were required to mentally rearrange the list so that numbers were recalled first in ascending order, followed by letters in alphabetical order (e.g., 1, 7, K, T). Responses were typed using a keyboard. The task began with one letter and one number and increased to a maximum of four

letters and four numbers. Letters were always presented first within each list, and there was no time limit for responding. After correctly completing three trials, the length of the list increased by either one number or letter. The task terminated when three trials were completed incorrectly. Participants were given a single score, ranging from 0 to 8, which corresponded to the length of the last string which was answered correctly before the task ended.

4.2.4.3 Selective attention

A modified version of the arrow flanker task (Eriksen & Eriksen, 1974) was used to measure the ability to focus attention and ignore peripheral information. Participants were required to indicate whether the middle arrow was pointing to the right or left by pressing the corresponding button on a keyboard. Either side of the central arrow were two distractors. In the congruent (easiest) condition, the distractors were pointing in the same direction as the target arrow (>>>>>), whereas in the incongruent (hardest) condition the arrows were pointing in the opposite direction (>><>>). There was also a neutral (intermediate) condition, whereby participants were told to respond as normal (□□<u>≤</u>□□), and an inhibition condition (XX<XX) whereby participants were told to withhold any response. A stimulus remained on screen for 1.8 seconds or until a key was pressed. There was a randomly varying inter-stimulus interval of between 1 and 3 seconds. Participants viewed 60 congruent trials, 60 incongruent trials, 30 neutral trials, and 30 inhibition trials. Stimuli were presented pseudo-randomly, and participants completed a practice trial before beginning. Only correct responses were included in the analyses, and the test was scored as the mean percentage of correct responses and mean reaction times in milliseconds for congruent and incongruent trials. In addition, the mean percentage of correct response for inhibition trials were also analysed.

4.2.4.4 Simple and choice reaction times

The simple and choice reaction times task measured processing speed. Eight lamps were arranged in a semicircle, approximately 5.5 inches from a central (home) button. Beneath each lamp was a large blue button. To start the task participants placed their index finger on the home button which triggered a warning signal within one to two seconds. After a random interval of 1 to 4 seconds, a single lamp illuminated. Participants were instructed to extinguish the lamp as quickly as possible by pressing the button directly below the lamp, using the same hand that was placed on the home button. The first 20 trials illuminated the same lamp, which measured simple reaction times. The remaining 20 trials illuminated any one of the eight lamps, which measured choice reaction times. Movement times were scored as the time taken to leave

the home button and press the button below the illuminated light. Decision times were scored as the delay between the light illuminating and the hand being removed from the home button.

4.2.5 Mood

4.2.5.1 Visual analogue scales

Changes in mood throughout the morning of testing were measured using six 100mm VAS anchored by pairs of mood-related adjectives: Agreeable-Hostile, Confused-Clearheaded, Composed-Anxious, Depressed-Elated, Confident-Unsure, and Tired-Energetic. These adjectives corresponded to the six scales of the Profile of Mood States (POMS) questionnaire (McNair et al., 1981). Participants were instructed to report how they felt "at this moment" by placing an "X" on each of the scales. Scores ranged from 0 to 100 and were calculated by measuring the distance from the negative anchor to where the "X" was marked. Higher scores indicated a more positive mood state. Mood was measured at the start of each session and 30, 60, 90, 120, 150, and 180 minutes after consuming the glucose drink (Appendix 20).

4.2.5.2 Profile of Mood States-Bipolar

The POMS-Bipolar (POMS-BI) (Lorr & McNair, 1988) was used to assess changes in mood between each visit (Appendix 22). The questionnaire contained 72 mood adjectives grouped into six bipolar scales: Agreeable-Hostile, Confused-Clearheaded, Composed-Anxious, Depressed-Elated, Confident-Unsure, and Tired-Energetic. Participants were instructed to rate how they felt during the past month, using a 4-point Likert scale: much unlike this (0), slightly unlike this (1), slightly like this (2), and much like this (3). Six scores were calculated corresponding to the six scales. The maximum score is 36, with higher scores indicating more positive mood states.

4.2.6 Thirst and hunger

Two 100cm VAS were used to measure thirst and hunger and were administered at the same time as the mood VAS (Appendix 20). Participants were asked to report how hungry and thirsty they felt "at this moment" using a VAS ranging from not at all (0) to extremely (100). Higher scores reflected stronger feelings of hunger and thirst.

4.2.7 Biochemical measures

All biochemical assessments were made using capillary whole blood collected via finger pricks.

4.2.7.1 Glucose tolerance

Fasting and OGTT profiles were measured using an Accu-Chek Performa Nano device (Mannheim, Germany). The OGTT consisted of 75 g of glucose, which was dissolved in approximately 280 ml of water. Participants were instructed to consume the glucose load within five minutes, and blood glucose levels were measured 30, 60, 90, 120, 150, and 180 minutes thereafter. Fasted HbA1c was measured using a EUROLyser CUBE (EUROLyser Diagnostica GmbH, Salzburg, Austria), prior to the intake of the glucose load.

4.2.7.2 Lipid profiles

Lipid profiles (LDL-cholesterol, HDL-cholesterol, total cholesterol, and triglycerides) were measured using a Cobas b 101 (Roche Diagnostics) capillary blood analyser. LDL-cholesterol values were calculated using the Friedewald equation. Lipid levels were measured at the beginning (pre-glucose drink) and end (180-minutes post-glucose drink) of each visit.

4.2.7.3 Inflammation

The EUROLyser CUBE (EUROLyser Diagnostica GmbH, Salzburg, Austria) was also used to measure CRP concentrations. CRP levels were measured at the beginning (pre-glucose drink) and end (180-minutes post-glucose drink) of each visit.

4.2.8 Procedure

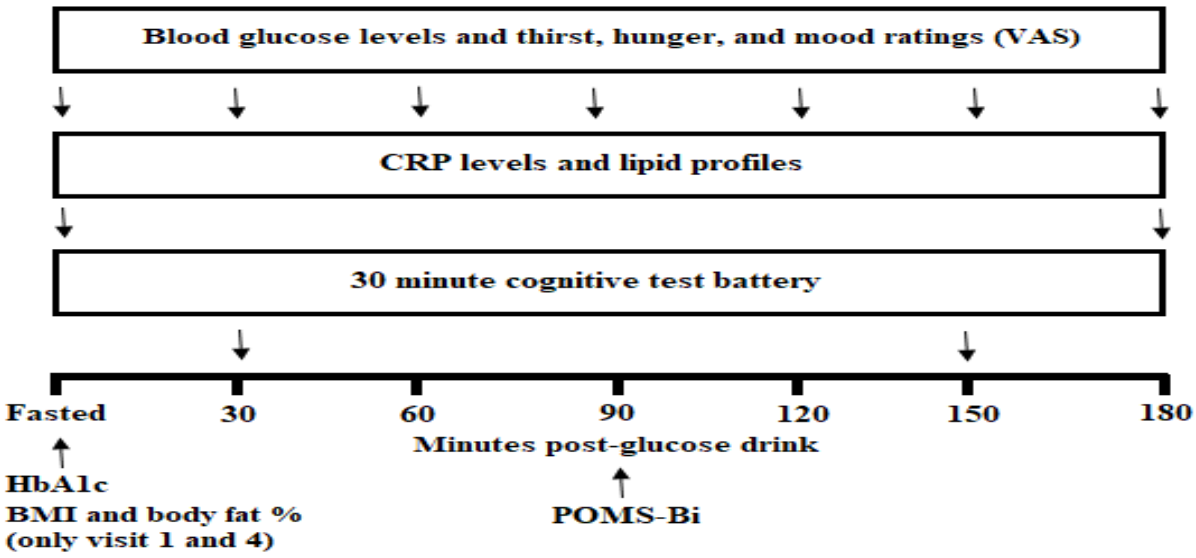


Figure 20. Polyphenol study procedure. *Note.* Times are approximate. POMS-Bi = Profile of Mood States Bipolar, CRP = c-reactive protein, VAS = visual analogue scale, BMI = body mass index, HbA1c = haemoglobin A1C.

Figure 20 illustrates the procedure followed during each test session. Participants arrived at the laboratory between 8.30am and 9.30am; each session took approximately 3 to 4 hours. Participants were instructed to fast for 12 hours before attending the laboratory, which included no food, drink, or caffeine. Water was permitted during the fast and throughout the morning of testing. Descriptive information and written informed consent were obtained during the first session. During the first and fourth visit, weight, height, and body fat percentage were measured using a Tanita scale. Each visit was almost identical. Upon arrival, fasting blood glucose levels, HbA1C, CRP, and lipid profiles were measured, followed by baseline ratings of mood, hunger, and thirst using VAS. An OGTT was then performed. During the OGTT, the same cognitive test battery was administered between 30 to 60 minutes and 150 to 180 minutes post-drink consumption. This corresponded to when blood glucose levels were expected to be at their highest and lowest, respectively. The cognitive test battery was completed in the following order: immediate word list recall task, arrow flanker task, n-back task, letter-number sequencing task, reaction time task, and delayed word list recall task. Participants completed the POMS-Bi (Lorr & McNair, 1988) during the break between the two cognitive test batteries. At the end of each visit, CRP and lipid profiles were measured again. Participants were instructed to maintain their habitual dietary and exercise patterns, as much as possible, throughout the study and prior to each visit.

4.2.9 Statistical analysis

Statistical analyses were performed using IBM SPSS statistics for Windows, Version 28 (IBM, Corp., Armonk, NY, USA). To determine whether the active group and placebo group were matched, baseline continuous data were analysed using independent t-tests, and baseline categorical data were analysed using chi-squared tests. A series of mixed ANOVA were performed. Supplement was always a between-subjects factor with two levels (active or placebo). To examine the effect of supplementation on OGTT profiles and ratings of hunger, thirst, and mood throughout each visit, the following three-way mixed ANOVA was performed: Supplement X Visit (1, 2, 3, and 4) X Time (0 [fasted], 30, 60, 90, 120, 150, and 180 minutes). The following three-way mixed ANOVA was performed to access changes in CRP levels and lipid profiles: Supplement X Visit (1, 2, 3, and 4) X Time (0 and 180 minutes). Changes in HbA1c levels were examined using a two-way mixed ANOVA: Supplement X Visit (1, 2, 3, and 4). To examine the effect of supplementation on BMI and body fat percentage, a two-way mixed ANOVA was performed: Supplement X Visit (1 and 4). For all cognitive tests, other than the arrow flanker task, the following three-way mixed ANOVA was performed: Supplement X Visit (1, 2, 3, and 4) X Time (30 [test battery A] and 150 [test battery B] minutes). Changes in performance on the arrow flanker task were assessed using a four-way mixed ANOVA: Supplement X Visit (1, 2, 3, and 4) X Time (30 and 150 minutes) X Trial (congruent and incongruent). Changes in POMS-Bi scores were assessed using a three-way mixed ANOVA: Supplement X Visit (1, 2, 3, and 4) X Subscale (Agreeable-Hostile, Confused-Clearheaded, Composed-Anxious, Depressed-Elated, Confident-Unsure, and Tired-Energetic).

Significant interactions were followed up by appropriate post hoc t-tests. A Bonferroni correction was applied to all post hoc tests to control for multiple comparisons. Mauchly's Test of Sphericity was used to determine whether the sphericity assumption had been violated. If necessary, a Greenhouse-Geisser correction was used and reported in the results. Normality was assessed using a Shapiro-Wilks test, which revealed that some data violated the normality assumption. However, mixed ANOVAs were still performed for the same reasons specified in Section 3.2.9. Outliers were detected using Cook's distance. When outliers were identified (>0.2), the analysis was run with and without the outliers and results were compared. Outliers were removed if their inclusion altered the significance of a main effect or interaction.

4.3 Results

4.3.1 Baseline characteristics

Baseline data are displayed in Table 15. The active group and placebo group did not significantly differ on any of these measure at baseline (all p = NS).

Table 15. Baseline data in the active and placebo group.

	Active group (n = 13)	**Placebo group (n = 15)**
Females (n)	7	7
Males (n)	6	8
Age (years)	65.23 (8.65)	64.14 (7.94)
Weight (kg)	68.78 (11.17)	71.05 (13.24)
BMI	20.45 (3.48)	21.37 (3.45)
Body fat (%)	26.89 (9.71)	27.05 (9.18)
Fasted glucose (mmol/L)	5.69 (0.58)	5.91 (1.14)
2-hour glucose[1] (mmol/L)	7.33 (1.68)	7.57 (2.75)
Total cholesterol (mg/dL)	187.85 (32.64)	200.13 (43.59)
LDL-cholesterol (mg/dL)	93.77 (31.22)	109.33 (38.89)
HDL-cholesterol (mg/dL)	62.38 (19.44)	65.60 (15.86)
Triglycerides (mg/dL)	157.92 (59.53)	126.40 (45.41)
HbA1c (%)	6.7 (1.39)	6.14 (1.02)
CRP (mg/dL)	0.42 (0.43)	0.24 (0.07)
Alcohol use (number of unit's p/w)	3.23 (1.22)	3.40 (2.26)
Physical exercise (hours p/w)	2.46 (2.33)	2.53 (3.25)
Use of prescribed medication (n)	7	8

Note. Data are shown as group means (SD), apart from gender and use of medication. BMI = body mass index, HbA1c = haemoglobin A1C, kg = kilograms, mmol/L = millimoles per litre, mg/dL = milligrams per decilitre, p/w = per week, LDL = low-density lipoprotein, HDL = high-density lipoprotein, CRP = c-reactive protein. 1 = 2-hours post-OGTT.

4.3.2 Primary analyses

4.3.2.1 Blood glucose levels

4.3.2.1.1 Oral glucose tolerance test

Mean OGTT profiles during each visit are shown in Figure 21. Outliers were identified but retained in the analysis as they did not influence the results. Mauchly's Test of Sphericity indicated that the within-subjects factor Time ($\chi2(20) = 98.976$, $p = 0.001$) and Visit X Time interaction ($\chi2(170) = 239.988$, $p = 0.001$) had violated the assumption of sphericity, therefore Greenhouse-Geisser corrections were applied when appropriate. Both the Visit X Time X Supplement interaction ($F(8.863,230.438) = .781$, $p = 0.632$, $np^2 = .029$) and main effect of Supplement ($F(1,26) = .281$, $p = 0.601$, $np^2 = .011$) were non-significant. However, the main effect of Time was significant ($F(2.637,68.574) = 67.530$, $p = 0.001$, $np^2 = .722$). After applying a Bonferroni correction for six tests ($\alpha = 0.008$), fasted blood glucose levels were significantly lower than blood glucose levels at 30, 60, 90, and 120 minutes (all $p < 0.001$) and significantly higher than blood glucose levels at 180 minutes ($p = 0.006$).

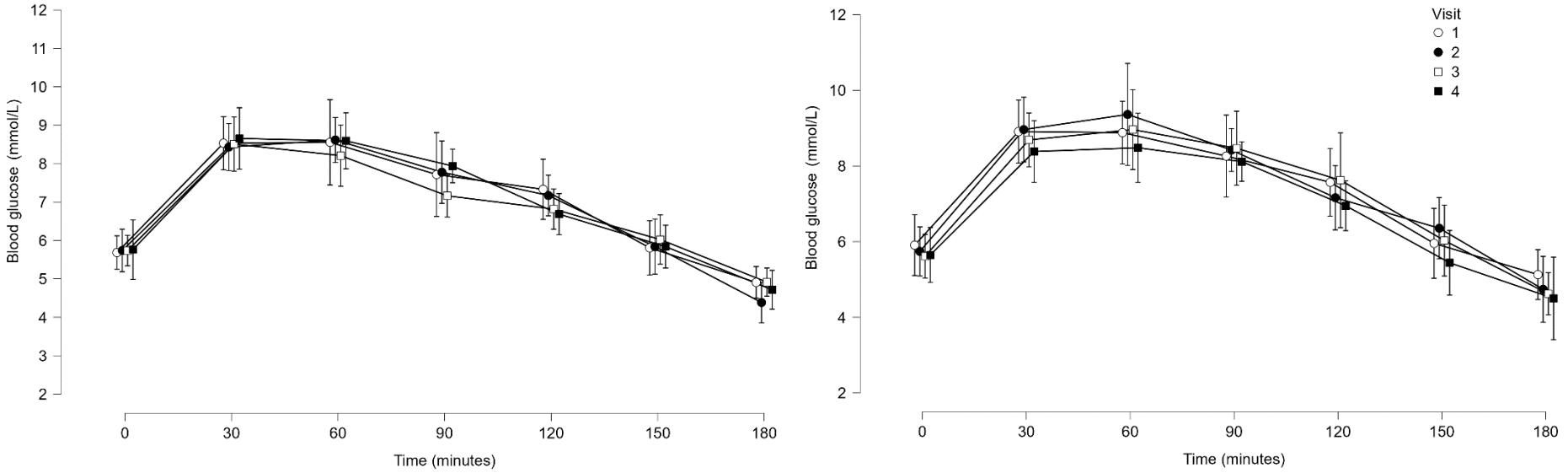


Figure 21. Oral glucose tolerance profiles during each visit in the active (left) and placebo group (right). The interaction Visit X Time X Supplement was non-significant ($F(8.863,230.438) = 0.781$, $p = 0.632$, $np^2 = .029$). Fasting glucose and OGTT profiles did not significantly differ between the active group and placebo group after one, two, or three months of supplementation. *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 4 X 7 mixed ANOVA, with Supplement (active or placebo) as a between-subjects factor, and both Visit (1, 2, 3, and 4) and Time (0 [fasted], 30, 60, 90, 120, 150, and 180 minutes) as within-subjects factors. Active group (n = 13) and placebo group (n = 15).

4.3.2.1.2 HbA1c

Two outliers were identified but retained in the analysis. Mean HbA1c levels during each visit are displayed in Figure 22. The Visit X Supplement interaction was non-significant ($F(3,78) = .586$, $p = 0.626$, $\eta p^2 = .022$), as well as the main effect of Supplement ($F(1,26) = 1.163$, $p = 0.291$, $\eta p^2 = .043$). The main effect of Visit was significant ($F(3,78) = 2.854$, $p = 0.043$, $\eta p^2 = .099$). HbA1c levels were lower during visit 4 (mean = 5.86, SD = 0.36) compared to visit 1 (mean = 6.42, SD = 0.97, $p = 0.02$), however this just missed significance after applying a Bonferroni correction for three tests ($\alpha = 0.016$).

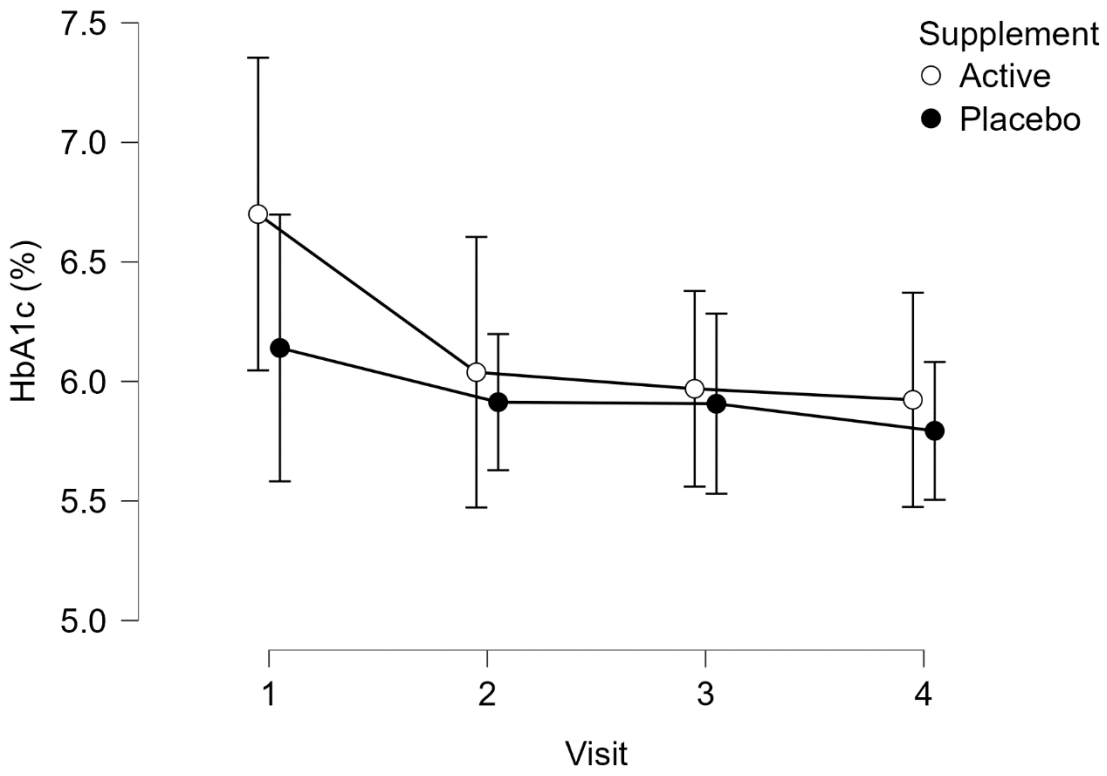


Figure 22. Hba1c percentage during each visit in the active and placebo group. The Visit X Supplement interaction was non-significant ($F(3,78) = 0.586$, $p = 0.626$, $\eta p^2 = .022$). HbA1c percentage in the active and placebo group did not significantly differ after one, two, or three months of supplementation. *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 4 mixed ANOVA, with Supplement (active or placebo) as a between-subjects factor and Visit (1, 2, 3, and 4) as a within-subjects factor. Active group (n = 13) and placebo group (n = 15).

4.3.2.2 Cognition

There were no baseline cognitive differences between the active group and placebo group (all p = NS).

4.3.2.2.1 Immediate episodic memory

Mean immediate episodic memory scores are shown in Table 16. No outliers were identified. The Visit X Time X Supplement interaction was non-significant ($F(3,78) = .976$, $p = 0.408$, $\eta p^2 = .36$). The main effect of Supplement was non-significant ($F(1,26) = .540$, $p = 0.469$, $\eta p^2 = .020$). The main effect of Time ($F(1,26) = 39.069$, $p = 0.001$, $\eta p^2 = .600$) was significant, whereby significantly more words were recalled during cognitive test battery A (mean = 9.66, SD = 2.29) than B (mean = 7.93, SD = 1.82). The main effect of Visit was also significant ($F(3,78) = 4.668$, $p = 0.005$, $\eta p^2 = .152$). After applying a Bonferroni correction for three tests ($\alpha = 0.016$), immediate episodic memory was significantly better during visit 3 (mean = 9.24, SD = 2.16, p = 0.003) and visit 4 (mean = 9.13, SD = 2.33, p = 0.004) than visit 1 (mean = 8.16, SD = 2.04).

Table 16. Immediate episodic memory scores in the active and placebo group.

Time	Active group (n = 13)	Placebo group (n = 15)
	Visit 1	
A	8.77 (3.56)	8.40 (2.80)
B	7.08 (2.57)	8.40 (2.59)
	Visit 2	
A	9.38 (3.35)	9.73 (3.22)
B	7.31 (2.56)	8.20 (2.60)
	Visit 3	
A	9.62 (3.33)	10.67 (3.13)
B	8.15 (2.76)	8.53 (2.50)
	Visit 4	
A	10 (3.74)	10.73 (2.55)
B	7.31 (3.61)	8.47 (2.92)

Note. Data reflect the mean number of words correctly recalled (SD). A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.2 Delayed episodic memory

Mean delayed episodic memory scores are shown in Table 17. No outliers were identified. The Visit X Time X Supplement interaction was non-significant ($F(3,78) = .102$, $p = 0.958$, $\eta p^2 = .004$). The main effect of Supplement was non-significant ($F(1,26) = .021$, $p = 0.886$, $\eta p^2 = .001$). The main effect of Time ($F(1,26) = 36.871$, $p = 0.001$, $\eta p^2 = .586$) and Visit ($F(3,78) = 7.957$, $p = 0.001$, $\eta p^2 = .234$) were significant. Performance was significantly better during cognitive test battery A (mean = 6.88, SD = 2.57) than B (mean = 4.67, SD = 1.73). After applying a Bonferroni correction for three tests ($\alpha = 0.016$), delayed episodic memory was significantly better during visit 3 (mean = 6.33, SD = 2.20, p = 0.007) and visit 4 (mean = 6.22, SD = 2.42, p = 0.01) than visit 1 (mean = 5.41, SD = 2.08).

Table 17. Delayed episodic memory scores in the active and placebo group.

Time	Active group (n = 13)	Placebo group (n = 15)
	Visit 1	
A	6.69 (4.17)	5.87 (3)
B	4.85 (2.27)	4.53 (2.48)
	Visit 2	
A	5.92 (3.55)	6.20 (3.2)
B	4.15 (2.30)	4.60 (2.53)
	Visit 3	
A	7.92 (3.86)	7.60 (3)
B	5.38 (2.90)	5.13 (2.64)
	Visit 4	
A	7.92 (4.01)	8 (3.44)
B	5 (3.29)	4.80 (2.91)

Note. Data reflect the mean (SD) number of words correctly recalled after a 30-minute delay. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.3 Letter-number sequencing task

Mean scores on the letter-number sequencing task are displayed in Table 18. One outlier was identified but retained in the analysis. The interaction between Visit X Time X Supplement was non-significant ($F(3,78) = .898$, $p = 0.446$, $\eta p^2 = .033$). The main effect of Supplement was non-significant ($F(1,26) = .833$, $p = 0.370$, , $\eta p^2 = .031$). The main effect of Time ($F(1,26) = 4.833$, $p = 0.037$, $\eta p^2 = .157$) and Visit ($F(3,78) = 6.636$, $p = 0.001$, $\eta p^2 = .203$) were both

significant. Performance was significantly better during cognitive test battery B (mean = 6.31, SD = 0.81) than A (mean = 6.05, SD = 0.81). After applying a Bonferroni correction for three tests ($\alpha = 0.016$), performance was significantly better during visit 3 (mean = 6.37, SD = 0.91, p = 0.002) and visit 4 (mean = 6.43, SD = 0.86, p = 0.001) than visit 1 (mean = 5.76, SD = 0.89).

Table 18. Scores on the letter-number sequencing task in the active and placebo group.

Time	Active group (n = 13)	Placebo group (n = 15)
	Visit 1	
A	5.23 (1.36)	5.73 (1.58)
B	5.54 (1.51)	6.40 (1.18)
	Visit 2	
A	6.08 (1.32)	6.07 (1.53)
B	6.15 (0.99)	6.47 (1.19)
	Visit 3	
A	6.31 (0.95)	6.40 (1.40)
B	6.15 (1.21)	6.67 (1.23)
	Visit 4	
A	6.08 (1.12)	6.53 (1.13)
B	6.62 (1.26)	6.53 (1.30)

Note. Data are presented as mean (SD) number of correct responses. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.4 N-back task

Each level of the n-back task (0-back, 1-back, and 2-back) was analysed separately as some participants failed to follow task instructions but only on certain levels of the task.

4.3.2.2.4.1 Accuracy

Mean number of correct responses on each level of the n-back task are shown in Table 19. For 0-back, one outlier was removed from the active group. Mauchly's Test of Sphericity indicated that the within-subjects factor Visit ($\chi2(5) = 51.486$, p = 0.001), and Visit X Time ($\chi2(5) = 55.447$, p = 0.001), and had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. The interaction Visit X Time X Supplement was non-significant ($F(1.426,35.651) = 0.555$, p = 0.521, $\eta p^2 = .022$). The main effect of Supplement was also non-significant ($F(1,25) = 0.063$, p = 0.804, $\eta p^2 = .003$). For 1-back, one outlier was

removed from the active group. The Visit X Time X Supplement interaction was non-significant ($F(3,75) = 1.950$, $p = 0.129$, $\eta p^2 = .072$). However, the Visit X Supplement interaction was significant ($F(3,75) = 3.014$, $p = 0.035$, $\eta p^2 = .108$). Follow-up tests failed to reveal any significant differences. The main effect of Supplement was non-significant ($F(1,25) = 1.925$, $p = 0.178$, $\eta p^2 = .072$). For 2-back, one outlier was removed from the analysis. The Visit X Time X Supplement interaction was non-significant ($F(3,75) = .637$, $p = 0.593$, $\eta p^2 = .025$). The main effect of Time ($F(1,25) = 10.86$, $p = 0.003$, $\eta p^2 = .303$) and Visit ($F(3,75) = 9.325$, $p = 0.001$, $\eta p^2 = .272$) were significant. Performance was significantly better during cognitive test battery A (mean = 9.52, SD = 1.31) than B (mean = 8.79, SD = 1.65). After applying a Bonferroni correction for three tests ($\alpha = 0.016$), performance was significantly better during visit 3 (mean = 9.77, SD = 1.57, $p < 0.001$) and visit 4 (mean = 9.53, SD = 1.48, $p < 0.001$) than visit 1 (mean = 8.22, SD = 1.74).

Table 19. Correct responses on the n-back task in the active and placebo group.

Visit	Time	Active group (n = 12)			Placebo group (n = 15)		
		0-back	**1-back**	**2-back**	**0-back**	**1-back**	**2-back**
1	**A**	12 (0.00)	11.50 (0.52)	8.75 (2.22)	12 (0.00)	11.53 (0.92)	8.93 (1.94)
	B	11.92 (0.29)	10.58 (1.67)	7.92 (2.87)	11.93 (0.26)	11.40 (0.83)	7.27 (2.19)
2	**A**	11.83 (0.58)	11.67 (0.65)	10.17 (2.48)	11.53 (1.30)	11.73 (0.46)	9.27 (1.98)
	B	11.67 (1.15)	10.42 (1.98)	8.75 (3.11)	11.80 (0.56)	11.53 (0.64)	8.40 (2.67)
3	**A**	12 (0.00)	11.75 (0.62)	10.67 (1.23)	12 (0.00)	11.67 (0.62)	9.53 (1.88)
	B	11.92 (0.29)	10.58 (1.83)	10.42 (2.19)	11.87 (0.35)	11.73 (0.59)	8.47 (2.72)
4	**A**	11.75 (0.62)	11.67 (0.65)	9.50 (2.32)	11.93 (0.26)	11.40 (0.74)	9.47 (1.85)
	B	11.75 (0.45)	11.25 (1.29)	9.67 (1.97)	11.93 (0.26)	10.67 (1.59)	9.47 (2.09)

Note. Data are presented as mean (SD) number of correct responses. Different outliers were removed from each analysis. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.4.2 Reaction times

Mean reaction times on each level of the n-back task are shown in Table 20. For 0-back, one outlier was removed from the analysis. Mauchly's Test of Sphericity indicated that the within-subjects factor Visit ($\chi2(5) = 26.885$, $p = 0.001$) had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. The Visit X Time X Supplement interaction was non-significant ($F(2.748, 68.691) = .716$, $p = 0.534$, $\eta p^2 = .028$). The main effect of Supplement was also non-significant ($F(1,25) = 1.813$, $p = 0.190$, $\eta p^2 = .068$), whereas

the main effect of Time was significant ($F(1,25) = 30.822$, $p = 0.001$, $\eta p^2 = .552$). Reaction times were significantly faster during cognitive test battery A (mean = 499.77, SD = 45.79) than B (mean = 524.88, SD = 45.71). For 1-back, one outlier was removed. Mauchly's Test of Sphericity indicated that the Visit X Time interaction ($\chi 2(5) = 15.003$, $p = 0.01$) had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. The interaction Visit X Time X Supplement was not significant ($F(2.164,54.097) = .363$, $p = 0.713$, $\eta p^2 = .014$). The main effect of Supplement just missed significance ($F(1,25) = 4.099$, $p = 0.054$, $\eta p^2 = .141$), which reflected a trend towards faster reaction times overall in the placebo group (mean = 544.11, SD = 81.76) than active group (mean = 608.23, SD = 81.75). The main effect of Time was significant ($F(1,25) = 10.937$, $p = 0.003$, $\eta p^2 = .304$). Reaction times were faster during cognitive test battery A (mean = 558.09, SD = 47.59) than B (mean = 593.36, SD = 66.34). For 2-back, one outlier was removed. The Visit X Time X Supplement interaction was non-significant ($F(3,75) = 1.507$, $p = 0.220$, $\eta p^2 = .057$). There was a trend towards a main effect of Supplement ($F(1,25) = 3.646$, $p = 0.068$, $\eta p^2 = .127$), which reflected faster reaction times in the placebo group (mean = 662.90, SD = 123.06) than active group (mean = 756.82, SD = 122.69).

Table 20. Reaction times on the n-back task in the active and placebo group.

Visit	Time	Active group (n = 12)			Placebo group (n = 15)		
		0-back	**1-back**	**2-back**	**0-back**	**1-back**	**2-back**
1	**A**	483.90	563.95	725.28	488.06	545.01	649.64
		(36.35)	(60.49)	(155.29)	(55.18)	(105.57)	(160.02)
	B	507.82	592.87	799.07	508.56	545.66	641.06
		(30.14)	(88.95)	(139.30)	(47.16)	(77.58)	(137.82)
2	**A**	495.01	592.39	755.51	478.26	512.58	613.82
		(40.33)	(86.39)	(165.99)	(49.93)	(71.73)	(149.68)
	B	523.76	655.99	773.33	512.36	553.41	669.17
		(46.47)	(161.11)	(140.17)	(48.65)	(89.69)	(181.58)
3	**A**	500.68	595.66	740.87	477.33	527.25	652.18
		(32.01)	(87.45)	(158.51)	(43.81)	(75.04)	(144.54)
	B	529.39	636.60	783.63	507.08	559.35	707.33
		(43.17)	(130.48)	(135.72)	(54.05)	(106.27)	(144.50)

4	**A**	507.62	584.29	722.69	494.26	550.73	702.08
		(42.45)	(90.62)	(132.60)	(57.66)	(90.91)	(175.65)
	B	532.82	644.07	754.16	513.25	558.92	667.92
		(54.44)	(124.87)	(163.79)	(67.80)	(120.96)	(183.55)

Note. Data are presented as mean (SD) response times. Different outliers were removed from each analysis. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.5 Arrow flanker task

4.3.2.2.5.1 Reaction times

Mean reaction times for congruent and incongruent trials in the active and placebo group are shown in Table 21. Two outliers were removed from the analysis. Mauchly's Test of Sphericity indicated that the Visit X Time interaction ($\chi 2(5) = 15.007$, $p = 0.01$) had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. The interaction Visit X Time X Supplement X Trial was non-significant ($F(2.683,64.389) = 0.394$, $p = 0.736$, $\eta p^2 = .016$). The main effect of Supplement was non-significant ($F(1,24) = 1.109$, $p = 0.303$, $\eta p^2 = .044$). The main effect of Trial was significant ($F(1,24) = 92.264$, $p = 0.001$, $\eta p^2 = .794$). As expected, reaction times were faster for congruent trials (mean = 570.42, SD = 67.87) than incongruent trials (mean = 615.02, SD = 71.54). The main effect of Visit was also significant ($F(2.282,54.762) = 20.510$, $p = 0.001$, $\eta p^2 = .461$). A Bonferroni correction for three tests was applied ($\alpha = 0.016$). Reaction times significantly improved from visit 1 (mean = 629.12, SD = 85.97) to visit 2 (mean = 595.24, SD = 69.86), visit 3 (mean = 573.37, SD = 72.10), and visit 4 (mean = 573.15, SD = 63.94, all $p < 0.001$).

Table 21. Reaction times on the arrow flanker task in the active and placebo group.

	Active group (n = 12)		**Placebo group (n = 14)**	
Time	**Congruent trials**	**Incongruent trials**	**Congruent trials**	**Incongruent trials**
		Visit 1		
A	636.43 (103.45)	680.19 (121.87)	596.99 (95.84)	659.12 (116.34)
B	601.30 (65.59)	652.60 (72.74)	575.72 (70.49)	630.60 (69.79)
		Visit 2		
A	593.93 (81.01)	629.63 77.47)	552.60 (74.98)	604.92 (77.92)
B	581.10 (75.78)	623.00 75.88)	564.28 (60.35)	612.46 (70.42)
		Visit 3		
A	560.52 (76.32)	604.44 (74.17)	539.08 (72.82)	582.09 (75.93)

B	575.20 (84.53)	612.88 (79.66)	535.80 (71.31)	576.91 (75.40)
		Visit 4		
A	575.78 (85.48)	615.53 (86.27)	529.25 (57.49)	574.98 (71.25)
B	565.37 (62.38)	602.87 (61.46)	543.43 (59.88)	578.01 (58.00)

Note. Data are presented as mean (SD) reaction times. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.5.2 Accuracy

Mean percentage of correct responses in the active and placebo group are displayed in Table 22. Three outliers in the placebo group were removed from the analysis. Mauchly's Test of Sphericity indicated that the within-subjects factor Visit ($\chi2(5) = 14.536$, $p = 0.013$) and Visit X Scale interaction ($\chi2(5) = 12.920$, $p = 0.024$) had violated the assumption of sphericity, therefore Greenhouse-Geisser corrections were applied. The interaction Visit X Time X Supplement X Trial was non-significant ($F(2.770,63.70) = 0.804$, $p = 0.488$, $\eta p^2 = .034$), as well as the main effect of Supplement ($F(1,23) = .086$, $p = 0.772$, $\eta p^2 = .004$). However, the Visit X Time X Supplement interaction was significant ($F(2.448,56.308) = 3.232$, $p = 0.038$, $\eta p^2 = .123$). Performance during cognitive test battery A improved from visit 1 to visit 4 ($p = 0.015$), but only in the active group. Conversely, performance during cognitive test battery B improved from visit 1 to visit 4, but only in the placebo group ($p = 0.005$). However, after applying a Bonferroni correction for 12 tests ($\alpha = 0.004$), there were no significant differences in scores between groups. The Time X Trial interaction ($F(1,24) = 6.604$, $p = 0.017$, $\eta p^2 = .216$) was also significant. Bonferroni corrected post hoc t-tests indicated that participants performed significantly better on congruent trials than incongruent trials during cognitive test battery A ($p = 0.001$) and B ($p = 0.005$). The main effect of Trial was significant ($F(1,23) = 23.981$, $p = 0.001$, $\eta p^2 = .500$), which reflected better performance for congruent trials (mean = 98.71, SD = 1.19) than incongruent trials (mean = 97.19, SD = 1.82). The main effect of Visit was also significant ($F(1.414,33.931) = 4.662$, $p = 0.03$, $\eta p^2 = .163$), whereby performance was better during visit 4 (mean = 98.63, SD = 1.2) compared to visit 1 (mean = 97.39, SD = 2.1, $p = 0.01$). This remained significant after applying a Bonferroni correction for three tests ($\alpha = 0.016$).

Table 22. Correct responses on the arrow flanker task in the active and placebo group.

	Active group (n = 13)		**Placebo group (n = 12)**	
Time	**Congruent trials**	**Incongruent trials**	**Congruent trials**	**Incongruent trials**
		Visit 1		

A	98.72 (1.94)	95.65 (3.51)	98.75 (2.03)	96.95 (3.16)
B	98.85 (1.25)	97.18 (3.15)	97.50 (3.29)	95.56 (3.50)
		Visit 2		
A	99.10 (0.87)	96.67 (2.89)	99.03 (1.32)	96.11 (3.04)
B	98.59 (1.64)	97.56 (1.88)	97.65 (3.21)	97.22 (1.88)
		Visit 3		
A	98.59 (1.64)	97.18 (3.29)	98.75 (1.61)	97.36 (2.97)
B	98.08 (2.44)	97.95 (2.65)	98.47 (1.94)	97.92 (2.03)
		Visit 4		
A	99.49 (1.05)	98.20 (2.20)	99.17 (1.33)	97.50 (2.41)
B	99.1 (1.46)	97.56 (3.38)	99.58 (0.76)	98.47 (1.50)

Note. Data are presented as mean (SD) percentage of correct responses. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.5.3 Accuracy for inhibition trials

Mean accuracy scores on inhibition trials are shown in Table 23. Four participants were removed from the analysis as they did not follow task instructions. The Visit X Time X Supplement interaction was non-significant ($F(3,66) = 0.728$, $p = 0.539$, $\eta p^2 = .032$). The main effect of Supplement was non-significant ($F(1,22) = 0.380$, $p = 0.544$, $\eta p^2 = .017$). However, the main effect of Time ($F(1,22) = 14.752$, $p = 0.001$, $\eta p^2 = .401$) was significant. Performance was significantly better during cognitive test battery B (mean = 93.72, SD = 4.61) than A (mean = 90.56, SD = 6.71). The main effect of Visit ($F(3,66) = 13.216$, $p = 0.001$, $\eta p^2 = .375$) was also significant, whereby performance significantly improved from visit 1 (mean = 88.89, SD = 7.01) to visit 2 (mean = 91.59, SD = 7.20, $p = 0.002$), visit 3 (mean = 93.54, SD = 5.29, $p = 0.001$), and visit 4 (mean = 94.51, SD = 4.53, $p = 0.001$). These remained significant after applying a Bonferroni correction ($\alpha = 0.016$).

Table 23. Response inhibition on the arrow flanker task in the active and placebo group.

Time	Active group (n = 12)	Placebo group (n = 12)
	Visit 1	
A	86.67 (8.29)	84.44 (1.40)
B	92.78 (5.66)	91.67 (6.28)
	Visit 2	
A	91.39 (6.11)	88.89 (9.88)

B	94.17 (6.53)	91.95 (7.84)
	Visit 3	
A	93.06 (6.11)	92.50 (6.53)
B	95.83 (3.22)	92.78 (7.08)
	Visit 4	
A	92.78 (6.33)	94.72 (5.94)
B	95.83 (4.05)	94.72 (5.02)

Note. Data are presented as mean (SD) percentage of correct responses. A = cognitive test battery A and B = cognitive test battery B.

4.3.2.2.6 Simple and choice reaction times

Mean simple and choice reaction times are shown in Table 24. Due to a technical error, data were not obtained from three participants. One participant was removed from the analysis as they did not follow task instructions. The Visit X Time X Supplement X Trial interaction was non-significant ($F(3,66) = 1.682$, $p = 0.179$, $\eta p^2 = .071$). The main effect of Supplement was non-significant ($F(1,22) = 1.351) = 0.258$, $\eta p^2 = .058$). The main effect of Trial was significant ($F(1,22) = 10.591$, $p = 0.004$, $np^2 = .325$), whereby simple reaction times (mean = 376.03, SD = 62.65) were faster than choice reaction times (mean = 386.92, SD = 51.58).

Table 24. Simple and choice reaction times in the active and placebo group.

	Active group (n = 11)		**Placebo group (n = 13)**	
Time	**Simple**	**Choice**	**Simple**	**Choice**
		Visit 1		
A	386.15 (80.52)	381.62 (50.85)	382.78 (61.22)	391.25 (52.74)
B	373.02 (87.03)	383.18 (32.79)	364.37 (99.87)	383.35 (50.88)
		Visit 2		
A	374.61 (53.60)	403.65 (54.47)	353.79 (61.44)	373.96 (38.88)
B	364.80 (62.35)	397.81 (58.57)	352.43 (43.97)	382.60 (50.25)
		Visit 3		
A	387.10 (71.81)	382.02 (43.43)	351.86 (55.88)	380.94 (55.48)
B	359.13 (54.89)	374.92 (45.52)	316.87 (34.90)	385.67 (58.10)
		Visit 4		
A	377.52 (83.30)	384.91 (51.67)	335.03 (44.02)	406.71 (61.65)
B	337.20 (61.93)	408.95 (80.17)	322.66 (45.66)	372.40 (39.92)

Note. Data are mean (SD) reaction times. A = cognitive test battery A and B = cognitive test battery B.

4.3.3 Secondary analyses

4.3.3.1 Inflammation

Mean CRP levels during each visit in the active group and placebo group are shown in Table 25. Two outliers were removed from the analysis. Mauchly's Test of Sphericity indicated that the within-subjects factor Visit ($\chi2(5) = 20.928$, $p = 0.001$), and Visit X Time interaction ($\chi2(5) = 15.800$, $p = 0.007$), had violated the assumption of sphericity therefore Greenhouse-Geisser corrections were applied. The interaction Visit X Time X Supplement was non-significant ($F(2.160,51.841) = .147$, $p = 0.878$, $\eta p^2 = .006$), as well as the main effect of Supplement ($F(1,24) = .630$, $p = 0.435$, $\eta p^2 = .026$). The main effect of Time was significant ($F(1,24) = 11.036$, $p = 0.003$, $\eta p^2 = .315$), whereby fasted CRP levels (mean = 0.29, SD = 0.09) were significantly higher than CRP levels 180-minutes after consuming the glucose drink (mean = 0.25, SD = 0.06).

Table 25. C-reactive protein levels in the active and placebo group.

	Active (N = 11)	**Placebo (N = 15)**
	Visit 1	
A	0.26 (0.07)	0.24 (0.07)
B	0.24 (0.04)	0.24 (0.06)
	Visit 2	
A	0.28 (0.08)	0.28 (0.11)
B	0.23 (0.05)	0.21 (0.03)
	Visit 3	
A	0.32 (0.16)	0.33 (0.22)
B	0.26 (0.09)	0.27 (0.12)
	Visit 4	
A	0.29 (0.14)	0.37 (0.21)
B	0.23 (0.03)	0.33 (0.21)

Note. Data are presented as group means (SD), using mg/dL). A = fasted & B = 180 minutes after an OGTT.

4.3.3.2 Lipid profiles

4.3.3.2.1 Total cholesterol levels

Mean total cholesterol levels during each visit are displayed in Table 26. No outliers were identified. Mauchly's Test of Sphericity indicated that the Visit X Time interaction violated the assumption of sphericity ($\chi 2(5) = 11.870$, $p = 0.037$), therefore a Greenhouse-Geisser correction was applied. The Visit X Time X Supplement interaction was non-significant ($F(2.341,60.876) = .313$, $p = 0.766$, $\eta p^2 = .012$). The main effect of Supplement was non-significant ($F(1,26) = 1.655$, $p = 0.210$, $\eta p^2 = .060$). However, there was a significant main effect of Time ($F(1,26) = 14.075$, $p = 0.001$, $\eta p^2 = .351$). Fasted total cholesterol levels (mean = 193.19, SD = 36.87) were significantly than lower than 180-minute levels (mean = 198.03, SD = 37.24).

Table 26. Total cholesterol levels in the active and placebo group.

	Active group (n = 13)	**Placebo group (n = 15)**
	Visit 1	
A	187.85 (32.64)	200.13 (43.59)
B	189.54 (31.54)	202.27 (42.82)
	Visit 2	
A	184.15 (34.59)	201 (42.09)
B	186.08 (26.05)	206.93 (43.60)
	Visit 3	
A	182.92 (38.58)	199.93 (41.22)
B	190.08 (42.68)	207 (41.04)
	Visit 4	
A	183.08 (33.27)	206.46 (40.02)
B	189.38 (32.46)	212.93 (40.74)

Note. Data are presented as mean values (SD). The measurement used is mg/dL. A = fasted and B = 180 minutes post-OGTT.

4.3.3.2.2 LDL-cholesterol

Mean LDL-cholesterol in the active group and placebo group are shown in Table 27. Data were not obtained from two participants. No outliers were identified in the analysis. The Visit X Time X Supplement interaction ($F(3,72) = 1.586$, $p = 0.200$, $\eta p^2 = .062$) and main effect of Supplement were non-significant ($F(1,24) = .791$, $p = 0.383$, $\eta p^2 = .032$). The main effect of

Time was significant ($F(1,24) = 16.716$, $p = 0.001$, $\eta p^2 = .411$), whereby fasted LDL-cholesterol levels (mean = 105.46, SD = 34.10) were significantly lower than 180-minute levels (mean = 111.46, SD = 33.09).

Table 27. LDL-cholesterol levels in the active and placebo group.

	Active group (n = 11)	**Placebo group (n = 15)**
	Visit 1	
A	93.91 (30.31)	109.33 (38.89)
B	101.82 (27.89)	113.07 (36.31)
	Visit 2	
A	94.73 (31.65)	109.67 (38.40)
B	109.36 (28.07)	115.20 (39.55)
	Visit 3	
A	97.36 (32.09)	108.67 (37.33)
B	102.73 (32.63)	118.53 (36.18)
	Visit 4	
A	99.16 (34.12)	114.53 (36.30)
B	104.64 (33.85)	125.33 (36.24)

Note. Data are shown as mean values (SD). The measurement used is mg/dL. A = fasted and B = 180 minutes post-OGTT.

4.3.3.2.3 HDL-cholesterol levels

Mean HDL-cholesterol levels in the active group and placebo group are displayed in Table 28. One outlier was removed from the analysis. There was a trend towards a Visit X Time X Supplement interaction ($F(3,75) = 2.545$, $p = 0.062$, $np^2 = .092$). In the active group, the level of HDL-cholesterol 180 minutes post-OGTT declined from visit 1 to visit 3 ($p = 0.034$). In the placebo group, fasted HGL-cholesterol levels declined from visit 1 to visit 4 ($p = 0.04$), and 180-minute levels declined from visit 1 to visit 4 ($p = 0.05$). However, these were no longer significant after applying a Bonferroni correction. The main effect of Supplement was non-significant ($F(1,25) = 0.699$, $p = 0.411$, $\eta p^2 = .027$). However, the main effect of Time ($F(1,25) = 20.202$, $p = 0.001$, $np^2 = .447$) and Visit ($F(3,75) = 3.903$, $p = 0.012$, $np^2 = .135$) were significant. Fasted HGL-cholesterol levels were significantly lower (mean = 60.57, SD = 12.45) than 180-minute levels (mean = 62.19, SD = 12.28). After applying a Bonferroni

correction for three tests (α = 0.016), HGL-cholesterol levels were significantly higher during visit 1 (mean = 64.12, SD = 13.88) than during visit 4 (mean = 59.32, SD = 12.81, p = 0.006).

Table 28. HDL-cholesterol levels in the active and placebo group.

	Active group (n = 12)	**Placebo group (n = 15)**
	Visit 1	
A	60.50 (19.02)	65.60 (15.86)
B	63.01 (19.64)	67.33 (15.8)
	Visit 2	
A	59.83 (17.52)	62.60 (14.01)
B	59.58 (17.97)	64.87 (14.33)
	Visit 3	
A	56.75 (16.42)	62.27 (15.13)
B	57.58 (15.81)	64.87 (14.32)
	Visit 4	
A	55.83 (15.96)	61.13 (17.02)
B	57.92 (15.44)	62.41 (16.09)

Note. Data are shown as means (SD). The measurement used is mg/dL. A = fasted and B = 180 minutes post-OGTT.

4.3.3.2.4 Triglyceride levels

Mean triglyceride levels in the active group and placebo group are shown in Table 29. Outliers were identified but retained in the analysis. The Visit X Time X Supplement interaction was non-significant ($F(3,75) = 1.695$, $p = 0.175$, $np^2 = .064$). The main effect of Supplement was non-significant ($F(1,25) = 0.054$, $p = 0.818$, $\eta p^2 = .002$). The main effect of Time was significant ($F(1,25) = 13.981$, $p = 0.001$, $\eta p^2 = .359$). Fasted triglyceride levels (mean = 143.21, SD = 45.83) were significantly higher than 180-minute levels (mean = 117.26, SD = 37.82).

Table 29. Triglyceride levels in the active and placebo group.

	Active group (n = 13)	**Placebo group (n = 15)**
	Visit 1	
A	157.92 (59.53)	126.40 (45.41)
B	112.62 (38.22)	109.133 (45.99)
	Visit 2	

A	163.50 (144.21)	142.87 (74.88)
B	130.67 (73.19)	134.07 (64.06)
	Visit 3	
A	132.83 (44.12)	145 (73.26)
B	113.92 (44.54)	117.40 (56.59)
	Visit 4	
A	124.58 (47.79)	153.73 (59.49)
B	107.42 (25.81)	113.67 (71.29)

Note. Data are presented as mean values (SD) using mg/dL. A = fasted and B = 180 minutes post-OGTT.

4.3.3.3 Mood

4.3.3.3.1 Profile of Mood States-Bipolar

One outlier was identified but retained in the analysis. Mauchly's Test of Sphericity indicated that the within-subjects factors Scale ($\chi2(14) = 25.958$, $p = 0.03$) had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. The Visit X Subscale X Supplement interaction was non-significant ($F(7.617,182.805) = .685$, $p = 0.697$, $\eta p^2 = .028$), as well as the main effect of Supplement ($F(1,24) = .001$, $p = 0.976$, $\eta p^2 = .000$).

4.3.3.3.2 Visual Analogue Scales

Mood was assessed seven times throughout the morning of each test session using six VAS (Agreeable/Hostile, Confused/Clearheaded, Composed/Anxious, Depressed/Elated, Confident/Unsure, and Tired/Energetic). Separate analyses were performed for each subscale. All Visit X Time X Supplement interactions and main effects of Supplement were non-significant (all p = NS). The main effects of Time were significant for all six subscales; results are shown in Appendix 22 (all $p < 0.05$). Bonferroni corrected post hoc t-tests indicated that ratings of Agreeable/Hostile, Confused/Clearheaded, Composed/Anxious, and Tired/Energetic declined throughout the morning, reflecting a worsening of mood. The same pattern occurred for ratings of Confident/Unsure, but these tests were no longer significant after applying a Bonferroni correction. In contrast, participants reported feeling significantly more elated 30 minutes post-glucose drink compared to pre-glucose drink. The main effect of Visit was significant only for ratings of Agreeable/Hostile ($F(2.211,57.495) = 5.450$, $p = 0.005$, $np^2 = .173$). After applying a Bonferroni correction for three tests ($\alpha = 0.016$), ratings significantly declined from visit 1 to visit 2 ($p = 0.001$) and visit 3 ($p = 0.006$).

4.3.3.4 Thirst

Mauchly's Test of Sphericity indicated that the within-subjects factors Visit ($\chi2(5) = 16.244$, $p = 0.006$), and Time ($\chi2(20) = 94.795$, $p = 0.001$), had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. Both the Visit X Time X Supplement interaction ($F(8.652,224.950) = 1.255$, $p = 0.213$, $\eta p^2 = .046$), and main effect of Supplement ($F(1,26) = .330$, $p = 0.570$, $\eta p^2 = .013$), were non-significant. However, the main effect of Time was significant ($F(2.686,69.829) = 18.912$, $p = 0.001$, $\eta p^2 = .421$). A Bonferroni correction was applied for six tests ($\alpha = 0.008$). Ratings of thirst significantly increased from pre-glucose drink (mean = 40.26, SD = 18.47) to 150 minutes (mean = 51.96, SD = 22.33, p = 0.006) and 180 minutes (mean = 63.85, SD = 23.44, p = 0.001) post-glucose drink.

4.3.3.5 Hunger

Mauchly's Test of Sphericity indicated that the within-subjects factors Time ($\chi2(20) = 60.383$, $p = 0.001$), and Visit X Time interaction ($\chi2(170) = 230.281$, $p = 0.004$), had violated the assumption of sphericity, therefore a Greenhouse-Geisser correction was applied. The interaction Visit X Time X Supplement was non-significant ($F(8.691,225.970) = .910$, $p = 0.514$, $\eta p^2 = .034$). The main effect of Supplement was also non-significant ($F`(1,26) = .669$, $p = 0.421$, $\eta p^2 = .025$). However, the main effect of Time ($F(6,85.911) = 4.308$, $p = 0.005$, $\eta p^2 = .142$) and Visit ($F(2.620,68.117) = 3.298$, $p = 0.031$, $\eta p^2 = .113$) were significant. Ratings of hunger were higher pre-glucose drink (mean = 43.43, SD = 19.31) compared to 30-minutes post-glucose drink (mean = 33.87, SD = 17.19, p = 0.009). However, this was no longer significant after applying a Bonferroni correction for six tests ($\alpha = 0.008$). Rating of hunger were lower during visit 1 (mean = 36.03, SD = 17.19) than visit 2 (mean = 43.88, SD = 15.45, p = 0.01) and visit 3 (mean = 45.03, SD = 20.79, p = 0.02). However, only the difference between visit 1 and visit 2 remained significant after applying a Bonferroni correction ($\alpha = 0.016$).

4.3.3.6 BMI and body fat percentage

BMI and body fat percentage were measured during visit 1 and visit 4. The Visit X Supplement interaction was non-significant for both BMI ($F(1,26) = .296$, $p = 0.591$, $\eta p^2 = .011$) and body fat percentage ($F(1,26) = .585$, $p = 0.451$, $\eta p^2 = .022$). The main effect of Supplement was also non-significant for BMI ($F(1.26) = .453$, $p = 0.507$, $\eta p^2 = .017$) and body fat percentage ($F(1,26) = .585$, $p = 0.451$, $\eta p^2 = .022$).

4.3.4 Exploratory analyses

4.3.4.1 HbA1c

The sample was divided using the median split of HbA1c percentage during visit 1 (median split = 6.3%). Changes in HbA1c levels from visit 1 to visit 2, 3, and 4 were calculated. The Supplement X Visit X GT interaction was non-significant ($F(2,48) = 1.850$, $p = 0.168$, $\eta p^2 = .072$). The main effect of Supplement was also non-significant ($F(1,24) = 0.918$, $= 0.347$, $\eta p^2 = .037$).

4.3.4.2 Fasting glucose

The sample was divided into two groups using the median split of fasting blood glucose levels during visit 1 (median split = 5.75 mmol/L). Changes in fasting glucose levels from visit 1 to visit 2, 3, and 4 were calculated. The Supplement X Visit X GT interaction was non-significant ($F(2,48) = 0.250$, $p = 0.780$, $\eta p^2 = .011$), as well as the main effect of Supplement ($F(1,24) = 1.541$, $p = 0.226$, $\eta p^2 = .060$).

4.3.4.3 2-hour glucose

Participants were divided into two groups using the median split of 2-hour blood glucose levels during visit 1 (median split = 7.2 mmol/L). Changes in 2-hour glucose levels from visit 1 to visit 2, 3, and 4 were calculated. There was a trend towards a Supplement X Visit X GT interaction ($F(2,48) = 2.860$, $p = 0.067$, $\eta p^2 = .106$), which is illustrated in Figure 23. A Bonferroni correction was applied for 12 tests ($\alpha = 0.004$). In the placebo group, the change in 2-hour glucose levels after three months of supplementation was significantly greater in those with higher compared to lower 2-hour glucose levels at baseline ($p < 0.001$, Figure 23). The same pattern occurred after one month of supplementation, but this was no longer significant after applying a Bonferroni correction ($p = 0.006$). In the active group, there was a larger fall in 2-hour glucose levels after one month of supplementation in those with higher 2-hour glucose levels at baseline, but this was also no longer significant after applying a Bonferroni correction ($p = 0.041$). The main effect of Supplement was non-significant ($F(1,24) = 0.279$, $p = 0.602$, $\eta p^2 = .011$).

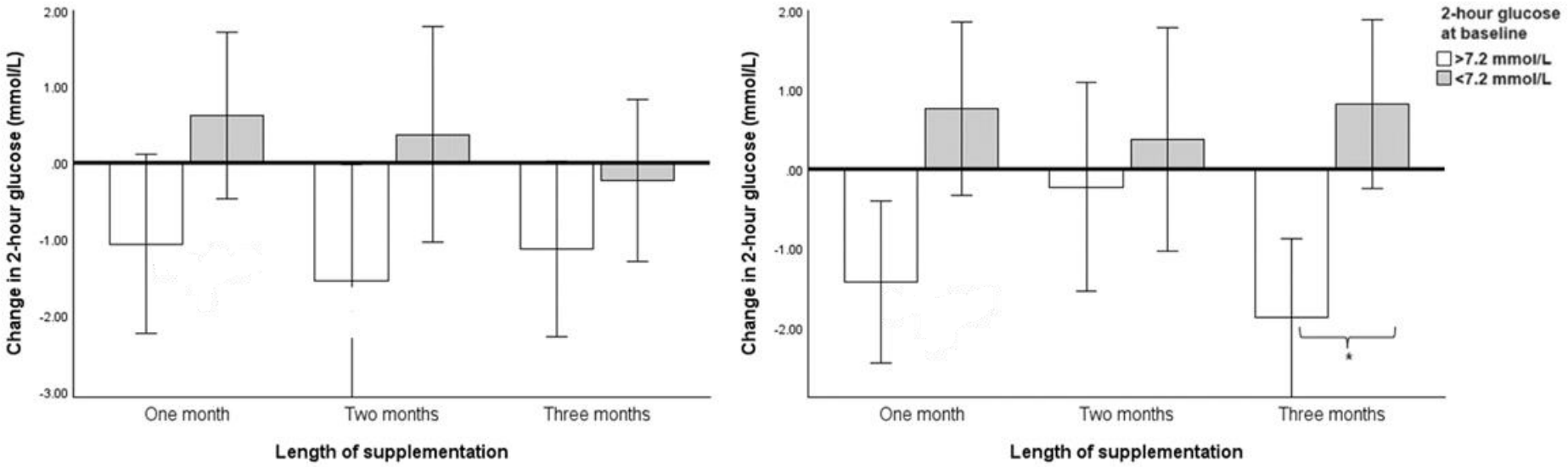


Figure 23. Change in 2-hour glucose levels in the active (left) and placebo group (right). There was a trend towards a Supplement X Visit X GT interaction ($F(2,48) = 2.860$, $p = 0.067$, $\eta p^2 = .106$). In the placebo group, there was a significantly larger fall in 2-hour glucose levels after three months of supplementation in those with higher compared to lower 2-hour glucose levels at baseline (* $p < 0.001$). The same pattern occurred after one month of supplementation, but this was no longer significant after applying a Bonferroni correction ($p = 0.006$). In the active group, there was a larger fall in 2-hour glucose levels after one month of supplementation in those with higher 2-hour glucose levels at baseline, but this was also no longer significant after applying a Bonferroni correction ($p = 0.041$). *Note.* Data are presented as means (SD). Error bars represent 95% CIs. Analysis model was a 2 X 2 X 4 mixed ANOVA, with Supplement (active or placebo) and GT (poorer or better GT) as between-subjects factors and Visit (1, 2, 3, and 4) as a within-subjects factor. Active group (n = 13) and placebo group (n = 15).

4.3.5 Summary of findings from polyphenol study

- Primary analyses: supplementation with cinnamon and turmeric/curcumin for one, two, and three months did not influence fasting glucose, OGTT profiles, HbA1c, and cognition.
- Secondary analyses: lipid profiles, CRP levels, BMI, body fat percentage, and subjective measures of mood, satiety, and thirst did not significantly differ between the active group and placebo group after one, two, or three months of supplementation.
- Exploratory analyses: a significantly larger decline in 2-hour glucose levels occurred after three months of placebo supplementation in those with higher compared to lower 2-hour glucose levels at baseline.

4.4 Discussion

4.4.1 Blood glucose levels

It was hypothesised that the active group would display larger improvements in fasting glucose levels, OGTT profiles, and HbA1c levels than the placebo group. However, no changes in these measures were detected after one, two, and three months of supplementation with cinnamon and turmeric/curcumin. Both Tang et al. (2008) and Oza (2017) reported no changes in measures of glycaemia following three to four weeks of turmeric supplementation in healthy adults. Studies have also reported no changes in fasting glucose levels (Ranasinghe et al., 2017) and HbA1c levels (Kizilaslan & Erdem, 2019) following chronic cinnamon supplementation. In contrast, Kizilaslan and Erdem (2019) reported that 3 g of cinnamon per day for 40 days improved postprandial glycaemia, whereas 6 g improved both fasting and postprandial blood glucose levels. Solomon and Blannin (2009) also reported that the consumption of 3 g of cinnamon per day for two weeks significantly reduced postprandial glycaemia and increased insulin sensitivity but had no impact on fasting glycaemia. It is therefore possible that the amount of cinnamon ingested in the present study (1 g per day) was not large enough to elicit significant reductions in fasting and/or postprandial glycaemia.

It was suggested that the combination of cinnamon and turmeric/curcumin may synergistically or additively improve blood glucose levels via the mechanisms discussed in Section 4.1.1 and 4.2.2. As such, the lack of significant changes in blood glucose levels after three months of supplementation are somewhat surprising. In addition to the dosage of cinnamon administered, sample heterogeneity may have also contributed to the non-significant effects. Although the

purpose of this study was to explore the effects of cinnamon and turmeric/curcumin in healthy middle-aged and older adults, a large proportion of the sample had clinically elevated blood glucose levels at baseline. Specifically, six participants had fasting glucose levels above 6.1 mmol/L, nine had 2-hour postprandial glucose levels above 7.8 mmol/L, and 18 had HbA1c percentages above 6.1%. Post hoc exploratory analyses were performed to determine whether individual differences in GT at baseline influenced the effects of supplementation. The total sample was divided into two groups using the median split of fasting glucose, 2-hour glucose, and HbA1c at baseline (visit 1). There was a trend towards an interaction between Visit, Supplement, and baseline 2-hour glucose levels (Figure 23). In the placebo group, 2-hour glucose levels fell to a significantly larger extent after three months in those with higher compared to lower 2-hour glucose levels at baseline. The same pattern occurred after one month of supplementation, but this was no longer significant after applying a Bonferroni correction. In the active group, there was a larger fall in 2-hour glucose levels after one month of supplementation in those with higher 2-hour glucose levels at baseline, but this was also no longer significant after applying a Bonferroni correction. As the present study was not sufficiently powered to perform this post hoc exploratory analysis, and that a major limitation of the Bonferroni correction method is that it increases the likelihood of type 2 errors (Perneger, 1998), it is possible that significant effects may have been missed. There are several possible explanations for significant improvements in the placebo group. Firstly, the placebo supplement contained small quantities of ingredients that could also improve glycaemic control, such as oat and barley flour (Tosh, 2013). Secondly, although participants were instructed to maintain their habitual diet, participants in the placebo group may have modified their diet or lifestyle during the study. Lastly, the larger fall in 2-hour glucose levels in those with higher 2-hour glucose levels at baseline may reflect regression to the mean.

4.4.2 Cognition

It was hypothesised that the active group would display larger improvements in cognitive performance throughout the study than the placebo group. Due to a lack of research at the time that this study was designed, it was not hypothesised that certain cognitive domains would be more sensitive to the effects of the active supplement than others. Results showed that three months of cinnamon and turmeric/curcumin supplementation did not influence immediate and delayed episodic memory, processing speed, and working memory. Consistent with this, Santos-Parker et al. (2018) reported that 12 weeks of curcumin supplementation (2 g per day)

did not improve processing speed, executive function, episodic memory, and working memory in healthy middle-aged and older adults. Similarly, Rainey-Smith et al. (2016) reported no improvements in episodic memory, semantic memory, psychomotor speed, working memory, and visual memory after 12 months of supplementation with 1.5 g of Biocurcumax™. However, executive function declined in the placebo group but not the active group.

In contrast with the present findings, studies have reported that chronic supplementation with curcumin improved working memory (Cox et al., 2015; Cox et al., 2020), spatial memory (Cox et al., 2020), and episodic memory (Small et al., 2018). It is widely agreed that curcumins poor bioavailability is the main factor limiting its clinical utility (Mohseni et al., 2021). Curcumin is poorly absorbed from the gastrointestinal tract and rapidly metabolised in the liver, where it is converted into conjugated curcumin and degradation products (Seddon et al., 2019; Toden & Goel, 2017). A range of methods have been used to increase the bioavailability of curcumin. Small et al. (2018) administered Theracurcumin™ which is a nanoparticle formulation of curcumin, whilst Cox et al. (2020) and Cox et al. (2015) administered Longvida™ which is a lipophilic formulation of curcumin. Both formulations protect curcumin from being rapidly metabolised and excreted. For example, Longvida™ curcumin is 100 times more bioavailable than unformulated curcumin (Seddon et al., 2019). This increases the concentration of unconjugated curcumin in the bloodstream which, unlike conjugated curcumin, can pass through the BBB. Indeed, Begum et al. (2008) reported that the concentration of curcumin in the brain was four times greater when solid lipid curcumin was administered in comparison to standard curcumin. It is likely that unconjugated curcumin is needed for cognitive benefits to occur via a central mechanism (Cox et al., 2015). Interestingly, Rainey-Smith et al. (2016) administered Biocurcumax™ which, like the supplement administered in the present study, enhances the bioavailability of curcumin by co-administering turmeric. Compared to standard curcumin, the bioavailability of Biocurcumax™ is 6.9-fold whereas the bioavailability of Longvida™ is 100-fold (Jamwal, 2018). This suggests that for improvements in cognition and mood to occur, highly bioavailable curcumin needs to be consumed.

The cognitive tasks administered in the present study have previously shown to be sensitive to variations in breakfast GL (Cooper et al., 2012; Ginieis et al., 2018; Nabb & Benton, 2006a). Whilst episodic memory may be particularly sensitive to variations in breakfast GL (Chapter 2), a recent meta-analysis found that chronic curcumin supplementation significantly improved working memory but not episodic memory and executive function (Tsai et al., 2021). Working memory was assessed using the letter-number sequencing task and n-back task in the present

study. However, based on past research (Cox et al., 2015; Cox et al., 2020), the serial subtraction task may be more appropriate. Ceiling effects were also observed for some of the tasks, which hinders the detection of subtle changes in cognition over time. During the first visit, 25 out of 28 participants obtained arrow flanker accuracy scores above 98% on congruent trials and 90% on incongruent trials. Similar accuracy rates were also found for the first two levels of the n-back task. Future research may therefore benefit from administering more difficult tasks or recruiting individuals with poorer cognition at baseline.

The analysis revealed that performance on most cognitive tasks differed during the two cognitive test batteries. Specifically, immediate and delayed word list recall, n-back accuracy (2-back level only), and n-back reaction times (0-back and 1-back levels only) were significantly better during cognitive test battery A than B. Better performance during cognitive test battery A than B for certain tasks may reflect the time-dependent and domain-specific beneficial effect of glucose on cognition (Peters et al., 2020; Smith et al., 2011; Sünram-Lea & Owen, 2017). Poorer performance during the second cognitive test battery may also be related to a decline in mood across the morning, which has been shown to hamper cognitive performance (LeBlanc, 2009; Skala & Zemková, 2022). Indeed, participants reported feeling significantly less agreeable, clearheaded, and energetic shortly before completing cognitive test battery B than at the start of the morning. In contrast, performance was poorer during cognitive test battery A than B for the letter number task and inhibition trials of the arrow flanker task. It is possible that the first cognitive test battery acted as a warm-up cognitive activity for these tasks, which has previously been reported using an inhibition task (Hine & Itoh, 2018).

There was also evidence of practise effects. Performance on all tasks, other than the simple and choice reaction times task, significantly improved from visit 1 to 4, and in some cases visit 1 to visit 2 and 3. Practise effects are problematic as they can mask significant nutrient effects (Bell et al., 2018). Future studies could overcome this issue by including a practise session prior to the first experimental visit so that more accurate measures of baseline cognition are obtained.

4.4.3 Blood lipid levels

It was hypothesised that the active group would display larger improvements in lipid profiles than the placebo group. In contrast, three months of supplementation with cinnamon and turmeric/curcumin did not improve total cholesterol, HDL-cholesterol, LDL-cholesterol, and

triglyceride levels. Consistent with these findings, no changes in lipid profiles have been reported after one (Cox et al., 2015; Tang et al., 2008) and three months (Cox et al., 2020) of supplementation with turmeric/curcumin in healthy adults. In contrast, DiSilvestro et al. (2012) reported that four weeks of supplementation with Longvida™ curcumin (80 mg) improved triglyceride levels but had no effect on HDL-cholesterol and LDL-cholesterol. Pungcharoenkul and Thongnopnua (2011) reported improvements in triglyceride and total cholesterol levels after one week of supplementation with 500 mg of curcuminoids per day. Similarly, LDL-cholesterol and total cholesterol levels improved after four weeks of ingesting 400 mg of Longvida™ curcumin per day (Cox et al., 2015). There are large interindividual differences in the absorption, metabolism, and excretion of polyphenols, which may partly account for the inconsistent findings (Zhang et al., 2022).

With regards to cinnamon, Tang et al. (2008) reported that four weeks of cinnamon *cassia* supplementation (3 g per day) did not influence lipid profiles. Conversely, Ranasinghe et al. (2017) reported that three months of cinnamon supplementation, which increased at monthly intervals, reduced total cholesterol and LDL-cholesterol levels. Ranasinghe et al. (2017) administered cinnamon *zeylanicum*, whereas the present study administered cinnamon *cassia.* Although in *vivo* and in *vitro* studies have shown that both forms of cinnamon possess anti-hyperlipidaemic properties, the chemical structure of cinnamon *zeylanicum* is superior to cinnamon *cassia* (Suriyagoda et al., 2021). Specifically, cinnamon *cassia* has a lower polyphenol content and higher coumarin content, which can be toxic at certain doses (Senevirathne et al., 2022). Therefore, different effects may have occurred if cinnamon *zeylanicum* was administered. Another factor that may have contributed to the non-significant findings is sample heterogeneity. Eleven participants met the criteria for clinically elevated triglyceride levels and seven met the criteria for clinically elevated LDL-cholesterol levels. As previously stated, this heterogeneity may have masked improvements in lipid profiles following cinnamon and turmeric/curcumin supplementation.

Irrespective of the type of supplement consumed, fasted triglyceride levels were significantly higher than levels obtained 180-minutes post-glucose drink. This is consistent with past research (Can et al., 2016; Vossen et al., 2011). The opposite pattern occurred for total cholesterol, LDL-cholesterol, and HDL-cholesterol levels; whereby fasted levels were significantly lower than 180-minute levels. Conversely, Ogita et al. (2008) reported that total cholesterol and LDL-cholesterol levels significantly declined from pre-OGTT to 180-minutes post-OGTT, whereas HDL-cholesterol levels did not change. HDL-cholesterol levels also

significantly declined from visit 1 to visit 4, irrespective of the type of supplement consumed. This finding may reflect the common phenomena that participants enrolled in RCTs tend to intentionally or unintentionally change their behaviour (Cook & Thigpen, 2019).

4.4.4 Inflammation

The results showed that three months of cinnamon and turmeric/curcumin supplementation did not influence CRP levels. This finding is consistent with Nieman et al. (2012), whereby one month of turmeric supplementation (2.8 g per day) did not influence CRP levels, or other markers of inflammation, in overweight non-diabetic females. DiSilvestro et al. (2012) also reported that CRP levels did not improve in healthy adults after one month of supplementation with Longvida™ curcumin. In contrast, Mashhadi et al. (2013) reported that six weeks of supplementation with 3 g of cinnamon resulted in a significant reduction in interleukin-6 levels in females. However, as baseline interleukin-6 levels in the cinnamon group were within the clinical range, it is possible that higher levels of inflammation are required for improvements to occur following cinnamon and turmeric/curcumin supplementation. In support of this suggestion, a meta-analysis of 12 studies that mostly involved patients with pre-existing inflammation found that cinnamon significantly reduced CRP levels (Zhu et al., 2020). Similarly, Belcaro et al. (2010) reported that curcumin supplementation (200 mg per day) significantly lowered CRP levels but only in a subpopulation of osteoarthritis patients with abnormally elevated baseline CRP levels (mean = 16.8 mg/dL). In the present study, 93% of participants had baseline CRP levels below 0.41 mg/dL. Future research may therefore benefit from targeting individuals with some degree of inflammation at baseline.

Although no intervention effects were observed in the present study, the analysis showed that fasted CRP levels were significantly higher than levels obtained 180-minutes post-OGTT. Consistent with this, Choi et al. (2013) reported that CRP levels significantly declined from baseline during an OGTT in individuals with NGT and T2DM. CRP levels have been shown to decrease in response to hyperinsulinemia in healthy participants (Ruotsalainen et al., 2010), potentially underlying the decline in CRP levels observed in the present study. Other measures of inflammation, including interlukin-6 and interlukin-8, have been shown to increase during an OGTT (Choi et al., 2013; Esposito et al., 2002; Straczkowski et al., 2003). Therefore, future research could determine whether cinnamon and turmeric/curcumin can reduce the increase in these measures during an OGTT.

4.4.5 Mood

Supplementation with cinnamon and turmeric/curcumin did not influence mood ratings throughout each visit and between each visit. In line with this results, Rainey-Smith et al. (2016) reported that 12 months of curcumin supplementation did not improve ratings of stress, depression, and anxiety in healthy older adults without depression. In contrast, four weeks of curcumin supplementation significantly reduced ratings of fatigue throughout the week before the follow-up visit, as well as levels of fatigue during the follow-up visit (Cox et al., 2015). Similarly, Esmaily et al. (2015) reported a reduction in anxiety levels, but not depression levels, in overweight females after 30 days of supplementation with curcumin. Small et al. (2018) also reported that 18 months of curcumin supplementation improved depression scores. As stated in Section 4.4.2, the bioavailability of the curcumin administered in the present study probably contributed to the lack of significant changes in mood. In addition, among other mechanisms, it was hypothesised that cinnamon and turmeric/curcumin may enhance mood and cognition via their anti-inflammatory and anti-hyperglycaemic properties. However, blood glucose levels and CRP levels did not change after three months of cinnamon and turmeric/curcumin supplementation, potentially contributing to the present findings.

4.4.6 Thirst and hunger

Contrasting with previous research (Mousavi et al., 2020; Qin et al., 2010; Yazdanpanah et al., 2020), no significant changes in BMI and body fat percentage occurred from visit 1 to visit 4. However, only five participants were classified as overweight, which may account for these findings. Ratings of hunger and thirst throughout the morning of each visit did not significantly differ between the active and placebo group. To the best of the authors knowledge, no studies have examined the chronic effects of turmeric, curcumin, or cinnamon on sensations of hunger and thirst. However, acute effects have been examined. Markey et al. (2011) reported that the addition of cinnamon (3 g) to a high fat meal did not influence gastric emptying rate, hunger ratings, thirst ratings, or subsequent food intake in a group of healthy adults. Similarly, Hlebowicz et al. (2009) reported that the addition of 3 g of cinnamon to rice pudding did not influence hunger ratings, but there was a significant increase in GLP-1 concentrations. In contrast, a study by Zanzer et al. (2017) reported that the consumption of a turmeric drink prior to a glucose challenge significantly lowered hunger ratings and increased plasma peptide tyrosine tyrosine. The discrepancies between changes in self-report measures of appetite and appetite-related hormones highlights the importance of obtaining both subjective and objective

measures of appetite in future studies. Although prolonged and repeated ingestion of curcumin could potentially result in the accumulation of curcumin at therapeutic plasma levels, it is probable that the dosage and bioavailability of curcumin administered in the present study was insufficient for this to occur.

4.4.7 Limitations

There are several limitations that potentially contributed to the findings. The sample was highly heterogenous and possibly too diverse to analyse as one group. Although participants fasted for 12 hours, a standardised evening meal was not consumed prior to each visit. Therefore, a second meal effect may have occurred, which is known to influence the glycaemic response to an OGTT (Wolever et al., 1988). Adherence to the study protocol was verbally checked at the beginning of each visit, however it is possible that participants did not comply with the protocol. Furthermore, cognitive performance was only assessed after the consumption of 75g glucose, which may have masked any subtle chronic effects of the active supplement due to the glucose facilitation effect (Benton, 2001; Smith et al., 2011; Sünram-Lea & Owen, 2017). This is also a potential issue for mood, as most ratings were obtained post-drink consumption (Mantantzis et al., 2019). Lastly, although there were no baseline between-group differences, the use of a between-subjects design inevitably introduced uncontrolled sources of variability that may have influenced the results, such as individual differences in habitual polyphenol intake, computer literacy, and socioeconomic status (Adolphus et al., 2017).

4.4.8 Recommendations for future research

More studies involving homogenous, healthy populations are needed to determine whether supplementation with cinnamon and turmeric can prevent the onset of abnormal GT and cognitive decline. Whilst this study examined the combined effect of cinnamon and turmeric/curcumin for the first time, studies could examine whether these spices have synergistic or additive effects. It would also be beneficial for studies to identify factors that moderate the health effects of polyphenols, such as gut microbiome composition and habitual polyphenol intake. Lastly, the optimal dose of cinnamon and turmeric for cognitive improvements in healthy populations is currently unknown, therefore dose-response studies could be conducted.

4.4.9 Conclusions

In conclusions, three months of cinnamon and turmeric/curcumin supplementation did not improve blood glucose levels, lipid profiles, CRP levels, cognition, mood, thirst, hunger, BMI, and body fat percentage in apparently healthy middle-aged and older adults. Methodological factors such as sample size, dosage of cinnamon, bioavailability of curcumin, and sample heterogeneity are likely to have contributed to the non-significant results. Despite the lack of improvements, further research is warranted given the increasing prevalence of IGT and T2DM (Tabák et al., 2012; Zheng et al., 2018). To increase the likelihood of observing significant changes in future, studies would benefit from verifying the bioavailability of curcumin beforehand and implementing a health screening visit.

Chapter 5

General discussion and guiding principles for future research

Some of the guiding principles in Section 5.2 were published in the following paper: Gaylor, C., Benton, D., Brennan, A., & Young, H. A. (2022). The impact of glycaemic load on cognitive performance: a meta-analysis and guiding principles for future research. *Neuroscience & Biobehavioural Reviews,* 141, 104824.

5.1 Summary of thesis findings

The broad aim of this thesis was to examine the impact of diet on blood glucose levels, cognition, and sleep using three different approaches.

The key findings of this thesis are:

- A lower breakfast GL benefitted immediate episodic memory, in adults, during the late postprandial period (>120 minutes post-breakfast; Chapter 2).
- The beneficial effect of a LGL breakfast on episodic memory was greater in younger adults (<35 years old) and those with better GT (fasting glucose <6.1 mmol/L and/or 2-hour glucose <7 mmol/L; Chapter 2).
- The consumption of drinks differing in GL shortly before bedtime affected certain aspects of sleep architecture and continuity, but most effects were trends or did not survive Bonferroni correction (Chapter 3).
- The consumption of drinks differing in GL shortly before bedtime did not affect subjective measures of sleep quality and sleep-dependent memory consolidation (Chapter 3).
- Three months of supplementation with cinnamon and turmeric/curcumin did not influence glycaemia, cognition, lipids, CRP, mood, thirst, hunger, body fat percentage, and BMI in a sample of apparently healthy middle-aged and older adults (Chapter 4).

5.1.1 Chapter 2

In Chapter 2, a systematic review of the effect of GL on acute cognitive performance in children, adolescents, and adults was performed. Due to a lack of data, only breakfast studies involving adults were included in the meta-analysis. The results of the meta-analysis suggested that the effect of breakfast GL on postprandial cognition may be time-dependent and subdomain specific. Relative to a HGL breakfast, a LGL breakfast significantly improved immediate episodic memory, but only during the late postprandial period (Figure 2). There was

also a non-significant trend for better delayed episodic memory during the late postprandial period following a LGL breakfast (Figure 4). Furthermore, the beneficial effect of a LGL breakfast on episodic memory was greater in younger adults (<35 years old; Figure 6) and those with better GT (fasting glucose <6.1 mmol/L and/or 2-hour glucose <7 mmol/L; Figure 3 and 5). In contrast, the consumption of breakfasts differing in GL did not significantly influence accuracy of working memory, accuracy of attention, and speed of attention. However, relative to episodic memory, a wider range of tasks were used to measure attention and working memory, which may account for the non-significant results.

With regards to children and adolescents, there was no consistent evidence that variations in breakfast GL influenced cognitive performance. However, the data suggested that episodic memory and accuracy of attention were most consistently benefitted by the consumption of a LGL breakfast. Specifically, breakfasts that slowly release glucose may protect against a decline in episodic memory and accuracy of attention during the late postprandial period (>120 minutes), which is consistent with the results of the meta-analysis. The relationship between breakfast GL and cognition in children and adolescents was also influenced by biological sex, age, and task difficulty hence these factors should be carefully considered in future. Five studies administered meals or drinks differing in GL after breakfast time, of which two reported that a HGL lunchtime meal significantly benefitted cognition (Jansen et al., 2020; Marchand et al., 2020). However, in Marchand et al. (2020), there was only a seven second difference in task performance between the HGL and LGL meal. In comparison to breakfast studies, it may be more difficult to detect cognitive differences during the afternoon and evening due to the shorter length of fast (Owen et al., 2012), increased variability in GT (Wolever & Bolognesi, 1996), and smaller difference in glycaemic responses between LGL and HGL meals/drinks (Leung et al., 2020; Wolever & Bolognesi, 1996).

Given the methodological heterogeneity between studies (e.g., sample characteristics, blinding, pre-test standardisation, macronutrient and energy composition of breakfasts, and control for type 1 errors), it is premature to make nutritional recommendations. However, if replicated, the present findings could have important implications. Within the United Kingdom, many staple breakfast foods consumed by adults are high in GI/GL, such as jam, white bread, and cereal (Van Bakel et al., 2009). Furthermore, a recent study in the United Kingdom found that children under 10 years of age consumed over 50% of their recommended daily allowance of sugar at breakfast via sugary cereals, drinks, and spreads (Taylor, 2017). Therefore, some adults and children are consuming breakfasts that may be negatively affecting cognitive functioning

throughout the morning. A LGL breakfast may be particularly advantageous for those with occupations (e.g., schoolchildren or University students) or jobs (e.g., pilots or medical professionals) that require long periods of attention, learning, and memory.

5.1.2 Chapter 3

Chapter 3 examined the effect of variations in pre-bedtime GL on sleep, sleep-dependent memory consolidation, and nocturnal glucose metabolism. Whilst variations in pre-bedtime GL did not influence sleep-dependent memory consolidation and subjective measures of sleep quality, there was some tentative evidence to suggest that certain measures of sleep architecture and continuity may be affected. Furthermore, some of these effects were influenced by the order of drink consumption. With regards to sleep architecture, when glucose was consumed first, the LGL drink was associated with a higher N3 sleep percentage across the whole night (not significant after applying a Bonferroni correction), and a non-significant trend towards less REM sleep during the second half of the night. Despite order effects occurring, the pattern of change is consistent with the effect of high carbohydrate and low carbohydrate meals/diets on N3 sleep and REM sleep (Benton et al., 2022; Vlahoyiannis et al., 2021). Furthermore, there is biological plausibility for an effect of GL on N3 sleep and REM sleep, including changes in the firing rate of sleep-promoting neurons in the VLPO and lateral hypothalamic area (Ahnaou et al., 2008; Burdakov & Adamantidis, 2020; Burdakov et al., 2005). Bayesian statistics were used post hoc to determine whether there was evidence of absence or absence of evidence (Appendix 16). Both analyses showed anecdotal evidence in favour of the alternative hypothesis thus more research is needed before definitive conclusions are made. With regards to sleep continuity, the analysis unexpectedly showed that WASO was longer after the LGL drink than HGL drink when glucose was consumed first, but this did not survive Bonferroni correction. The split-night analysis also showed that the LGL drink was associated with a significantly higher percentage of wake during the second half of the night than the HGL drink However, further research is needed given the novelty of these findings, the small sample size, and relatively small effects.

This study has several strengths that warrant consideration. To the best of the authors knowledge, this is the first study that examined whether manipulating pre-bedtime diet influenced sleep-dependent memory consolidation. Given that the consumption of a glucose load (Chapter 1) and breakfasts differing in GL (Chapter 2) can impact memory consolidation, further research is clearly warranted. Secondly, a caveat of many studies in this area of research

is that mixed macronutrient meals or diets were administered and therefore it is difficult to differentiate GL effects from macronutrient effects. The paradigm used in this study, however, enables the findings to be attributed to the glycaemic nature of a meal or drink with more certainty. Lastly, the use of continuous glucose monitoring throughout the night provided valuable insight into some of the potential mechanism that could underlie the effect of GL on sleep.

5.1.3 Chapter 4

In Chapter 4, the chronic effects of cinnamon and turmeric/curcumin on a) measures of glycaemia and cognition and b) lipid profiles, CRP levels, mood, thirst, hunger, BMI, and body fat percentage in healthy middle-aged and older adults were examined. There were no significant changes in any of these outcome measures after one, two, and three months of supplementation with cinnamon and turmeric/curcumin. Given the promising results of animal studies and randomised controlled trials involving type 2 diabetics, the primary aim of this study was to determine whether supplementation with cinnamon and turmeric/curcumin could improve a range of outcome measures in healthy middle-aged and older adults. All participants met the inclusion criteria and were apparently healthy, yet many were revealed to have clinically elevated blood glucose, LDL-cholesterol, and triglycerides levels during the study. Indeed, IGT and dyslipidaemia are often underdiagnosed, especially in older adults (Ladeira et al., 2012; Meijnikman et al., 2017; Shanmugasundaram et al., 2010). It is likely that the heterogenous sample was too diverse to analyse as one group.

To determine whether sample heterogeneity contributed to the lack of improvements in glycaemic control, three exploratory analyses were performed. Results indicated that there was a significantly larger fall in 2-hour glucose levels after three months in the placebo group in those with higher compared to lower 2-hour glucose levels at baseline (> and < 7.2 mmol/L, respectively). The same pattern occurred for the active group and placebo group after one month of supplementation, but differences were no longer significant after applying a Bonferroni correction. It was speculated that improvements in the placebo group may be due to factors such as the composition of the placebo supplement, intentional or unintentional behavioural changes following enrolment, or regression to the mean. The type of cognitive tasks administered, dosage of cinnamon, and bioavailability of curcumin may have also contributed to the lack of overall improvements. Although no changes were observed, a strength of this study is that the combined effects of cinnamon and turmeric/curcumin were

investigated, rather than their individual effects. This approach is more ecologically valid as spices are commonly consumed in varying combinations in everyday life.

5.2 Guiding principles for future research

Drawing from the strengths and limitations of previous research and the studies performed as part of this thesis, a series of guiding principles were created which outline some of the variables that should be considered when designing studies in future. The intention of these guiding principles is to facilitate a clearer understanding of the relationship between diet, blood glucose levels, cognition, and sleep. A summary is provided in Figure 24.

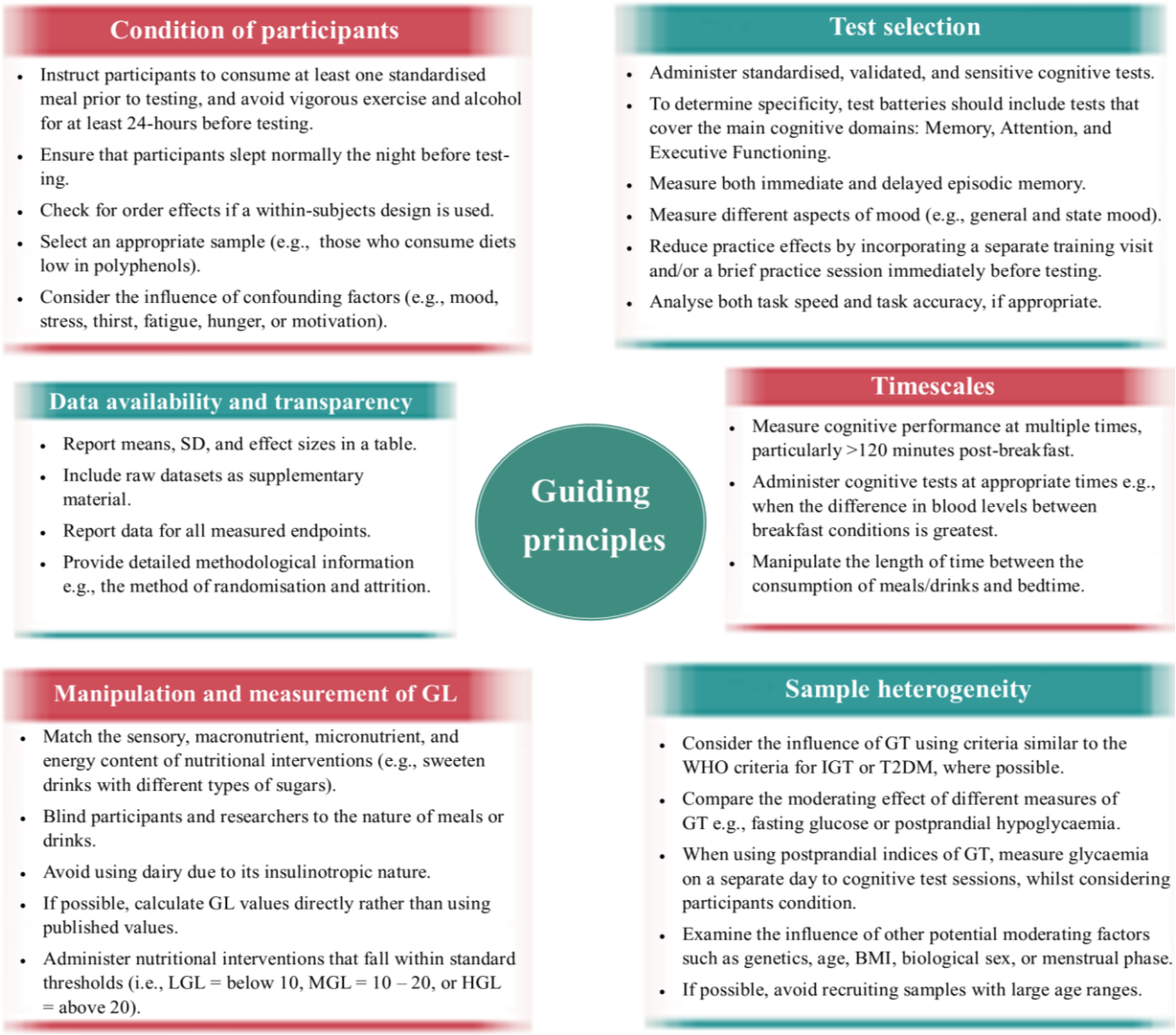


Figure 24. Guiding principles for future research. GT = glucose tolerance, GL = glycaemic load, BMI = body mass index.

5.2.1 Timescales

The studies reviewed in Chapter 2 measured cognitive performance at different times throughout the postprandial period, a factor that may have played a key role in producing conflicting literature. The meta-analysis revealed multiple lines of evidence to suggest that the beneficial effect of a LGL breakfast in adults may emerge during the mid-postprandial period (60 – 119 minutes) and, in particular, the late postprandial period (120 minutes or later). Studies in children and adolescents have reported similar findings, whereby a significant beneficial effect of a LGL breakfast only occurred after 120 minutes (Cooper et al., 2012, 2015; Ingwersen et al., 2007; Taib et al., 2012; Wesnes et al., 2003; Young & Benton, 2015). These findings suggest that a LGL breakfast may attenuate decrements in cognitive performance across the morning. As such, future studies would benefit from assessing cognitive performance at multiple time points, especially during the late postprandial period (120 minutes or later).

In many cases, participants did not undergo cognitive testing when the difference in blood glucose levels between breakfast conditions were greatest, times that are more likely to be cognitively relevant. For example, Deng et al. (2021) administered a cognitive test battery 60 minutes post-breakfast. Blood glucose levels after the HGL and LGL drink were almost identical at 60 minutes, possibly contributing to the lack of significant results. If the GL of nutritional interventions is calculated directly, on separate days to cognitive test sessions, then cognitive test batteries can be administered at the most appropriate time points during the postprandial period. This information would be particularly useful for researchers that choose to administer one test battery to reduce participant burden or school disruption. In addition, this approach would be useful in studies aiming to measure GT, as blood glucose levels can fall during periods of intense cognitive demand (Donohoe & Benton, 1999; Scholey et al., 2001),

With regards to the impact of GL on sleep, the length of time between drink/meal consumption and bedtime needs to be carefully considered. In Chapter 3, the experimental drinks were consumed approximately 15 minutes before bedtime hence most participants fell asleep whilst glucose levels were still rising. If the relationship between GL and sleep is, in part, mediated by the activity of glucose-sensing neurons, insulin, and counterregulatory hormones, then different effects are likely to occur if the interval between drink consumption and bedtime is extended. For example, one speculative suggestion is that the consumption of a HGL meal or drink may be associated with a longer SOL if bedtime coincides with when blood glucose

levels are falling (Benton et al., 2022; Burdakov et al., 2005). Core body temperature and the secretion of hormones, including melatonin, ghrelin, and growth hormone, are regulated by the circadian rhythm. Therefore, the impact of GL on sleep is also likely to differ depending on the stage of circadian rhythm.

5.2.2 Manipulation and measurement of glycaemic load

Studies often calculate the GL of nutritional interventions using published GI values. Indeed, this method was used to estimate the GL of the standardised evening meal and experimental drinks administered in Chapter 3. However, there are several issues with published values. The GI of the same two foods can vary depending on a range of factors, including the degree of ripeness, country of origin, variety, growing conditions, and cooking, processing, and storage methods (Aston et al., 2008; Henry et al., 2005). For example, grinding and flaking increases the GI of foods by decreasing their particle size, which renders the foods more vulnerable to digestive enzymes (Jayasinghe et al., 2013). Similarly, the greater the degree of starch gelatinisation during cooking, the greater the susceptibility to hydrolyzation by enzymes (Walton & Rhodes, 1997). Consequently, published values can overestimate the actual GI of a food by up to 55% (Dodd et al., 2011). Although it is more costly, future studies would benefit from calculating GL values directly. This would enable researchers to verify beforehand that HGL and LGL nutritional interventions produce significant differences in postprandial glycaemia, which is an issue that occurred in some breakfast studies (Smith & Foster, 2008b; van der Zwaluw et al., 2014).

A major limitation of the studies reviewed in Chapter 2, and hence the results of the meta-analysis, is that most breakfast interventions differed not only in terms of GL but also macronutrient and energy composition. This limits the extent to which findings can be attributed to differences in GL, as the provision of different amounts of energy, fat, protein, and carbohydrate can also impact postprandial cognition (Fischer et al., 2002; Kaplan et al., 2001). The importance of matching the macronutrient and energy content of meals was highlighted in Section 2.3.3.6, whereby inclusion of studies that matched the macronutrient and energy content of meals revealed a trend towards a beneficial effect of a LGL breakfast on accuracy of attention scores during the late postprandial period. The polyphenol, vitamin, and mineral content of breakfast interventions often differed, all of which can acutely modulate cognitive performance (Huskisson et al., 2007; Philip et al., 2019). Similarly, the effect of carbohydrate consumption on sleep has typically been examined by manipulating the

macronutrient content of meals or drinks. This limitation was overcome in Chapter 3 by administering identical, isocaloric drinks sweetened with either isomaltulose or glucose, allowing the results to be attributed to differences in GL with more certainty. Alternatively, different types of rice could be administered (Drozdowska et al., 2021; Jansen et al., 2020). An additional advantage of this method is that it enables randomised controlled trials to be double-blinded.

Another factor that needs consideration is the GL of nutritional interventions. As the GL of meals and drinks varied considerably between studies included in the systematic review, standard GL thresholds could not be applied (i.e., LGL = below 10, MGL = 10 – 20, or HGL = above 20). Instead, within each study, the two meals or drinks with the largest difference in GL were categorised as the HGL and LGL breakfast interventions. This resulted in large variability in the GL of LGL breakfast interventions, which ranged from 1.56 (Ginieis et al., 2018) to 50 (van der Zwaluw et al., 2014), and HGL breakfast interventions, which ranged from 11.3 (Anderson et al., 2018; Anderson et al., 2021) to 71 (Lamport et al., 2014; Lamport et al., 2013a). The GL of nutritional interventions administered before bedtime also differed considerably. In Herrera (2010) and both Afaghi et al. (2007) and Vlahoyiannis et al. (2018), the GL of the LGL meal/drink was 38 and 81, whilst the GL of the HGL meal/drink was 59 and 175, respectively. To facilitate more precise comparisons in future, research would benefit from administering meals or drinks that fall within the thresholds stated above. Dose-response studies could also be conducted using a range of GL values to determine the optimal GL of meals for improved cognition and sleep.

The difference in GL between LGL and HGL breakfast interventions also varied considerably. The smallest difference in GL was six (Benton et al., 2003) and the largest difference was 59 (Lamport et al., 2014; Lamport et al., 2013a). It is unclear what impact this has on the relationship between breakfast GL and cognitive performance as significant effects were reported after consuming breakfasts with smaller and larger differences in GL. Due to a limited number of studies, it was not possible to determine whether differences in GL influenced the results via subgroup analyses. However, there was some evidence to suggest that when the GL of breakfast was manipulated using different types of sugars, studies tended to demonstrate significant effects when there was a larger difference in GL. That is, when glucose was compared with isomaltulose or fructose (Ginieis et al., 2018; Taib et al., 2012; Young & Benton, 2014a, 2015), rather than when sucrose was compared with isomaltulose (Deng et al., 2021; Dye et al., 2010). However, this suggestion requires further investigation.

The use of milk as a vehicle should also be reconsidered since dairy products are insulinotropic. The addition of dairy to meals or drinks can shorten postprandial glucose profiles and produce lower GL values than anticipated (Blaak et al., 2012). This is problematic when the objective of a study is to compare the impact of different glycaemic profiles on cognition or sleep. It is plausible that by using a dairy-based vehicle, the difference in postprandial blood glucose levels between two meals is reduced to the point where it is no longer cognitively relevant (Blaak et al., 2012). As such, dairy products should be avoided where possible.

5.2.3 Sample heterogeneity

Research has repeatedly shown that individuals respond in different ways to the same nutritional interventions (Lampe et al., 2013). As such, an analysis of the average response to nutritional interventions may fail to reveal the range of responses produced (Blundell et al., 2010). Indeed, it is likely that sample heterogeneity played a key role in the lack of improvements following three months of cinnamon and turmeric/curcumin supplementation (Chapter 4). Although there are many other relevant factors, this section considers the influences of individual differences in GT, age, biological sex, and BMI. Additional sources of interindividual variability in glycaemic responses are also considered briefly in Section 5.2.3.5.

5.2.3.1 Glucose tolerance

In Chapter 2, the results of the meta-analysis highlighted the importance of considering the influence of GT on the relationship between GL and postprandial cognition. Studies have also reported that GT moderated the effect of breakfast GL on attention, inhibitory control, working memory, and visuospatial memory in adults (Anderson et al., 2018; Lamport et al., 2014; Nabb & Benton, 2006a, 2006b; Young & Benton, 2014a) and working memory in children (Anderson et al., 2020). Despite its importance, many studies reviewed in Chapter 2 did not measure GT, especially studies involving children. In those studies that did, some defined poorer GT using the WHO criteria (Lamport et al., 2014; Lamport et al., 2013a), whereas others used the median split of a GT parameter (Brindal et al., 2013; Nilsson et al., 2009, 2012; van der Zwaluw et al., 2014; Young & Benton, 2014a). Furthermore, a range of GT parameters were used, such as fasting glucose (Nabb & Benton, 2006a), 3-hour glucose (Nilsson et al., 2009), and glucose AUC (Nilsson et al., 2012). Subgroup analyses were performed in the meta-analysis by classifying participants as having poorer or better GT if fasting glucose levels were above or below 6.1 mmol/L and/or 2-hour glucose levels were above or below 7 mmol/L. Although these measures are related, they reflect different aspects of metabolism and therefore

it is questionable whether such measures should have been combined (Meyer et al., 2006). Elevated fasting glucose levels are primarily due to hepatic insulin resistance and impaired basal insulin secretion and first-phase insulin release, whereas elevated 2-hour glucose levels are primarily due to muscle insulin resistance and impaired first- and second-phase insulin release (Meyer et al., 2006). As this area of research evolves, future meta-analyses could examine the impact of both GT measures separately.

The influence of GT on the relationship between GL and sleep was not examined in Chapter 3 due to the small sample size, nor has this been considered by previous studies. Future research could explore whether certain indices of GT exert a stronger moderating effect on the relationship between GL, sleep, and sleep-dependent memory consolidation than others. For example, Owen et al. (2013) reported that fasting glucose levels moderated the glucose facilitation effect whereas 2-hour glucose levels did not, highlighting the importance of considering more than one GT parameter in future. In Chapter 4, several post hoc exploratory analyses were performed to determine whether unexpected heterogeneity in baseline GT contributed to the lack of improvements in GT throughout the study. Participants were divided into two GT subgroups using the median split of baseline fasting glucose, 2-hour glucose (post-OGTT), and HbA1c. This approach enabled comparisons between equally sized subgroups. However, a limitation of using the median split is that definitions of poorer and better GT are arbitrary and sample dependent, limiting comparisons between studies. Alternatively, future studies could directly compare the glucose-lowering effects of cinnamon and turmeric in individuals who meet the WHO criteria for NGT, IGT, and T2DM.

The findings from a recent study by Anderson et al. (2018) also suggest that future research may benefit from analysing GT as a continuous variable rather than a dichotomous variable. Anderson et al. (2018) compared the cognitive effects of a breakfast drink containing milk or apple juice in young adults. Using a linear mixed model, the authors identified specific fasting glucose levels where cognitive differences between breakfast conditions were observable. Importantly, these levels varied depending on the nature of the task (working memory, attention, or inhibitory control) and outcome measure (speed vs. accuracy), indicating that the domain specific response to GL might reflect a variability in the threshold at which specific domains are impacted.

5.2.3.2 Age

In Chapter 2, the meta-analysis revealed that the beneficial effect of a LGL breakfast on delayed episodic memory was greater in younger adults (mean age <35 years). It was suggested that this finding may reflect the increased interindividual variability in cognition, GT, hydration, and nutritional status with age (Asamane et al., 2020; Ferrucci & Kuchel, 2021; Mungas et al., 2010; Zulman et al., 2011). Therefore, null findings in studies with large age ranges may reflect a failure to test for age effects rather than no effect of breakfast GL. Similarly, some studies analysed children and adolescents as one group (Cooper et al., 2015; Wesnes et al., 2003). However, children and adolescents should ideally be analysed separately given the abundance of metabolic, behavioural, and hormonal changes associated with puberty (Kawakubo et al., 2011). Adolescence is associated with a transient state of insulin-resistance that begins at the onset of puberty and increases insulinemic responses to HGI and LGI meals (Cooper et al., 2017; Moran et al., 1999). The rate of cerebral glucose utilisation is also higher in young children compared to adolescents (Chugani, 1998), potentially making young children more sensitive to fluctuations in postprandial glycaemia. Indeed, Álvarez-Bueno et al. (2019) reported that delayed episodic memory scores were significantly higher after a LGI breakfast, compared to HGI breakfast, in children but not adolescents.

There is clear evidence that ageing is associated with changes in sleep architecture and continuity. Relative to younger adults, older adults tend to spend less time in REM sleep and N3 sleep and more time in light sleep (Espiritu, 2008). Furthermore, ageing is associated with decreased sleep efficiency and total sleep time and increased SOL and WASO (Floyd et al., 2000). Cherdieu et al. (2014) also reported that the beneficial effect of sleep on declarative memory consolidation was weaker in older adults than younger adults. This has also been reported in middle-aged adults relative to younger adults (Backhaus et al., 2007). Given the age-related changes in sleep and sleep-dependent memory consolidation, studies could examine whether the effects of pre-bedtime GL are influenced by age, ideally by directly comparing different age groups within the same study.

5.2.3.3 Anthropometric differences

As shown in Table 2, few studies assessed whether measures of obesity influenced the relationship between breakfast GL and postprandial cognition in adults. This is surprising given the strong association between obesity, cognitive dysfunction, and GT throughout adulthood (Fellows & Schmitter-Edgecombe, 2018). Although a larger number of studies involving

children and adolescents included BMI as a covariate, there was no evidence to suggest that BMI moderated the effect of breakfast GL on cognitive performance (Table 4). However, other than Anderson et al. (2020), all participants had BMIs within the normal, healthy range. As glycaemic responses to HGI meals are greater in overweight adolescents and adults, compared to normal weight individuals (Yalçın et al., 2017; Zakrzewski & Tolfrey, 2012), it is possible that BMI or other measures of obesity exert a moderating effect on the relationship between GL and cognition.

The moderating effect of BMI was not considered in Chapter 3 and 4 as most participants had a BMI within the normal range. However, the effect of diet composition on sleep may be influenced by BMI. Nehme et al. (2014) reported that the consumption of a high carbohydrate diet for a week increased sleep duration in obese adults but not normal weight adults. Studies have also examined whether cinnamon differentially affects postprandial glycaemia in normal weight adults and obese/overweight adults. Zare et al. (2019) reported a larger improvement in glycaemic control and lipid profiles in type 2 diabetics with higher BMIs. Similarly, Wang et al. (2021) reported that the addition of 6 g of cinnamon to oatmeal produced a larger reduction in postprandial insulin AUC in overweight/obese adults than normal weight adults. Conversely, Magistrelli (2010) administered cereal with and without 6 g of cinnamon. Whilst the addition of cinnamon to the meal significantly reduced postprandial glycaemic responses, this effect did not differ between BMI groups. Discrepancies may be due to the use of test meals differing in macronutrient content and sample characteristics. In comparison to Magistrelli (2010), Wang et al. (2021) recruited older adults with poorer glycaemic control at baseline. The impact of BMI on the relationship between diet, cognition, and sleep warrants further exploration, especially given the increasing prevalence of obesity (Keaver et al., 2020).

5.2.3.4 Biological sex

Several breakfast studies in children reported that female children (ranging from 6 to 12 years of age) were more susceptible to variations in breakfast GL than male children (Anderson et al., 2020; Brindal et al., 2013; Mahoney et al., 2005). This finding may be due to sex differences in insulin sensitivity and cortisol levels, both of which have been suggested to underlie the effect of GL on acute cognitive performance (Cooper et al., 2012; Lamport et al., 2013a). In adults, no study reported that sex moderated the cognitive effects of breakfast GL. However, it has previously been reported that the consumption of glucose enhanced episodic memory in

older males but not older females (Craft et al., 1994). Therefore, further exploration of this factor is warranted.

As the menstrual cycle influences sleep architecture and sleep-dependent memory consolidation (Baker & Driver, 2007; Genzel et al., 2012), females were excluded from the study in Chapter 3. For example, Genzel et al. (2012) reported that sleep benefitted declarative and procedural memory performance in both males and females, but only when females were in their luteal phase. In addition, an increase in the number of sleep spindles post-encoding only occurred during the luteal phase, which may be due to increased progesterone and oestrogen. There are also sex differences in sleep, whereby females typically have better PSG-defined sleep quality than men, but poorer self-reported sleep quality (Mong & Cusmano, 2016). Females also tend to spend more time in N3 sleep than males (Ohayon et al., 2004). To the best of the authors knowledge, no randomised controlled trial has examined whether the impact of diet on sleep and memory is influenced by biological sex or the phase of menstrual cycle. However, these findings suggest that both factors need to be considered when exploring the relationship between diet, sleep, and sleep-dependent memory consolidation.

There is also some suggestion that the beneficial effects of polyphenols are influenced by biological sex. Kuszewski et al. (2020) examined the effects of supplementation with curcumin, fish oil, or both for 16 weeks in overweight/obese middle-aged and older adults. Curcumin improved episodic memory and fish oil improved processing speed in males but not females. Importantly, no treatment effects occurred when males and females were analysed together. It was suggested that sex differences may have been due to better baseline cognition in females. Schiborr et al. (2014) compared the bioavailability of three different types of curcumin and reported that females consistently absorbed curcumin more efficiently than males (1.4-fold higher in females). It is unclear why these sex differences occurred, but differences in body weight, blood volume, and body fat between males and females may play a role.

5.2.3.5 Genetic differences

The impact of GL on cognition may interact with an individual's genetic profile. The apolipoprotein e4 allele (ApoE4) is the main genetic risk factor for Alzheimer's disease. Hanson et al. (2015) examined the acute effects of a HGI/high saturated fat meal and a LGI/low saturated fat meal in older adults with and without cognitive impairment and/or the ApoE4 genotype. ApoE4 non-carriers with normal cognitive function displayed poorer delayed memory after an HGI/high fat meal compared to a LGI/low fat meal, whereas ApoE4 carriers

with normal cognitive function exhibited better delayed memory after a HGI/high fat meal. A cross-sectional study of older adults also reported that higher, relative to lower, carbohydrate consumption was associated with poorer episodic memory in ApoE4 non-carriers and poorer attention in ApoE4 carriers (Gardener et al., 2017). Gentreau et al. (2020) conducted a 12-year follow-up study using food frequency questionnaire data from elderly participants. In ApoE4 carriers, a HGL afternoon snack was associated with a decline in visual memory, episodic memory, and global cognition. Conversely, in ApoE4 non-carriers, a medium or high GL lunch was associated with better executive function over time. These findings, albeit inconsistent, suggest that the effects of carbohydrate quality and quantity on cognition are moderated by an individual's ApoE4 status and/or pre-existing cognitive function. If genetically susceptible groups are identified, the effect of GL on episodic memory and attention may be stronger than previously thought.

5.2.3.6 Additional interindividual sources of variability

There are a number of other interindividual factors that can also influence the glycaemic response to meals. The glycaemic and insulinemic response to food is influenced by the extent of mastication (Goh et al., 2021; Nilsson et al., 2009; Ranawana et al., 2014; Zhu et al., 2013). For example, Ranawana et al. (2014) reported that chewing 15 times, compared to 30 times, significantly attenuated the glycaemic response to rice. Mandel and Breslin (2012) reported that individuals with higher endogenous salivary α-amylase activity had significantly lower glycaemic responses to a starch solution. An emerging area of research is precision nutrition, which aims to optimise cognitive function and prevent disease by developing personalised dietary recommendations based on genetic, metabolic, environmental, and social factors (Soldevila-Domenech et al., 2019). Within this field, studies have shown that postprandial glycaemia is not only predicted by the nutritional content of a food (e.g., GI and GL) but also genetics, gut microbiome composition, dietary and lifestyle habits, blood parameters, and anthropometric measures (Berry et al., 2020; Mendes-Soares et al., 2019; Zeevi et al., 2015). For example, Søndertoft et al. (2020) reported that microbial features (e.g., richness of metagenomics species) predicted up to 14% of the variance in postprandial glucose levels. Therefore, it is plausible that interindividual differences in the aforementioned factors may have contributed to inconsistencies within the literature to date. Indeed, there is growing evidence that individual differences in gut microbiome composition may influence the effectiveness of polyphenol interventions (Zhang et al., 2022). For example, individuals whose fasting insulin levels improved after six weeks of supplementation with grape pomace had

significantly lower levels of *Prevotella* and Firmicutes in faecal samples at baseline than non-responders (Ramos-Romero et al., 2021).

5.2.4 Selection of cognitive tests

In Chapter 4, cognition was assessed using a battery of cognitive tasks that had previously shown to be sensitive to the effects of breakfast GL (Cooper et al., 2012; Ginieis et al., 2018; Nabb & Benton, 2006a). However, no changes were detected in this study, which may partly be due to insufficient task sensitivity and/or difficulty. Consistent with this suggestion, baseline accuracy scores were above 90% on the arrow flanker task and the first two levels of the n-back task. Cox et al. (2015) and Cox et al. (2020) reported that curcumin supplementation for four and 12 weeks, respectively, significantly improved working memory, which was assessed using a serial subtraction task. Therefore, this task may be a more appropriate choice for measuring changes in working memory following curcumin supplementation. However, it is important to note that performance on this task is strongly influenced by pre-existing mathematical skill (Bristow et al., 2016).

The studies reviewed in Chapter 2 administered a wide range of tests to measure the same cognitive subdomain. This suggests that tests may have been selected due to convenience rather than their sensitivity to previous nutritional interventions (Adolphus et al., 2021). As such, a null finding may be due to a lack of test sensitivity rather than a lack of effect of GL. For example, Ingwersen et al. (2007) created an attention composite score using a reaction time task and digit vigilance task, whereas Ingwersen (2011) administered a Continuous Attention Task. Although the same breakfasts were administered in both studies, and children were of a similar age, the consumption of a LGL breakfast only improved attention in Ingwersen et al. (2007). The authors suggested that the discrepant findings may be due to differences in cognitive demand and hence task sensitivity.

To gain a better understanding of the impact of GL on postprandial cognition, future studies would benefit from using standardised, validated tests that are known to be sensitive to the subtle, but important, effects of nutritional interventions (Adolphus et al., 2017). Based on the results of the meta-analysis, word list recall tasks are sensitive to the effect of breakfast GL on episodic memory in adults. Both immediate and delayed episodic memory should be measured, and words matched for the number of syllables, the frequency with which they occur in English, the number of abstract and concrete words, and imageability (Young & Benton, 2014a). Due

to the wide range of tests used to measure other cognitive domains and subdomains, it is difficult to state whether a test is sensitive to the effects of breakfast GL. The results of a recent systematic review by Peters et al. (2020) could also be used to inform test selection. The authors found that the medial temporal and frontal lobes and networks, which underpin episodic memory and attentional processes, may be preferentially affected by carbohydrate consumption. Despite the sensitivity of episodic memory to glycaemic manipulations, as evidenced in the present meta-analysis, many studies did not measure this subdomain. It would be useful if future work continued to assess episodic memory so that firm conclusions could be made regarding the conditions that elicit beneficial effects of LGL or HGL breakfasts.

The outcome measures assessed also need to be appropriate. Some studies included in the systematic review only measured task speed (Deng et al., 2021; Micha et al., 2011). However, faster performance does not necessarily equate to better performance as speed may increase at the expense of accuracy, which is suggestive of an impulsive response style (Schmitt et al., 2005). To avoid misleading conclusions, measures of both speed and accuracy should be reported where possible, especially as studies reported that variations in breakfast GL influenced speed but not accuracy, and vice versa (Cooper et al., 2012, 2015; Ingwersen et al., 2007; Nilsson et al., 2012; Wesnes et al., 2003).

The influence of practice effects also needs to be considered. Practice effects are a particular issue for tests involving memory and learning (Bartels et al., 2010) and tend to occur mostly between the first and second administration of a test (Bell et al., 2018). Using parallel versions of the same test, the influence of practice effects can therefore be reduced by incorporating a separate test familiarisation visit and a brief practice session immediately before testing begins (Bell et al., 2018). Practice sessions can also minimise the negative impact of stress and anxiety, due to a lack of task familiarity, on performance. However, it is important that the length of a practice session is appropriate so that fatigue effects do not impact performance (Süss & Schmiedek, 2000).

5.2.5 Condition of participants and controlling for confounding factors

In order to gain a better understanding of the relationship between blood glucose levels, cognition, and sleep, it is critical that the influence of confounding factors is minimised (Schmitt et al., 2005). For example, the composition of one meal can influence the glycaemic response to a subsequent meal, termed the second meal effect. This also has consequences for

postprandial cognition, termed the second meal cognitive effect. Lamport et al. (2013b) reported that the consumption of a HGL evening meal, compared to a LGL evening meal, was associated with better episodic memory following the consumption of a HGL breakfast. In Chapter 3, this issue was minimised by instructing participants to consume similar meals and drinks on the day of testing and administering a standardised HGL evening meal approximately 4 hours before the experimental drinks were consumed. However, ideally, dietary intake throughout the day of testing would have been standardised across participants. A factor that was not considered in Chapter 4 is evening alcohol consumption, which can negatively impact cognition the next morning (Gunn et al., 2018) and interact with the effect of breakfast GL on memory (Benton & Nabb, 2004). For example, Benton and Nabb (2004) reported that a low GL breakfast only benefitted memory in participants who had consumed alcohol the previous evening.

Physical activity levels prior to testing should also be standardised. Alley et al. (2015) reported that resistance training reduced SOL and WASO, irrespective of whether exercise took place at 8am, 1pm, and 7pm. A single session of moderate-intensity exercise improved postprandial glucose levels for up to 24 hours in type 2 diabetics (Adams, 2013) and 24-hour insulin sensitivity in healthy males (Koopman et al., 2005). The quality of sleep can also interact with the metabolic effects of breakfast (Tsereteli et al., 2022). A short sleep duration augmented the glycaemic response to a 75 g glucose load to a greater extent than a high carbohydrate and a high fat breakfast. Taken together, these findings suggest that studies should administer a standardised meal prior to the experimental meal/drink, prohibit exercise and alcohol intake during the preceding 24 hours, and ensure that participants sleep normally the night before testing. Within this area of research, caffeine consumption is usually restricted for several hours before testing. As such, some participants are in a state of acute caffeine withdrawal during testing, which can influence cognition and sleep quality (Bernstein et al., 1998; James, 1998). Whilst this is less of a problem if a within-subjects design is used as the effects of withdrawal are constant across conditions, studies should ideally exclude caffeine consumers or excessive caffeine consumers. This is also the case for nicotine users (Hughes et al., 1994; Leventhal et al., 2007). Additional factors that can influence glucose metabolism and/or cognition include mood, stress, illness, fatigue, hydration, hunger, and motivation (Micha et al., 2010; Schmitt et al., 2005). This is especially the case for young children (Isaacs & Oates, 2008). Differences in GL may influence cognitive performance indirectly via some of these factors, hence it is important that studies consider their influence (Adolphus et al., 2016).

The type of study design used should also be carefully considered. One of the main advantages of using a within-subjects design is that nutritional interventions are evaluated in the same group of participants thus reducing the confounding effect of between-person variability (Harris & Raynor, 2017). However, if nutritional interventions are not blinded, pre-existing knowledge or beliefs held by participants about the properties of a specific food or drink (e.g., sugary drinks) may impact cognition and sleep (Adolphus et al., 2016). Furthermore, as shown in Chapter 3, order effects can occur which complicates the interpretation of findings. In some cases, no effects were observed when order of drink consumption was not included in the analysis, suggesting that effects may have been masked in studies that did not statistically account for order effects. Breakfast studies have also reported that differences in cognition only occurred when breakfast interventions were consumed in a specific order (Nilsson et al., 2009, 2012; Young & Benton, 2015).

In contrast, between-subjects designs reduce the risk of expectancy, fatigue, and order effects but increase the risk of interindividual variability distorting results. However, when the chronic effects of diet are examined, such as in Chapter 4, the use of a between-subjects design can significantly reduce participant burden and the timeframe of studies. It is common practice for researchers to statistically test for baseline differences between groups. However, a covariate can be balanced between groups, according to a non-significant *p* value, but still exert a meaningful influence on the relationship between a treatment and outcome (Knol et al., 2012; Peterson et al., 2017). This is especially true for studies with small samples, often leading to the omission of important covariates (De Boer et al., 2015). Ideally, factors that are known to influence the cognitive effects of nutritional manipulations (e.g., baseline cognitive performance or socioeconomic status) should be identified a priori and incorporated into statistical models as covariates (Peterson et al., 2017). By adjusting for known covariates, whether significant or not, the effect estimate will be more precise and closer to the 'true' effect (De Boer et al., 2015).

It is also important to consider the impact of participants current nutritional status and habitual dietary intake on the effects of a nutritional intervention. For example, it is currently unknown whether polyphenols exert larger effects in habitual polyphenol consumers or non-consumers. The gut microbiome of the former group may more efficiently absorb and metabolise polyphenols than the latter group (Lamport & Williams, 2020). However, it is feasible that beneficial effects are more likely to occur in individuals who consume low amounts of the nutrient under investigation (Young et al., 2022). Habitual polyphenol intake was not assessed

in Chapter 4. However, future studies would benefit from specifically testing the combined effects of cinnamon and turmeric/curcumin in individuals who do not consume polyphenol-rich diets or supplements.

5.2.6 Data availability and transparency

In Chapter 2, limited data availability and the use of different scores (i.e., post scores or change scores) prevented a meta-analysis of child and adolescent studies. For this area of research to evolve, there needs to be more transparency and consistency when reporting results. It would therefore be beneficial if future studies reported means, effect sizes, and SD in a table and, ideally, provided raw datasets as supplementary material. This would facilitate a more accurate and robust synthesis of the literature, as well as a better understanding of the moderating effects of time and other methodological factors. Future work may also benefit from providing more detailed information about, for example, the method of randomisation or the number of withdrawals. This would ensure that a study is correctly classified as high or low quality.

5.3 Concluding remarks

To conclude, this thesis provided evidence that the impact of breakfast GL on cognition is influenced by the timing of testing, cognitive subdomain, GT, and age. There was also tentative evidence that the consumption of pre-bedtime drinks differing in GL may influence different measures of sleep architecture and sleep continuity. However, further research with larger sample sizes is needed. Although no improvements were observed in Chapter 4, further research is clearly warranted given the increasing prevalence of obesity, T2DM, and mild cognitive impairment (Keaver et al., 2020; Zheng et al., 2018). In order to facilitate a better understanding of the impact of diet on glycaemic control, cognition, and sleep in future, it is suggested that the guiding principles outlined above are taken into account when designing studies. No doubt other factors will emerge as the field progresses.

Conflict of interest

Chapter 3 – BENEO GmbH (Mannheim, Germany) supplied the test drinks and funded the study. The funders requested that the impact of Palatinose™ on sleep was measured using polysomnography. The funders made no other contributions to the design of the study, nor data collection, analysis, and interpretation. The author of this thesis also received a salary.

Chapter 4 – Neolife International supplied the active and placebo supplements and funded the study. Other than requesting that changes in glucose tolerance were assessed, the funders did not contribute to the design of the study, nor data collection, analysis, and interpretation. The author of this thesis also received a salary.

Appendices

Appendix 1. Prisma 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Y
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Y
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.1
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.	Section 2.1

Section and Topic	Item #	Checklist item	Location where item is reported
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Section 2.1
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.	Section 2.1
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.	Section 2.1
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.	Section 2.2
	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.	Section 2.2
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.	Section 2.4

Section and Topic	Item #	Checklist item	Location where item is reported
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.	Section 2.5.
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)).	Section 2.2. and 2.3.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 2.2.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1 and 2
	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.	Section 2.5.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Section 2.5.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Section 2.5.

Section and Topic	Item #	Checklist item	Location where item is reported
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 2.4.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section 2.4.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3.1 and Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2.2 and 3.3.2.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.2.1 and 3.3.1

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Section 3.2.3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 3.2.1 and 3.3.1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Section 3.2.3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Section 3.2.3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Section 3.2.3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Section 3.2.1 and 3.3.1

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Section 3.2.1 and 3.3.1. Table S3 and S4.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 25 – 30
	23b	Discuss any limitations of the evidence included in the review.	Page 42
	23c	Discuss any limitations of the review processes used.	Page 42
	23d	Discuss implications of the results for practice, policy, and future research.	Page 42 – 43
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4 - 5

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4 - 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 44
Competing interests	26	Declare any competing interests of review authors.	Page 44
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 44

Appendix 2. Cochrane Risk of Bias 2 assessment of adult studies

Study	Randomisation process	Bias arising from period and carryover effects	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Anderson et al. (2018)	!	+	-	+	!	!	!
Anderson et al. (2021)	!	+	-	+	!	!	!
Benton et al. (2003)[1]	+	N/A	+	+	!	!	!
Deng et al. (2021)	+	+	+	+	+	+	+
Dye et al. (2010)	!	+	+	+	+	!	+
Ginieis et al. (2018)	+	+	+	+	+	!	+
Kaplan et al. (2000)	!	+	-	+	!	!	!
Lamport et al. (2013a)	!	+	-	+	!	+	!
Lamport et al. (2014)	!	+	-	+	!	+	!
Nabb & Benton (2006a)[1]	+	N/A	+	+	!	!	!
Nabb & Benton (2006b)[1]	+	N/A	+	+	!	!	!

Nilsson et al. (2009)	!	+	-	+	!	!	!
Nilsson et al. (2012)	!	+	-	+	!	!	!
Papanikolaou et al. (2006)	!	+	-	+	!	!	!
Sanchez-Aguadero et al. (2020)	+	+	-	+	!	+	+
Van der Zwaluw et al. (2014)	!	!	!	+	!	!	!
Young & Benton (2014)	+	N/A	+	+	+	+	+

Note. '+' = low risk of bias, '-'= high risk of bias, and '!' = some concerns of bias. 1 = corresponded with author about method of randomisation/allocation concealment.

Appendix 3. Certainty of evidence (GRADE) of adult studies

Cognitive subdomain	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall
Immediate Episodic memory	Serious[1]	Serious[2]	Not serious	Serious[3]	Not serious	⊕⊕
Delayed episodic memory	Serious[1]	Serious[2]	Not serious	Serious[3]	Serious[5]	⊕⊕
Working memory	Serious[1]	Serious[2]	Not serious	Very serious[4]	N/A	⊕
Attention (speed)	Serious[1]	Serious[2]	Not serious	Very serious[4]	Serious[5]	⊕
Attention (accuracy)	Serious[1]	Serious[2]	Not serious	Very serious[4]	Serious[5]	⊕

Note. ⊕ = very low, ⊕⊕ = low, ⊕⊕⊕ = moderate, ⊕⊕⊕⊕ = high level of certainty.

1 = studies generally suffered from methodological flaws. No issues with attrition rates or the choice of cognitive tests.

2 = I^2 values ranged from 0 to 34%, suggesting that heterogeneity was not substantial. However, CI were large, and the results reported by individual studies varied considerably.

3 = small sample sizes and wide CI.

4 = small sample sizes, limited number of studies/datasets, and wide CI.

5 = funnel plots showed some degree of asymmetry.

Appendix 4. Sensitivity analysis using the leave-one-out method.

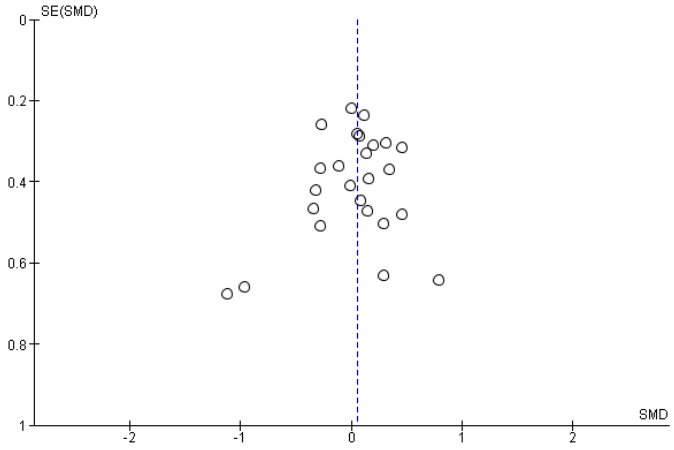
	***p* value range**	**Pooled effect size range**
Immediate episodic memory, early PPP	0.33 (PGT data from Young & Benton, 2014) to 0.74 (BGT data from Young & Benton, 2014).	0.02 (BGT data from Young & Benton, 2014) to -0.07 (PGT data from Young & Benton, 2014).
Immediate episode memory, mid PPP	0.19 (PGT LCHPHF data from Nabb & Benton, 2006a) to 0.50 (BGT data from Young & Benton, 2014).	0.05 (BGT data from Young & Benton, 2014) to 0.11 (PGT LCHPHF data from Nabb & Benton, 2006a).
Immediate episodic memory, late PPP	0.02 (PGT LCHPHF & LCHPLF data, & BGT LCHPHF data, from Nabb & Benton, 2006a) to 0.15 (Benton et al., 2003)	0.12 (Benton et al., 2003) to 0.19 (PGT LCHPHF & LCHPLF data, & BGT LCHPHF data, from Nabb & Benton, 2006a)
Delayed episodic memory, early PPP	0.06 (PGT data from Young & Benton, 2014) to 0.60 (BGT data from Young & Benton, 2014).	0.05 (BGT data from Young & Benton, 2014) to 0.17 (PGT data from Young & Benton, 2014).
Delayed episode memory, mid PPP	0.04 (PGT data from Young & Benton, 2014) to 0.22 (Benton et al., 2003)	0.09 (Benton et al., 2003) to 0.15 (PGT data from Young & Benton, 2014).
Delayed episodic memory, late PPP	0.04 (BGT LCLPHF data from Nabb & Benton, 2006a) to 0.24 (Benton et al., 2003)	0.10 (Benton et al., 2003) to 0.17 (BGT LCLPHF data from Nabb & Benton, 2006a).
Working memory, early PPP	0.16 (Van der Zwaluw et al., 2014) to 0.59 (removal of BGT group from Young & Benton, 2014)	0.05 (removal of BGT group from Young & Benton, 2014) to 0.13 (Van der Zwaluw et al., 2014)
Working memory, mid PPP	0.21 (Anderson et al., 2021) to 0.51 (removal of BGT	0.06 (removal of BGT group from Young & Benton,

	group from Young & Benton, 2014)	2014) to 0.13 (Anderson et al., 2021)
Working memory, late PPP	0.43 (Anderson et al., 2018) to 0.99 (removal of BGT group from Young & Benton, 2014)	-0.01 (removal of PGT group from Young & Benton, 2014) to 0.08 (Anderson, 2018)
Accuracy of attention, early PPP (1-minute analysis)	0.64 (BGT LCHPHF data from Nabb & Benton, 2006a) to 0.99 (PGT data from Young & Benton, 2014 or PGT LCLPHF data from Nabb & Benton, 2006a).	-0.01 (BGT data from Young & Benton, 2014) to 0.04 (BGT LCLPHF, LCHPHF, & LCLPLF data from Nabb & Benton, 2006a).
Accuracy of attention, mid PPP (1-minute analysis)	0.20 (LCMF data from Nabb & Benton, 2006b) to 0.77 (PGT data from Young & Benton, 2014).	0.03 (PGT data from Young & Benton, 2014) to 0.12 (LCMF data from Nabb & Benton, 2006b).
Accuracy of attention, late PPP (1-minute analysis)	0.21 (BGT LCLPLF data from Nabb & Benton, 2006a) to 0.80 (PGT data from Young & Benton, 2014).	0.03 (PGT data from Nilsson et al., 2012) to 0.12 (BGT LCLPLF data from Nabb & Benton, 2006a).
Accuracy of attention, early PPP (5-minute analysis)	0.62 (BGT LCHPHF data from Nabb & Benton, 2006a) to 0.98 (PGT LCHPLF data from Nabb & Benton, 2006a).	-0.01 (BGT data from Young & Benton, 2014) to 0.04 (BGT LCLPHF, LCHPHF, & LCLPLF data from Nabb & Benton, 2006a).
Accuracy of attention, mid PPP (5-minute analysis)	0.52 (LCMF data from Nabb & Benton, 2006b) to 1.00 (BGT LCHPLF data from Nabb & Benton, 2006a).	-0.03 (MCHF data from Nabb & Benton, 2006b) to 0.05 (LCMF data from Nabb & Benton, 2006b).
Accuracy of attention, late PPP (5-minute analysis)	0.52 (BGT LCLPHF data from Nabb & Benton, 2006a) to 0.95 (PGT data from Nilsson et al., 2012)	-0.01 (PGT data from Nilsson et al., 2012) to 0.05 (BGT LCLPHF data from Nabb & Benton, 2006a).

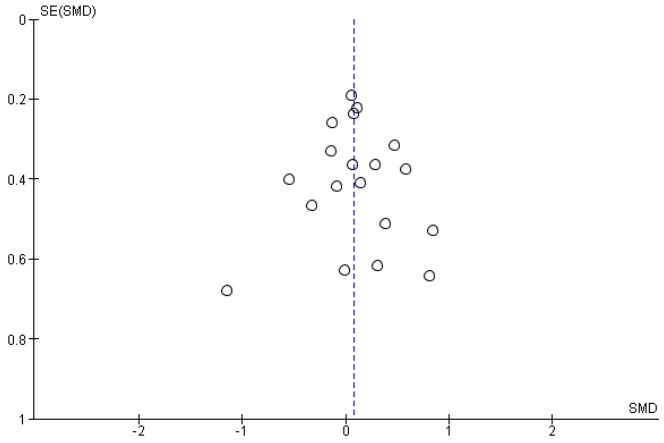
Speed of attention, early PPP (1-minute analysis)	0.18 (PGT data from Young & Benton, 2014) to 0.66 (LCMF data from Nabb & Benton, 2006b)	0.05 (BGT LCHPLF data from Nabb & Benton, 2006a) to 0.13 (PGT data from Young & Benton, 2014).
Speed of attention, mid PPP (1-minute analysis)	0.55 (LCMF data from Nabb & Benton, 2006b) to 0.99 (PGT LCLPLF data from Nabb & Benton, 2006a).	-0.05 (PGT LCHPLF data from Nabb & Benton, 2006a) to 0.01 (PGT LCHPHF data from Nabb & Benton, 2006a).
Speed of attention, late PPP (1-minute analysis)	0.10 (BGT data from Young & Benton, 2014) to 0.36 (Sanchez- Aguadero et al., 2020)	-0.08 (BGT LCHPHF data from Nabb & Benton, 2006a) to -0.13 (BGT data from Young & Benton, 2014)
Speed of attention, early PPP (5-minute analysis)	0.37 (LCLF data from Nabb & Benton, 2006b) to 0.97 (LCMF data from Nabb & Benton, 2006b).	-0.09 (LCLF data from Nabb & Benton, 2006b) to -0.00 (LCMF data from Nabb & Benton, 2006b).
Speed of attention, mid PPP (5-minute analysis)	0.44 (BGT data from Young & Benton, 2014) to 0.93 (PGT LCLPHF data from Nabb & Benton, 2006a)	0.01 (PGT LCLPHF data from Nabb & Benton, 2006a) to 0.06 (MCHF data from Nabb & Benton, 2006b)
Speed of attention, late PPP (5-minute analysis)	0.18 (PGT LCHPLF data from Nabb & Benton, 2006a) to 0.43 (Sanchez-Aguadero et al., 2020)	-0.07 (PGT LCHPHF data from Nabb & Benton, 2006a) to -0.11 (PGT LCHPLF data from Nabb & Benton, 2006a)

Appendix 5. Funnel plots.

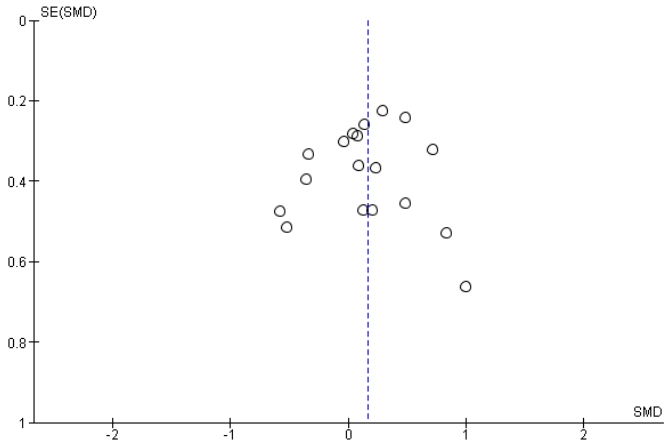
Appendix 5a. Funnel plot of immediate episodic memory scores during the early postprandial period.



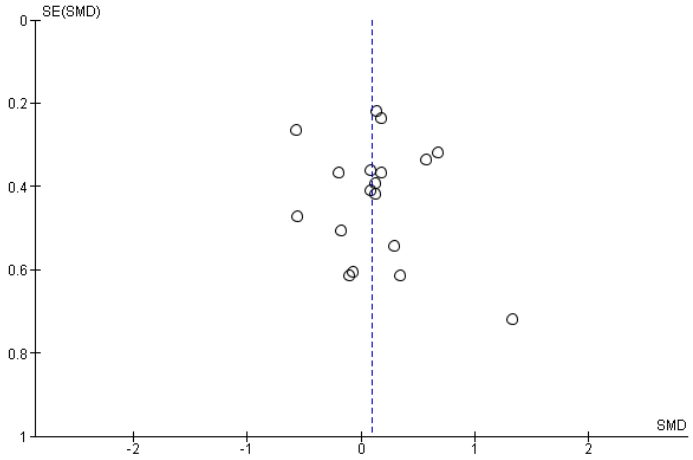
Appendix 5b. Funnel plot of immediate episodic memory during the mid-postprandial period.



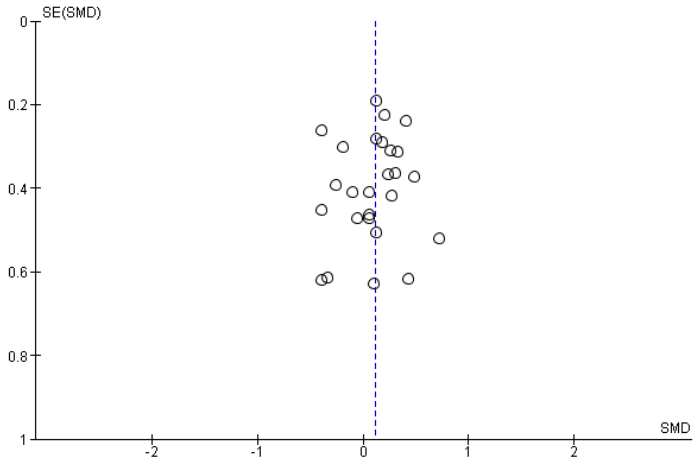
Appendix 5c. Funnel plot of immediate episodic memory during the late postprandial period.



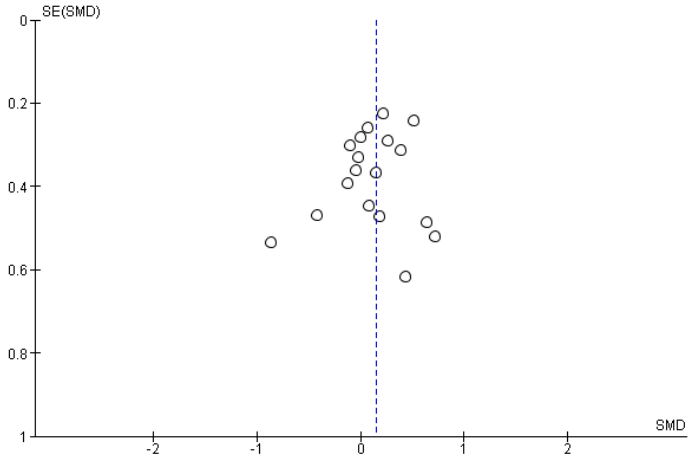
Appendix 5d. Funnel plot of delayed episodic memory scores during the early postprandial period.



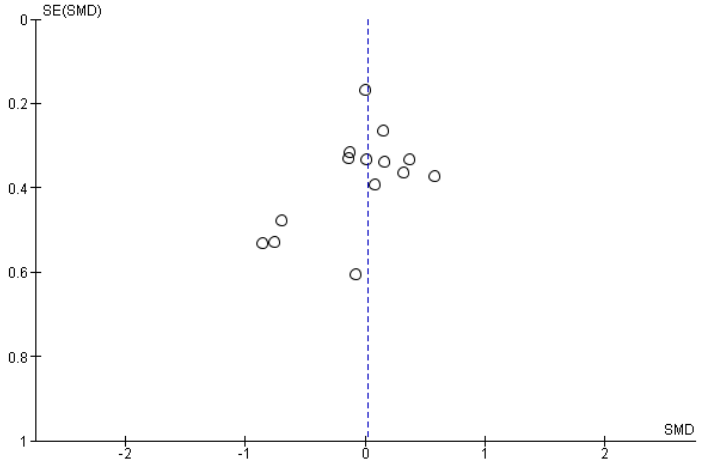
Appendix 5e. Funnel plot of delayed episodic memory during the mid-postprandial period.



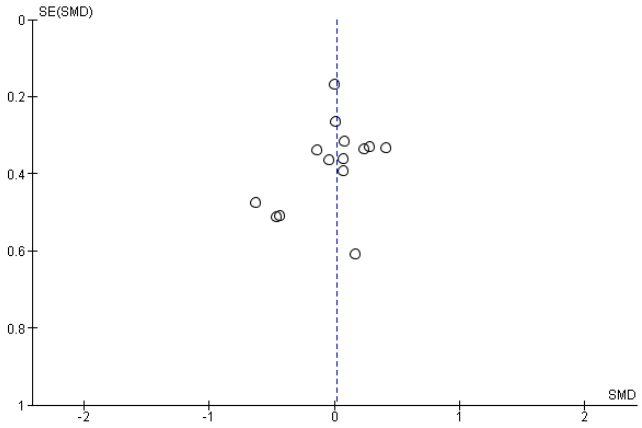
Appendix 5f. Funnel plot of delayed episodic memory during the late postprandial period.



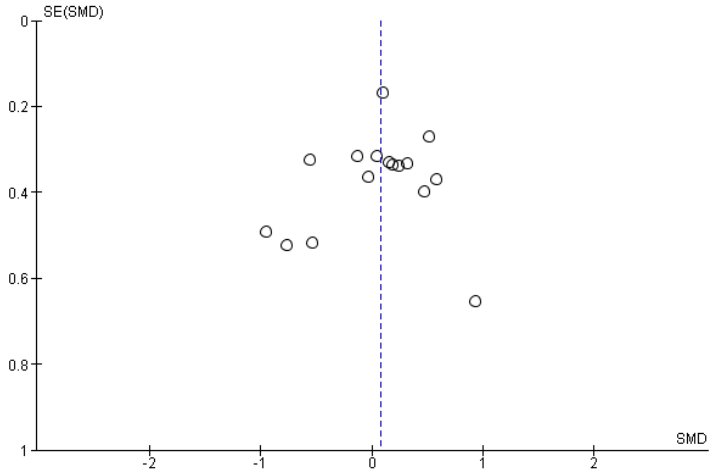
Appendix 5g. Funnel plot of accuracy of attention scores during the early postprandial period (including 1-minute scores)



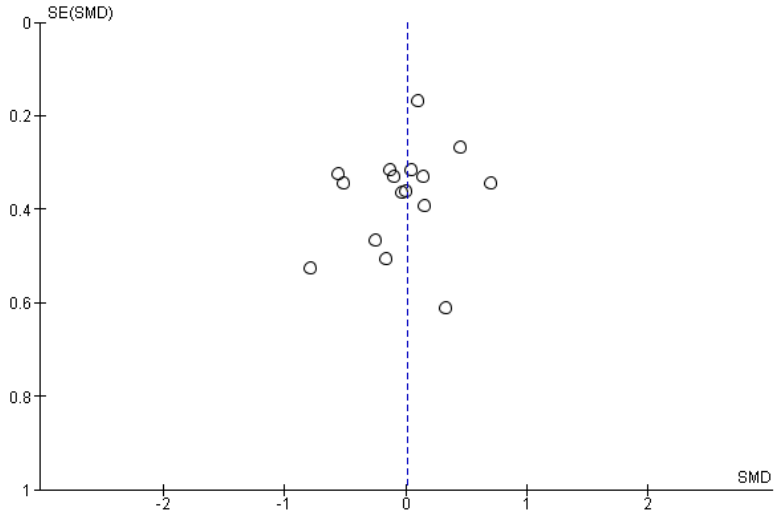
Appendix 5h. Funnel plot of accuracy of attention scores during the early postprandial period (including 5-minute scores)



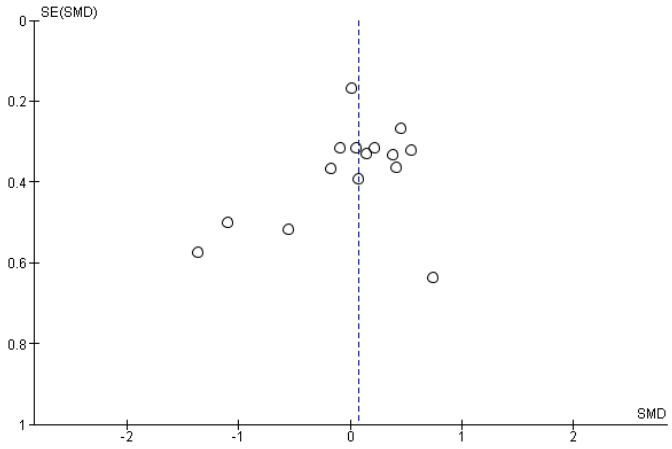
Appendix 5i. Funnel plot of accuracy of attention during the mid-postprandial period (including 1-minute scores)



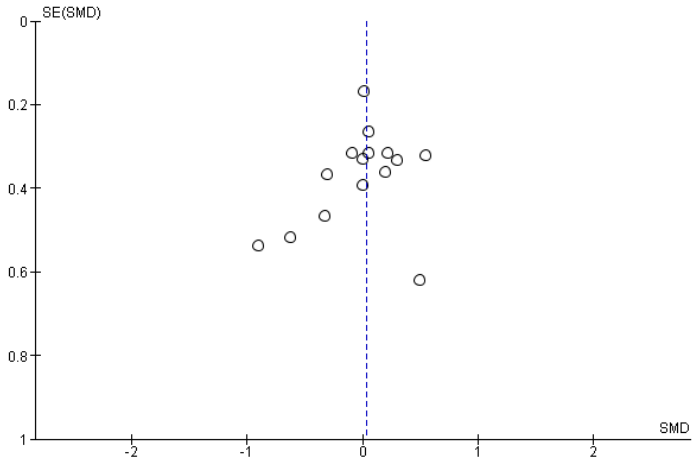
Appendix 5j. Funnel plot of accuracy of attention scores during the mid-postprandial period (including 5-minute scores)



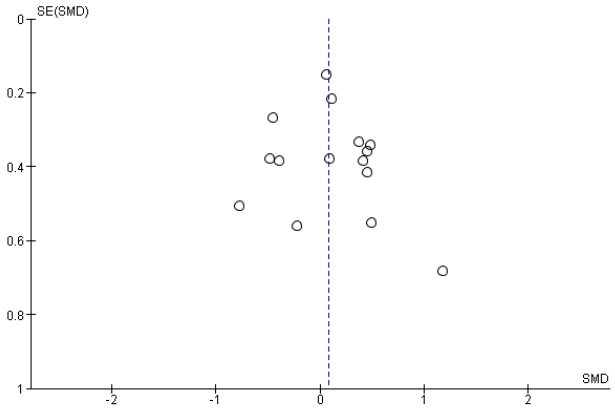
Appendix 5k. Funnel plot of accuracy of attention scores during the late postprandial period (including 1-minute scores)



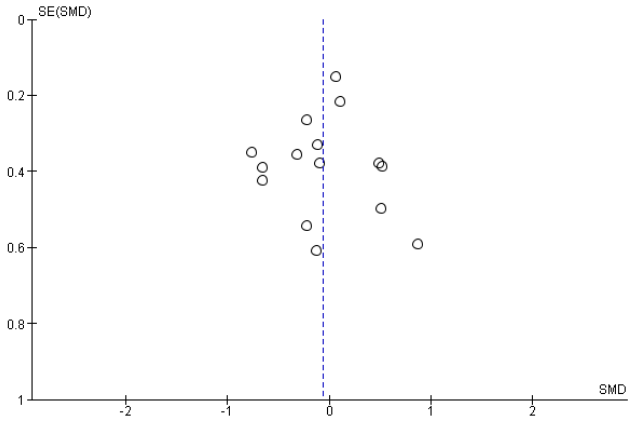
Appendix 5l. Funnel plot of accuracy of attention scores during the late postprandial period (including 5-minute scores)



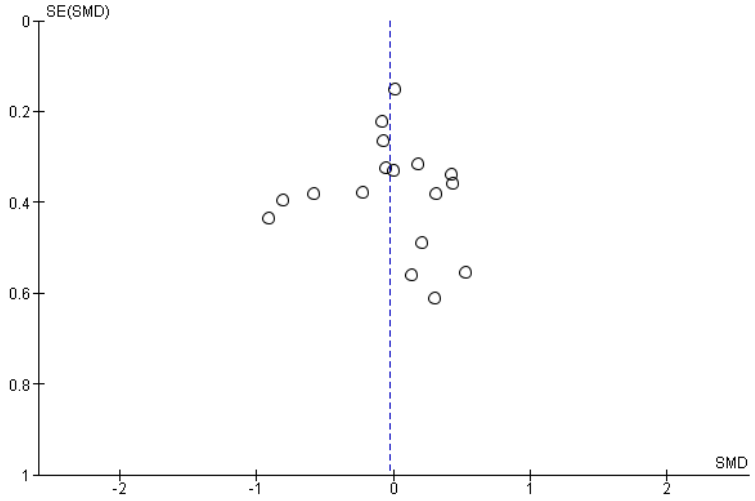
Appendix 5m. Funnel plot of speed of attention scores during the early postprandial period (including 1-minute scores).



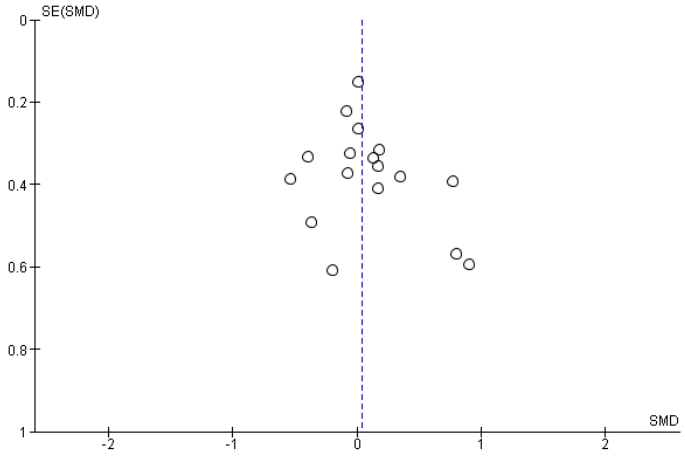
Appendix 5n. Funnel plot of speed of attention scores during the early postprandial period (including 5-minute scores)



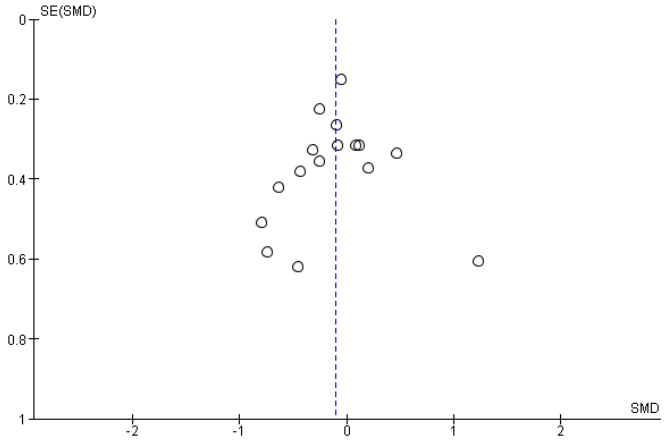
Appendix 5o. Funnel plot of speed of attention scores during the mid-postprandial period (including 1-minute scores).



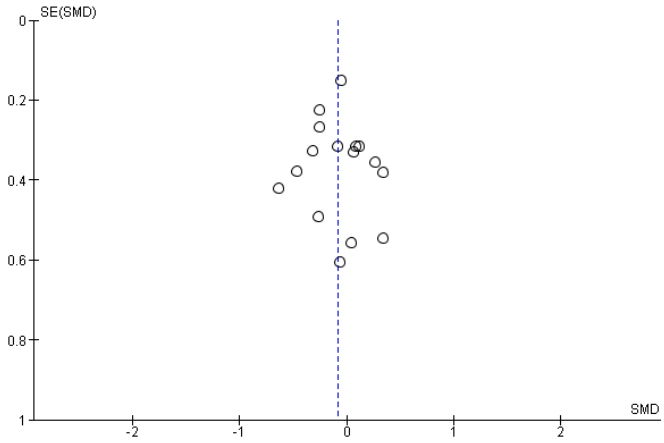
Appendix 5p. Funnel plot of speed of attention scores during the mid-postprandial period (including 5-minute scores)



Appendix 5q. Funnel plot of speed of attention scores during the late postprandial period (including 1-minute scores)



Appendix 5r. Funnel plot of speed of attention scores during the late postprandial period (including 5-minute scores)



Appendix 6. Cochrane Risk of Bias 2 assessment of child and adolescent studies.

Study	Randomisation process	Bias arising from period and carryover effects	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Anderson et al. (2020)	!	+	-	+	+	!	!
Benton et al. (2007b)	!	-	-	+	!	!	!
Brindal et al. (2012)	+	!	-	+	!	!	!
Brindal et al. (2013)	+	!	+	+	+	+	+
Cooper et al. (2012)	+	+	-	+	!	!	!
Cooper et al. (2015)	!	+	-	+	!	!	!
Ingwersen et al. (2007)	!	!	-	+	!	!	!
Ingwersen (2011)	!	N/A	+	+	!	!	!
Lee et al. (2019)	!	+	-	+	!	+	!
Mahoney et al. (2005, Study 1)	-	+	-	+	!	!	!

Mahoney et al. (2005, Study 2)	-	+	-	+	!	!	!
Micha et al. (2011)	!	+	+	+	+	!	+
Smith & Foster (2008)	!	N/A	+	+	!	!	!
Taib et al. (2012)	+	+	+	+	+	!	+
Wesnes et al. (2003)	!	!	-	+	!	!	!
Young & Benton (2015)	+	+	+	+	+	+	+

Note. '+' = low risk of bias, '-'= high risk of bias, and '!' = some concerns of bias.

Appendix 7. Pittsburgh Sleep Quality Index.

Name_____ Date_____

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 the questions.

1. During the past month, when have you usually gone to bed at night?

   usual bedtime_____

2. During the past month, how long (in minutes) has it usually taken to fall asleep each night?

   number of minutes_____

3. During the past month, when have you usually got up in the morning?

   usual getting up time_____

4. During the past month, how many hours of *actual* sleep did you get at night? (This may be different than the number of hours you spend in bed).

   hours of sleep per night_____

5. For each of the following questions, check the one best response. Please answer *all* 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**
Cannot get to sleep within 30 minutes				

Wake up in the middle of the night or early morning				
Have to get up to use the bathroom				
Cannot breathe comfortably				
Cough or snore loudly				
Feel too cold				
Feel too hot				
Had bad dreams				
Have pain				
Other reason(s), please describe:				

6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

   Not during the past month ___ Less than once a week ___ Once or twice a week ___ Three or more times a week ___

7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

   Not during the past month ___ Less than once a week ___ Once or twice a week ___ Three or more times a week ___

8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

   No problem at all_____

   Only a very slight problem___

   Somewhat of a problem_____

   A very big problem_____

9. During the past month, how would you rate your sleep quality overall?

Very good_____

Fairly good_____

Fairly bad_____

Very bad_____

10. Do you have a bed partner or roommate?

No bed partner or roommate _____

Partner/roommate in other room _____

Partner in same room, but not same bed ____

Partner in same bed _____

If you have a roommate or bed partner, ask him/her how often in the past month you have had:

	Not during the past month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
Loud snoring				
Long pauses between breaths while asleep				
Legs twitching or jerking while you sleep				
Episodes of disorientation or confusion during sleep				
Other restlessness				

while you sleep, please describe:				

Appendix 8. Depression, Anxiety, and Stress Scale-21 items.

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 = Did not apply to me at all

1 = Applied to me to some degree, or some of the time

2 = Applied to me to a considerable degree or a good part of time

3 = Applied to me very much or most of the time

1 (s)	I found it hard to wind down	0	1	2	3
2 (a)	I was aware of dryness of my mouth	0	1	2	3
3 (d)	I couldn't seem to experience any positive feeling at all	0	1	2	3
4 (a)	I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5 (d)	I found it difficult to work up the initiative to do things	0	1	2	3
6 (s)	I tended to over-react to situations	0	1	2	3
7 (a)	I experienced trembling (e.g. in the hands)	0	1	2	3
8 (s)	I felt that I was using a lot of nervous energy	0	1	2	3
9 (a)	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10 (d)	I felt that I had nothing to look forward to	0	1	2	3
11 (s)	I found myself getting agitated	0	1	2	3
12 (s)	I found it difficult to relax	0	1	2	3
13 (d)	I felt down-hearted and blue	0	1	2	3
14 (s)	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15 (a)	I felt I was close to panic	0	1	2	3
16 (d)	I was unable to become enthusiastic about anything	0	1	2	3
17 (d)	I felt I wasn't worth much as a person	0	1	2	3
18 (s)	I felt that I was rather touchy	0	1	2	3
19 (a)	I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	0	1	2	3
20 (a)	I felt scared without any good reason	0	1	2	3
21 (d)	I felt that life was meaningless	0	1	2	3

Appendix 9. Meal Patterns Questionnaire.

In this questionnaire we ask you how often you have had meals or snacks during the last 28 days. Please read these instructions thoroughly and indicate your answers by circling the number that best correspond to your situation. When you answer, please remember to take into account whether your eating habits are different during the weekdays or weekends.

A meal or snack is in this case warm or cold food, sandwiches, salad, yoghurt, cereals, porridge, fruits, nuts, smoothies, or similar.

Foods high in sugar and/or fat such as candy, cake, cookies, buns, crackers, potato chips, chocolate, energy bars, ice cream, dried fruits and similar are NOT considered meals or snacks.

Beverages (e.g., coffee, tea, soft drinks, energy drinks, juice) are NOT considered meals or snacks.

Please note that if you have had "brunch", it should be coded as lunch.

If you find it difficult to choose between two numbers, please circle the higher of the two.

If you find it very difficult to classify your meals (e.g., if you have a night job) please state the reason here _____.

Please circle the appropriate number on the right. Remember that the question refers to the past four weeks (28 days) only.

On how many of the past 28 days have you had…	No days	1-5 days	6-12 days	13-15 days	16-22 days	23-27 days	Every day
Breakfast	0	1	2	3	4	5	6
Mid-morning snack	0	1	2	3	4	5	6
Lunch	0	1	2	3	4	5	6
Mid-afternoon snack	0	1	2	3	4	5	6
Evening meal	0	1	2	3	4	5	6
Evening snack	0	1	2	3	4	5	6

Nocturnal eating (eating during the night after having been to sleep)	0	1	2	3	4	5	6
A non-alcoholic drink before bed	0	1	2	3	4	5	6

Appendix 10. Sleep study information sheet.

The influence of diet on sleep and memory consolidation: Proof of Concept

You are being invited to take part in some research. Before you decide whether or not to participate, it is important for you to understand why the research is being conducted and what it will involve. Please read the following information carefully.

What is the purpose of the research?

Although the exact purpose of sleep is not yet fully understood, it is clear that sleep plays a critical role in a number of functions including memory, learning, mood, and glucose metabolism. Despite its importance, few studies have tested the usefulness of nutritional interventions for enhancing sleep. Therefore, this research aims to examine the effects of manipulating drink composition on sleep glucose metabolism, sleep architecture, and memory consolidation.

Can anyone take part?

We are looking for **MALE** participants aged between **18 to 35 years**, in good health, and not taking any medication known to effect sleep or metabolism.

You cannot take part if any of the following apply to you:

- A diagnosis of any physical or mental disorder (e.g., diabetes, cardiovascular disorders, gastrointestinal disorders, sleep problems, epilepsy, or mood disorders)
- Unhealthy weight
- Drink more than 300 mg of caffeine per day (3 - 4 standard sizes 8-oz cups)
- Work nights or shifts
- Smoke
- Regularly drink alcohol (>3 glasses per day)
- Used recreational drugs within the past six months
- Take part in > 3 hours of vigorous exercise per week.

If none of the above apply to you, you will be asked to complete additional online screening questionnaires to assess whether you have a normal sleep and eating schedule. You must also disclose any known food allergies or intolerances.

Who is carrying out the research?

The data is being collected by Chantelle Gaylor under the supervision of Dr Hayley Young, Professor David Benton, and Professor Mark Blagrove. This research has been approved by the College of Human and Health Sciences Research Ethics Committee.

What happens if I agree to take part?

The study requires you to stay at Swansea Universities Sleep Laboratory for three nights, each visit will be separated by one week. The purpose of the first visit is for you to get used to the laboratory conditions. A similar procedure will be used across the three visits, as described below. You will be asked to arrive at the Sleep Laboratory at approximately 7pm. For 24 hours prior to each visit, you will be asked to abstain from exercise and consume no alcohol. On the day of testing, you will be asked to consume no food or drink (other than water) after 2pm. You will also need to consume similar meals, snacks, and drinks prior to each visit. A continuous glucose monitor will be inserted in your arm on the morning/afternoon of testing. This will take a few minutes to set up and should not be painful, however you may experience some soreness in your arm for the first 24 hours. The continuous glucose monitor needs to be inserted several hours before the evening for it to "warm-up". When you arrive at the sleep laboratory, you will be provided with a standardised evening meal and drink. Throughout the evening, you will be asked to complete several mood questionnaires and cognitive tasks. A polysomnography (PSG) will be set up shortly before bed. A PSG involves gluing/sticking multiple sensors to your head to measure various signals whilst you sleep such as brain waves and heart rate. After this, you will be left to sleep and wake freely. In the morning, you will be asked to complete the questionnaires and memory tasks again. Breakfast will be provided; however, you can leave immediately after completing the tasks if you wish. The continuous glucose monitor needs to be worn until the evening (approximately 8pm). A pro-diary watch will also need to be worn throughout the day. It will prompt you to answer simple questions such as "how hungry are you right now?". A research assistant will meet you in the evening, at a suitable location, to remove the continuous glucose monitor and collect the pro-diary watch. After the third visit, you will be paid £250 for taking part.

Are there any risks associated with taking part?

The research has been approved by the College of Human and Health Sciences Research Ethics Committee. There are no significant risks associated with participation. The continuous glucose monitor will require pricking of the skin which may cause mild discomfort that will diminish shortly after.

Data Protection and Confidentiality

Your data will be processed in accordance with the Data Protection Act 2018 and the General Data Protection Regulation 2016 (GDPR). All information collected about you will be kept strictly confidential and anonymous. Your data will be viewed by the researcher/research team. However, all data will be kept anonymous by assigning you a participant number. Data will be anonymised from the beginning of the study. However, should you decide to withdraw from the study, your data can be removed if requested. All electronic data will be stored on a password-protected computer file, and all paper records will be stored in a locked filing cabinet, within the Psychology Department. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach.

What will happen to the information I provide?

An analysis of the information will form part of our report at the end of the study and may be presented to interested parties and published in scientific journals and related media. *Note that all information presented in any reports or publications will be anonymous and unidentifiable*.

Is participation voluntary and what if I wish to later withdraw?

Your participation is entirely voluntary – you do not have to participate if you do not want to. If you decide to participate, but later wish to withdraw from the study, then you are free to withdraw at any time, without giving a reason and without penalty. Please not that you will be paid £250 unless you complete all three visits.

Data Protection Privacy Notice

The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data and can be contacted at the Vice Chancellors Office. Your personal data will be processed for the purposes outlined in this information sheet. Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you. The legal basis that we will rely on to process your personal data will be processing is necessary for the performance of a task carried out in the public interest. This public interest justification is approved by the College of Human and Health Sciences Research Ethics Committee, Swansea University. The legal basis that we will rely on to process special categories of data will be processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes.

How long will your information be held?

Data will be preserved and accessible for a minimum of 10 years after completion of the research. Records from studies with major health, clinical, social, environmental or heritage importance, novel intervention, or studies which are on-going or controversial should be retained for at least 20 years after completion of the study. It may be appropriate to keep such study data permanently within the university, a national collection, or as required by the funder's data policy.

Appendix 11. Sleep study consent form.

Project title: The influence of diet on sleep and memory consolidation: proof of concept.

PhD student: Chantelle Gaylor

Supervisors: Dr Hayley Young and Professor David Benton

	Participant initial
1. I (the participant) confirm that I have read and understand the information sheet for the above study which is attached to this form.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reasons.	
3. I understand what my role will be in this research, and all my questions have been answered to my satisfaction.	
4. I understand that I am free to ask any questions at any time before and during the study.	
5. I have been informed that the information I provide will be safeguarded.	
6. I am happy for the information I provide to be used (anonymously) in academic papers and other formal research outputs.	
7. I am over 18 years of age.	
8. I have been provided with a copy of the Participant Information Sheet.	
9. I agree to the researchers processing my personal data in accordance with the aims of the study described in the Participant Information Sheet.	
10. I consent to having a continuous glucose monitor inserted into my arm	

Thank you for your participation in this study. Your help is very much appreciated.

Print name of participant **Signature** **Date**

Print name of researcher **Signature** **Date**

This study is being conducted by Swansea University, College of Human and Health Science.

Thank you for your participation in this study. Your help is very much appreciated.

Appendix 12. Leeds Sleep Evaluation Questionnaire.

Leeds Sleep Evaluation Questionnaire

How would you describe the way you currently fall asleep in comparison to usual?

1. More difficult than usual _____ Easier than usual
2. Slower than usual _____ More quickly than usual
3. I feel less sleepy than usual _____ More sleepy than usual

How would you describe the quality of your sleep compared to normal sleep?

4. More restless than usual _____ Calmer than usual
5. With more wakeful periods than usual _____ With less wakeful periods than usual

How would you describe your awakening in comparison to usual?

6. More difficult than usual _____ Easier than usual
7. Requires a period of time longer than usual _____ Shorter than usual

How do you feel when you wake up?

8. Tired _____ Alert

How do you feel now?

9. Tired _____ Alert

How would you describe your balance and co-ordination upon awakening?

10. More disrupted than usual _____ Less disrupted than usual

GTS - getting to sleep

QOS - quality of sleep

AFS – Awake following sleep

BFW – behaviour following wakening

Appendix 13. Epworth Sleepiness Scale.

How likely are you to doze off or fall asleep during the following situations, in contrast to just feeling tired?

For each of the situations listed below, give yourself a score of 0 to 3, where 0 = Would never doze; 1 = Slight chance; 2 = Moderate chance; 3 = High chance.

Work out your total score by adding up your individual scores for situations 1 to 8. (If you have not been in the following situations recently, think about how you would have been affected).

Situation	**Chance of dozing (0-3)**			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place (e.g., a theatre/meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch (when you've had no alcohol)	0	1	2	3
In a car, while stopped in traffic	0	1	2	3

Total score:

Appendix 14. Story recall task

Story	Valence	Total Word Count	Sentences	Scored buffer words	Scored content words	Total Scored Words
Hospital Visit	Positive	162	11	14	80	94
The Dental Exam	Negative	162	11	17	78	95
The Date	Neutral	162	11	18	69	87
The Cinema	Neutral	162	11	15	79	94
The Job Interview	Negative	161	11	18	78	96
Buying a Car	Neutral	161	11	15	83	98
The Contest	Positive	161	11	13	83	96
The Paris Trip	Positive	162	11	16	72	88
The Skateboard Race	Negative	160	11	11	79	90
The Birthday Present	Positive	163	11	20	75	95
	Neutral	163	11	14	75	89
	Negative	163	11	14	81	95

Type	Colour
Noun	
Verb	
Adjectives	
Adverb	

The Hospital Visit Original

(162 words, 11 sentences)

(14 buffer, 80 content, total 94)

A mother and her son are leaving home in the morning. She is taking him to visit his father's workplace. The father is a laboratory technician at Victoria Memorial Hospital. They check before crossing a busy road. While walking along, the mother receives a phone call to say her sister had given birth. The mother excitedly told her son that he had a new baby cousin called Sophie. At the hospital the boy rushes to his auntie's bedside so he can hold his baby cousin for the first time. The baby yawned, making cute babbling noises. She looked healthy, happy and rosy. The ward staff took a photograph of the smiling duo. After, while the boy stayed with his father and auntie, the mother left to phone her other child's pre-school. Feeling elated, she phoned the pre-school to tell them she would soon pick up her child. Heading to pick up her child, she hails a taxi at the number nine bus stop.

The Dental Exam

(162 words, 11 sentences)

(17 buffer, 78 content, 95 total)

Robert was a trainee dentist at the School of Clinical Medicine in Edinburgh. In the last phase of his training he would perform a supervised dental operation, his first one ever on a live patient. Robert had been preparing for this for months. In the exam things started to go wrong immediately. His drill slipped and pierced his patient's cheek. To stem the blood he grabbed a towel from a nearby rack but this only served to muffle the woman's desperate screams. She was clearly choking on her own blood. Panicking, Robert tried to extract the drill piece in one smooth motion however this brought with it a chunk of flesh. In tears, he cried for help, and his examiner quickly took over. Not only did Robert fail the exam, he did so in the fastest time ever recorded at the School of Clinical Medicine. He would later tell his friends this story at the pub, not skimping on the details.

The Date

(Words 162, 11 sentences)

(18 Buffer, 69 content, total 87)

Samantha works hard, and has been planning her day off all week. On Saturday she got on the train to South Kensington to visit the Natural History Museum. She was planning to meet up with a suitor she met through a dating website. Upon arrival, she saw a tall man talking to some tourists. The tourists asked the man to take a photo of them. She quickly saw that it was her prospective date, Chris. Chris was wearing a different jacket than she originally saw in his profile photo. They went for coffee where they both talked about politics and who they would vote for in the next election. Later on in the museum gift shop, he brought a book of stamps for some postcards he was planning to write. To top off the day, they walked through the geology exhibit up on the second floor of the museum. Samantha eventually made her excuses and left, catching the 7pm train back home.

The Cinema

(162 words, 11 sentences)

Jemma and her friend Beth are making plans for the evening. The pair decide to go to the cinema to watch a documentary about space engineering. It is raining so the women decide to wear waterproof coats on the way to the cinema. In the queue, Beth sees a poster for the film which shows a team of people working at computers in a command centre. A cinema worker wearing a red and blue striped shirt ushers the women to screen number 8. The opening scene shows a rocket being propelled into space. Suddenly, the screen goes black and the audio for the film cuts out. A message appears on the screen informing the audience that there is a technical difficulty. Jemma and Beth walk to customer service and are told that they can attend another viewing in 10 minutes. The pair agree to go to the second viewing. After the film, the women head home chatting about parts of the film.

The Job Interview

161 words, 11 sentences)

(18 buffer, 78 content, total 96)

Sarah is a marketing assistant at a large graphic design firm. The company usually holds group meetings on Monday's at 9 am. Instead, the head of the company, Jack, asks to meet with her alone. Sarah is worried as she knows she has not been performing well. Jack walks Sarah to his office and puts her employee file on a glass table. He pulls out her record from the file and says she has not met her targets for the last six months. Sarah fills up with tears and Jack angrily asks her why she should deserve another chance. Jack has no sympathy for her and tells her that because she has not improved since her last warning, she is being fired immediately. Sarah feels sick and worries about paying her rent. Jack firmly instructs Sarah to collect her things and leave. On her way out, she calls her best friend Rosie and plans to meet her at a local pub.

Buying a Car

(161 words, 11 sentences)

(15 buffer, 83 content, total 98)

Grace wants to use her savings to purchase a used car. She looks online and finds a small blue car with low mileage. She books an appointment to view the car on Saturday at 9 am. When Saturday arrives, Grace catches a train and then a bus to a small housing estate. Grace knocks on a door and meets a middle-aged woman with blonde hair called Sandra. Sandra asks Grace to wait outside whilst she collects the keys to the car so that they can both go for a test drive in the car. The pair drive to the local shops. Grace notices that the air conditioning does not work and asks Sandra if this can be fixed. Sandra gives the name of a small local business which repairs air conditioning for a low cost. Satisfied with the car, Grace agrees to purchase the car and drives home. Once home, Grace makes a hot cup of tea and calls her father.

The Radio Contest

(161 words, 11 sentences)

(13 buffer, 83 content, total 96)

Emma begins her commute in the car after a long day at work. She puts on her favourite radio station, Sun FM. The radio host tells listeners that it is time for a competition. Listeners must identify two songs in a row that are only played for two seconds each. Emma recognises both and calls the station immediately. Surprisingly, Emma is connected straight away and the host asks her for her answers. With both correct, the host congratulates her and tells her she has won the biggest prize the station has ever given away – a huge cash prize and a luxury holiday to Bali. Thrilled, Emma starts crying and thanks the host. Emma tells the host that she will spend some of the money on a new car and kitchen and will be able to save the rest. The host congratulates her again gives her instructions about how to collect her prize. Emma calls her husband to tell him the news.

The Paris Trip

(162 words, 11 sentences)

(16 buffer, 72 content, total 88)

Bella has earned some holiday allowance at work and books a short trip to Paris. After landing at the airport, she gets a taxi to her hotel and brings in her bags. Strolling around the centre of the French city, Bella spots an old school friend that she hasn't seen in years. She shouts to her old friend who turns around with a warm smile. Bella runs along the cobblestone street excitedly and embraces her friend. Grinning, the women are both shocked and surprised that they have bumped into each other in Paris. Her friend is very pleased to see Bella and is eager to tell her about her life since school. The pair decide to go to a wine bar and catch up over dinner. They tell each other fond stories of their childhood, laughing over funny stories. Later, they part with plans to meet up the next day. Bella hails for a taxi to take her back to her hotel.

The Skateboard Race

(160 words, 11 sentences)

(11 buffer, 79 content, total 90)

Josh decides to meet his friends at a park. His friend, Billy, invites him to race down a steep hill on their skateboards. Josh makes a quick start and is in the lead. As he gets faster, his board starts wobbling and suddenly slips from underneath him. Josh crashes to the ground and painfully slides over concrete, shredding his jeans. Coming to a stop, Josh feels a strong jolt of pain in his leg which is covered in blood. He tries to wipe some of the blood away to see where it is coming from and notices a large white lump in the middle of his shin. Josh screams as he realises his bone is poking out through his blood covered jeans. He calls for Billy who rushes over and gasps at the sight of his broken and bloody leg. Billy frantically calls for an ambulance and tries to keep Josh calm. Billy is silent and waits patiently with Josh.

The Return

(163 words, 11 sentences)

(14 buffer, 75 content, total 89)

Fiona was getting ready to go to town on a rainy afternoon. She needed to return some winter clothes and gardening tools that she had bought online on Friday, the week prior. She laid out her items on her living room floor, ready to package them. Fiona noticed that a thread from her carpet had become loose which created a loop that stuck out. She took her scissors and cut away the thread. One by one, she then put her items into plastic parcel bags and taped them closed. The only pen she could find to write the addresses was a large marker. Once she had packaged all of the items, she searched for her car keys, they were nowhere in sight. She lifted the sofa cushions to check underneath but still could not find them. Suddenly, she remembered that she had left them in the fruit bowl in the kitchen. After, Fiona got her coat and loaded her packages in the car.

The Birthday Present

(163 words, 11 sentences)

(20 buffer, 75 content, total 95)

Annie had just finished her last day of school at Woodfield Primary School. It was Annie's tenth birthday so she was eager to return home to her family for celebrations. At home, there was a large, wrapped, multicoloured box placed in the middle of the living room with a bow on top. Her mother said she could open the present, so she rushed over in excitement and ripped off the wrapping paper enthusiastically. In the box, Annie saw a tiny Labrador puppy with large brown eyes. It was no bigger than a football. The puppy seemed very happy to see Annie as it wagged its little, white, tail and jumped up at her. She gently lifted the Labrador up into her chest and cuddled it. She cried joyously as the puppy licked her face excitedly. Annie was so pleased as she had always wanted a dog. Annie's mother collected all of the discarded wrapping paper and put it into a black plastic bag.

The Presentation

(163 words, 11 sentences)

(14 buffer, 81 content, total 95)

Richard was wearing a blue shirt and a black striped tie. He wanted to look smart as he was about to give a presentation to hundreds of people. He was feeling extremely nervous as he wanted to make a good impression on his colleagues. As Richard walked anxiously across the stage to begin his speech, he tripped on a loose cable and fell headfirst into the audience. He was in excruciating pain as the fall had caused his shoulder to dislocate. The audience laughed, not realising that Richard had seriously hurt himself. To make matters worse, the fall had caused a table to tip over spilling boiling, hot drinks over people. Richard then climbed onto the stage to continue his presentation in an attempt to improve the situation. However, he found it difficult not to cry due to the pain and embarrassment. Tearful, he apologised to his peers and left the stage. Richard immediately called his wife to ask her to collect him.

Appendix 15. Sleep study debrief form.

The influence of isomaltulose on sleep and memory consolidation: Proof of Concept

Thank you for taking part in our research. We know it has involved a great deal of commitment over the past three weeks. Now that your contribution has finished, let me explain the rationale behind this work.

Although the exact purpose of sleep is not yet fully understood, it is clear that sleep plays a critical role in a number of functions, including memory, learning, mood, and glucose metabolism. Despite its importance, few studies have examined the effects of meal composition on sleep. Most studies have focused on carbohydrate manipulation; however, findings are sporadic and confounded by the manipulation of other macronutrients. The purpose of this study was to compare the effects of two different pre-bed drinks (isomaltulose and glucose) on sleep glucose metabolism, sleep architecture, and memory consolidation. These drinks differ in the amount they raise blood sugar levels, termed glycaemic index. This research may help to determine whether consuming certain types of foods or drinks, with a high or low glycaemic index, can facilitate better sleep and memory.

An analysis of the information will form part of our report at the end of the study and may be presented to interested parties and published in scientific journals and related media. *All information presented in any reports or publications will be anonymous and unidentifiable.* You may choose to withdraw your data, without penalty. All electronic data will be stored on a password-protected computer file, and all paper records will be stored in a locked filing cabinet, within the Psychology Department. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach. Your data will be stored for up to 10 years. If you would like to receive a copy of the final report of this study when it is completed, please feel free to contact the researcher.

If you feel affected by issues raised by this research and would like to discuss any concerns, please contact the study Supervisor using the details provided below. If you feel this piece of research may have health implications for you, we advise you to contact your GP (family doctor).

Appendix 16. Sleep study additional analyses

	Main effect/interaction	Follow-up tests
Additional analyses		
N1 sleep percentage	Main effect of Drink ($F(1,18) = 0.061$, $p = 0.81$, $np^2 = .003$, BFincl = 0.356) and Drink X Order interaction ($F(1,18) = 0.741$, $p = 0.40$, $np^2 = .040$, BFincl = 0.489) were non-significant.	N/A
N2 sleep percentage	Main effect of Drink ($F(1,18) = 0.137$, $p = 0.72$, $np^2 = .008$, BFincl = 0.327) and Drink X Order interaction ($F(1,18) = 0.155$, $p = 0.69$, $np^2 = .009$, BFincl = 0.406) were non-significant.	N/A
Wake percentage	The interaction Drink X Order was not significant ($F(1,18) = 0.016$, $p = 0.90$, $np^2 = .001$, BFincl = 0.42), as well as the main effect of Drink ($F(1,18) = 0.001$, $p = 0.98$, $np^2 = .000$, BFincl = 0.32).	N/A
Total sleep time	Drink X Order interaction ($F(1,18) = 0.059$, $p = 0.81$, $np^2 = .003$, BFincl = 0.19) and main effect of Drink ($F(1,18) = 0.762$, $p = 0.39$, $np^2 = .041$, BFincl = 0.52) were non-significant.	N/A
Arousal indices	Two extreme outliers were removed from the arousal index analysis; the Drink X Order interaction was non-significant ($F(1,16) = 0.054$, $p = 0.82$, $np^2 = .003$, BFincl = 0.19). The main effect of Drink was also not significant ($F(1,16) = 0.962$, $p = 0.34$, $np^2 = .057$, BFincl = 0.49).	N/A
Split-night – N1 sleep percentage	The Drink X Order X Time interaction was non-significant ($F(1,18) = 0.010$, $p =$	N/A

	0.922, np^2 = .001, BFincl = 0.49), as well as the main effect of Drink (F(1,18) = 0.035, p = 0.853, np^2 = .002, BFincl = 0.292).	
Split-night – N2 sleep percentage	Removal of two outliers in the N2 sleep analysis revealed a significant interaction between Drink X Time (F(1,16) = 6.369, p = 0.023, np^2 = .285, BFincl = 6.07). The main effect of Drink (F(1,16) = 0.025, p = 0.876, np^2 = .002, BFincl = 0.315) was non-significant. The main effect of Time was significant (F(1,16) = 23.491, p = 0.001, np^2 = .595, BFincl = 203.36).	A Bonferroni correction for four tests was applied (α = 0.012). Post hoc t-tests indicated that a significantly higher percentage of N2 sleep occurred during the second half of the night compared to the first half of the night after the HGL drink (p = 0.001, BF+0 = 5982.84), which remained significant after applying a Bonferroni correction. A higher percentage of N2 sleep also occurred during the second half of the night compared to the first half of the night after the LGL drink, but this was no longer significant after applying a Bonferroni correction (p = 0.047, BF+0 = 1.56). There was also a non-significant trend towards a higher percentage of N2 sleep after the HGL drink compared to LGL drink, but only during the second half of the night (p = 0.073, BF+0 = 1.12). The percentage of N2 sleep was greater during the second half of the night (mean = 61.48, SD = 5.51)

		compared to the first half of the night (mean = 48.02, SD = 6.35).
Split-night – wake percentage	Three outliers were removed from the analysis. A significant Drink X Time interaction was revealed ($F(15) = 10.695$, $p = 0.005$, $np^2 = .416$, BFincl = 82.173). The main effect of Drink was non-significant ($F(1,15) = 0.012$, $p = 0.916$, $np^2 = .001$, BFincl = 0.32), as well as the Drink X Order X Time interaction ($F(1,15) = 0.040$, $p = 0.843$, $np^2 = .003$, BFincl = 0.47).	A Bonferroni correction for four tests was applied ($\alpha = 0.012$). During the second half of the night, the LGL drink was associated with a significantly higher percentage of wake compared to the HGL drink ($p = 0.011$, BF+0 = 5.01). Only the HGL drink was associated with a higher wake percentage during the first half of the night compared to the second half of the night, but this did not remain significant after applying a Bonferroni correction ($p = 0.020$, BF+0 = 3.7).
Bayesian statistics for primary/secondary/exploratory variables		
N3 sleep percentage	Three outliers were removed. There was a significant Drink X Order interaction ($F(1,15) = 5.595$, $p = 0.032$, $np^2 = .272$, BFincl = 2.61). The main effect of Drink was non-significant ($F(1,15) = 1.149$, $p = 0.301$, $np^2 = .071$, BFincl = 0.42).	The LGL drink was associated with a higher N3 percentage when glucose was consumed first, but this did not survive Bonferroni correction ($p = 0.032$, BF+0 = 2.27). The effect when isomaltulose was consumed first was not significant ($p = 0.361$, BF+0 = 0.17).
REM sleep percentage	The interaction Drink X Order was not significant ($F(1,18) = .003$, $p = 0.957$, $np^2 = .000$, BFincl = 0.18), and neither was the main effect of Drink ($F(1,18) = 1.539$, $p = 0.231$, $np^2 = .079$, BFincl = 0.46).	N/A
Split night – N3 sleep percentage	The interaction Drink X Order X Time was non-significant ($F(1,18) = .565$, $p =$	N/A

	0.462, np^2 = .030, BFincl = 0.504). The main effect of Drink was non-significant (F(1,18) = 0.124, p = 0.729, np^2 = .007, BFincl = 0.277).	
Split-night - REM sleep	The Drink X Order X Time interaction was significant (F(1,17) = 4.647, p = 0.046, np^2 = .215, BF_{incl} = 7.230). The main effect of Drink was non-significant (F(1,17) = 0.566, p = 0.462, np^2 = .032, BF_{incl} = 0.372).	In those who consumed the HGL drink first, there was a trend towards a higher percentage of REM sleep during the second half of the night after the HGL drink than LGL drink (p = 0.058). The Bayesian analysis indicated that there was anecdotal evidence in favour of the alternative hypothesis (BF+0 = 1.23).
LSEQ	'Getting to sleep' subscale - Drink X Order interaction (BFincl = 0.551) and main effect of Drink (BFincl = 0.308). 'Quality of sleep' subscale – Drink X Order interaction (BFincl = 0.425) and main effect of Drink (BFincl = 0.45). 'Ease of waking from sleep' subscale - Drink X Order interaction (BFincl = 0.363) and main effect of Drink (BFincl = 0.325). 'Behaviour following sleep' subscale - Drink X Order interaction (BFincl = 0.417) and main effect of Drink (BFincl = 0.312).	N/A
ESS	Drink X Order interaction (BFincl = 0.74) and main effect of Drink (BFincl = 0.45).	N/A
Sleep efficiency	Drink X Order interaction (BFincl = 0.12) and main effect of Drink (BFincl = 0.37).	N/A

WASO	The Drink X Order interaction (BF_{incl} = 2.02) and main effect of Drink (BFincl = 0.32).	When glucose was consumed first, there was a longer WASO after the LGL drink. (p = 0.026, BF_{+0} = 3.09). However, this was no longer significant after applying a Bonferroni correction for four tests. When isomaltulose was consumed first follow-up tests were not significant (p = 0.368, BF_{+0} = 0.44).
SOL	Two outliers were removed. The Drink X Order interaction just missed significance ($F(1,16) = 4.305$, p = 0.054, np^2 = 212, BFincl = 2.12). The main effect of Drink was non-significant (BFincl = 0.35).	When isomaltulose was consumed first, there was a trend towards a longer SOL after the LGL drink (p = 0.092, BF+0 = 1.23). When glucose was consumed first follow-up tests were not significant (p= 0.964, BF+0 = 0.14).
Total number of words recalled	Drink X Order X Valence interaction (p = 0.35, BFincl = 0.754) and main effect of Drink (p = 0.58, BFincl = 0.29) were non-significant. Main effect of Valence just missed significance (p = 0.06, BFincl = 0.79).	More words were forgotten overnight from the positive stories than neutral stories (p = 0.022, BF+0 = 0.19). However, this was no longer significant after applying a Bonferroni correction for three tests ($\alpha = 0.016$).
Total number of content words recalled	Drink X Order X Valence interaction (p = 0.179, BFincl = 0.49), main effect of Drink (p = 0.869, BFincl = 0.26), and main effect of Valence (p = 0.249, BFincl = 0.32) were non-significant.	N/A
Total number of buffer words recalled	Main effect of Drink (p = 0.445, BFincl = 0.327) and Drink X Valence X Order interaction (p = 0.100, BFincl = 0.397) were non-significant. Main effect of	Bonferroni corrected post hoc t-tests ($\alpha = 0.016$) revealed that significantly more words were forgotten overnight from the positive stories than negative stories

	Valence was significant (p = 0.007, BFincl = 0.40).	(p = 0.008, BF+0 = 0.48) and neutral stories (p = 0.011, BF+0 = 0.721).
Story recall task		
Preliminary check – total score (learning phase versus recall phase)	Main effect of Time (F(1,19) = 11.572, p = 0.003)	Scores were poorer in the morning than evening.
Preliminary check – total content score (learning phase versus recall phase)	Main effect of Time (F(1,19) = 7.245, p = 0.014)	Scores were poorer in the morning than evening.
Preliminary check – total buffer score (learning phase versus recall phase)	Main effect of Time (F(1,19) = 23.245, p = 0.001)	Scores were poorer in the morning than evening.
Preliminary check – total score (differences in scores during the learning phase between drink conditions)	Main effect of Drink (F(1,19) = .002, p = 0.968, ηp^2 = .000). Drink X Valence interaction (F(2,38) = .690, p = 0.508, ηp^2 = .035).	No differences during the learning phase between drink conditions.
Preliminary check – total content score (differences in scores during the learning phase between drink conditions)	Main effect of Drink (F(1,19) = 0.023, p = 0.882, ηp^2 = .001). Drink X Valence interaction (F(2,38) = .511, p = 0.604, ηp^2 = .026).	No differences during the learning phase between drink conditions.
Preliminary check – total buffer score (differences in scores during the learning phase between drink conditions)	Main effect of Drink (F(1,19) = .077, p = 0.785, ηp^2 = .004). Drink X Valence interaction (F(2,38) = .459, p = 0.635, ηp^2 = .024).	No differences during the learning phase between drink conditions.
Story ratings	A three-way Valence X Scale X Drink ANOVA was performed.	Ratings of 'incomprehensible-comprehensible', 'difficult-easy', 'abstract-concrete', 'unrelatable-

		relatable', and 'unfamiliar-familiar' did not differ between the three types of stories (all p = NS). Negative and positive stories were rated as significantly more interesting, emotional, and startling than neutral stories (all p = 0.05). Negative stories were rated as significantly more negative than both positive and neutral stories, and more important and arousing than neutral stories (all p = 0.05). Positive stories were rated as significantly more amusing and positive than both negative and neutral stories (all p = 0.05).
Finger tapping task		
Preliminary check – mean scores (learning phase versus recall phase)	Main effect of Time ($F(1,17) = 74.054$, $p = 0.001$, $\eta p^2 = .473$).	Mean performance was significantly better in the morning than evening.
Preliminary check – best scores (learning phase versus recall phase)	Main effect of Time ($F(1,17) = 11.689$, $p = 0.091$, $\eta p^2 = .159$).	No difference in best performance during the evening and morning.
Preliminary check – mean scores (differences in scores during the learning phase between drink conditions)	Main effect of Drink ($F(1,17) = .022$, $p = 0.885$, $\eta p^2 = .001$).	No differences during the learning phase between drink conditions.
Preliminary check – best scores (differences in scores during the	Main effect of Drink ($F(1,17) = .040$, $p = 0.844$, $\eta p^2 = .002$).	No differences during the learning phase between drink conditions.

learning phase between drink conditions)		

Appendix 17. Polyphenol study information sheet.

The influence of various nutrients on glycaemic control, cognition, and mood in middle-age and older adults.

What is the purpose of the research?

The purpose of the study is to investigate the impact of diet on blood glucose control, mood, and cognition.

Who is carrying out the study?

The research is being conducted by Chantelle Gaylor, under the supervision of Professor David Benton and Dr Hayley Young in the Department of Psychology at Swansea University. The research has been approved by the Swansea Psychology Research Ethics Committee.

Can anybody take part?

We are looking for males and females aged 60+ who are native English Speakers. Unfortunately, you will ***not*** be able to take part if you have any of the following:

- Diabetes / take medication to control blood glucose levels
- Have chronic liver or kidney disease
- Have a history of a neuropsychological disease
- Have gastrointestinal problems that may interfere with absorption.
- Have severe cardiovascular disease
- Are taking medications for blood pressure such as ACE inhibitors/water tablets
- Smoke

Please also inform of us of any other medication you use before participating in the study.

What happens if I agree to take part?

Over the course of three months, you will be asked to attend the Psychology Laboratory on four separate occasions. Each visit will begin at 9am and should take no longer than 4-5 hours. You will also be asked to fast for 12 hours before attending the laboratory.

Each visit will be almost identical. We will collect data regarding your general health, including current/average blood glucose levels (via finger pricks), body fat, weight, height, blood pressure, heart rate, blood lipids, and blood inflammation. Urine samples will also be collected. You will then be asked to consume a glucose drink, and your blood glucose levels will be measured every 30 minutes. Throughout the morning, you will also complete several computer tasks measuring memory, attention, and reaction times, as well as mood and dietary questionnaires.

At the end of each visit, you will be given a pack of nutritional supplements. You will be required to take a nutritional supplement twice a day for three months. At the end of the study, you will be given £200 for taking part.

Are there any risks associated with taking part?

The research has been approved by the Department of Psychology's Research Ethics Committee. There are no significant risks associated with participation.

Data protection and confidentiality

Your data will be processed in accordance with the General Data Protection Regulation 2016 (GDPR). All information collected about you will be kept strictly confidential and anonymous. All electronic data will be stored on a password-protected computer file in Room 706 Vivian Tower. All paper records will also be stored in a locked filling cabinet in Room 706. Your consent information will be kept separately from your responses to minimise risk in the event of a data breach.

What will happen to the information I provide?

Your data will only be viewed by the researcher/research team. An analysis of the information will form part of our report at the end of the study and may be presented to interested parties and published in scientific journals/related media, but you will not be personally identifiable within this data.

Is participation voluntary and what if I wish to later withdraw?

It is entirely voluntary – you do not need to participate if you do not want to. Even if you start the study, you are free to withdraw at any stage, without giving a reason.

Data Protection Privacy Notice

The data controller for this project will be Swansea University. The University Data Protection Officer provides oversight of university activities involving the processing of personal data and can be contacted at the Vice Chancellors Office: XXXXXX. Swansea University's Data Protection Officer is Bev Buckley, and she may be contacted at XXXXXX **.**

Your personal data will be processed for the purposes outlined in this information sheet. Standard ethical procedures will involve you providing your consent to participate in this study by completing the consent form that has been provided to you. However, the legal basis on which this task is being performed is public interest, approved by the departmental Research Ethics Committee.

Appendix 18. Polyphenol study consent form.

THE INFLUENCE OF VARIOUS NUTRIENTS ON THE CONTROL OF BLOOD GLUCOSE

- I have been given, and have had the opportunity to read, the participant information sheet. Any questions have been answered in a satisfactory way.

- I understand what I am required to do during the study.

- I understand that I can ask any questions that arise at any point during the procedure.

- I understand that the supplements I will take contain only substances found in food, but if there is any suggestion of an adverse response then I will stop taking them immediately and inform the experimenter.

- If the study identifies any pre-existing medical condition, for example the early stages of diabetes, I will be informed and if I agree this information will be forwarded to your doctor.

- I agree that the data will be stored so that I cannot be identified and understand, that after statistical analysis, I will not be identified.

- I understand that participation is voluntary and I am free to withdraw from the study at any point.

- I am over 18 years of age.

NAME (Print) …… Sign ……

Address …… Date …….

Appendix 19. List of words used in the word list recall task.

List 1: Pedal, Globe, Daisy, Brick, Flute, Linen, Spike, Paste, Beard, Shark, Prune, Cedar, Tooth, Ankle, Queen, Chart, Plane, Belly, Organ, Arrow, Crypt, Mixer, Honey, River, Trunk, Couch, Ruler, Ivory, Spade, Elbow.

List 2: Beach, Thick, Table, Meant, Rifle, Force, Earth, Brief, Horse, Clear, Chain, Reach, Paper, Least, Woman, Order, Shore, Guess, Drink, Eight, Glass, Issue, Coast, Think, Truck, Worse, Child, Quick, Staff, Value.

List 3: Chest, Whole, River, Moral, Light, Quiet, Blood, Claim, Metal, Under, Smile, Dozen, Phone, Right, Frame, Extra, Uncle, South, Wheel, Allow, Knife, Leam, Crowd, Rural, Heart, Truth, Teeth, Apart, Court, Proud

List 4: Spoke, Power, Cover, Phase, Radio, Alone, Judge, Short, Flesh, Minor, Bible, Ideal, Money, Happy, Stone, Wrote, Hotel, Carry, Water, Might, Novel, Empty, China, Event, Plant, Break, Dress. Theme, Board, Style.

Appendix 20. Mood, thirst, and hunger visual analogue scales.

Please cross each line to indicate the way you feel at this moment. If neither adjective describes how you feel then put a cross in the middle. If you tend towards one end of the line then put a cross at the point that reflects the extent to which the adjective describes how you feel now (use the entire line)

Example:

Happy — **Sad**

I am neither happy nor sad

Happy — **Sad**

I am extremely happy

Happy — **Sad**

I am slightly happy

Agreeable — **Hostile**

Confused — **Clearheaded**

Composed — **Anxious**

Depressed — **Elated**

Confident — **Unsure**

Tired — **Energetic**

HOW HUNGRY DO YOU FEEL RIGHT NOW?

Extremely — **Not at all**

HOW THIRSTY DO YOU FEEL RIGHT NOW?

Not at all — **Extremely**

Appendix 21. Profile of Mood States Questionnaire-Bipolar.

Below are a list of words that describe feelings and moods people have. Please read EVERY word carefully. Then fill in ONE space under the answer which best describes how you have been feeling DURING THE PAST WEEK INCLUDING TODAY.

	Much unlike this	Slightly unlike this	Slightly like this	Much like this
Composed	○	○	○	○
Angry	○	○	○	○
Cheerful	○	○	○	○
Weak	○	○	○	○
Tense	○	○	○	○
Confused	○	○	○	○
Lively	○	○	○	○
Sad	○	○	○	○
Friendly	○	○	○	○
Tired	○	○	○	○
Strong	○	○	○	○
Clearheaded	○	○	○	○
Untroubled	○	○	○	○
Grouchy	○	○	○	○
Playful	○	○	○	○
Timid	○	○	○	○
Nervous	○	○	○	○
Mixed-up	○	○	○	○
Vigorouos	○	○	○	○
Dejected	○	○	○	○
Kindly	○	○	○	○
Fatigued	○	○	○	○
Bold	○	○	○	○
Efficient	○	○	○	○
Peaceful	○	○	○	○
Furious	○	○	○	○
Lighthearted	○	○	○	○
Unsure	○	○	○	○
Jittery	○	○	○	○
Bewildered	○	○	○	○
Energetic	○	○	○	○
Lonely	○	○	○	○
Sympathetic	○	○	○	○
Exhausted	○	○	○	○
Powerful	○	○	○	○
Attentive	○	○	○	○
Serene	○	○	○	○
Bad tempered	○	○	○	○
Joyful	○	○	○	○
Self-doubting	○	○	○	○
Shaky	○	○	○	○
Perplexed	○	○	○	○
Active	○	○	○	○
Downhearted	○	○	○	○
Agreeable	○	○	○	○
Sluggish	○	○	○	○
Forceful	○	○	○	○
Able to concentrate	○	○	○	○
Calm	○	○	○	○
Mad	○	○	○	○
Jolly	○	○	○	○

Uncertain	○	○	○	○
Anxious	○	○	○	○
Muddled	○	○	○	○
Ready to go	○	○	○	○
Discouraged	○	○	○	○
Good natured	○	○	○	○
Weary	○	○	○	○
Confident	○	○	○	○
Business like	○	○	○	○
Relaxed	○	○	○	○
Annoyed	○	○	○	○
Elated	○	○	○	○
Inadequate	○	○	○	○
Uneasy	○	○	○	○
Dazed	○	○	○	○
Full of pep	○	○	○	○
Gloomy	○	○	○	○
Affectionate	○	○	○	○
Drowsy	○	○	○	○
Self-assured	○	○	○	○
Mentally alert	○	○	○	○

Appendix 22. Polyphenol study additional analyses.

Measure	Main effect/interaction	Follow-up tests
VAS – agreeable ratings	Main effect of Time ($F(2.332,60.631) = 7.231$, $p = 0.001$, $np^2 = .218$).	After applying a Bonferroni correction for six tests ($\alpha = 0.008$), ratings were significantly higher at baseline that at 30 minutes ($p = 0.003$), 60, 90, and 120 minutes ($p < 0.001$), 150 minutes ($p = 0.004$), and 180 minutes ($p = 0.003$).
	Main effect of Visit ($F(2.211,57.495) = 5.450$, $p = 0.005$, $np^2 = .173$).	After applying a Bonferroni correction for three tests ($\alpha = 0.016$), ratings significantly declined from visit 1 to visit 2 ($p = 0.001$) and visit 3 ($p = 0.006$).
VAS – clearheaded ratings	Main effect of Time ($F(3.399,88.387) = 12.964$, $p = 0.001$).	After applying a Bonferroni correction for six tests ($\alpha = 0.008$), ratings declined significantly from baseline to 60 and 90 minutes ($p < 0.001$), 120 minutes ($p = 0.007$), 150 minutes ($p = 0.004$), and 180 minutes ($p < 0.001$).
VAS – composed ratings	Main effect of Time ($F(6,156) = 4.056$, $p = 0.001$).	After applying a Bonferroni correction for six tests ($\alpha = 0.008$), rating declined significantly from baseline to 60 minutes ($p = 0.003$) and 180 minutes ($p < 0.001$).
VAS – elated ratings	Main effect of Time ($F(3.484,90.575) = 3.114$, $p = 0.024$).	After applying a Bonferroni correction for six tests ($\alpha =$

		0.008), ratings increased significantly from baseline to 30 minutes post-drink consumption ($p = 0.001$).
VAS – confidence ratings	Main effect of Time ($F(3.044,79.137) = 4.651$, $p = 0.005$).	A Bonferroni correction was applied for six tests ($\alpha = 0.008$). Ratings of confidence declined from baseline to 60 minutes ($p = 0.045$) and 180 minutes ($p = 0.026$). These were no longer significant after applying a Bonferroni correction.
VAS – energetic ratings	Main effect of Time ($F(4.123,107.201) = 12.276$, $p = 0.001$).	After applying a Bonferroni correction for six tests ($\alpha = 0.008$), ratings significantly declined from baseline to 150 minutes ($p = 0.002$) and 180 minutes ($p < 0.001$).

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