The effects of sleep disturbance on dyspnoea and impaired lung function following COVID-19 hospitalisation in the UK: a prospective multi-centre cohort study

Callum Jackson[1], Iain Stewart[2], Tatiana Plekhanova[3,4], Peter Cunningham[5], Andrew L Hazel[1], Bashar Al-Sheklly[6], Raminder Aul[7], Charlotte E Bolton[8,9], Trudie Chalder[10,11], James D Chalmers[12], Nazia Chaudhuri[13], Annemarie B Docherty[14], Gavin Donaldson[2], Charlotte L Edwardson[3,4], Omer Elneima[4], Neil J Greening[4,15], Neil A Hanley[6], Victoria C Harris[4,15], Ewen M Harrison[14], Ling-Pei Ho[16,17], Linzy Houchen-Wolloff[18,19,20], Luke S Howard[2,21], Caroline J Jolley[22], Mark Jones[23,24], Olivia C Leavy[25], Keir E Lewis[26,27], Nazir I Lone[28,29], Michael Marks[30,31,32], Hamish J C McAuley[4,15], Melitta A McNarry[26], Brijesh Patel[33], Karen Piper-Hanley[5,34,35], Krisnah Poinasamy[36], Betty Raman[16,37], Matthew Richardson[4,38], Pilar Rivera-Ortega[39,40], Sarah L Rowland-Jones[41,42], Alex V Rowlands[3,4], Ruth M Saunders[4], Janet T Scott[43], Marco Sereno[4,38], Ajay M Shah[22], Aarti Shikotra[4], Amisha Singapuri[4,15], Stefan C Stanel[40], Mathew Thorpe[14], Daniel G Wootton[44,45], Thomas Yates[3,15], Gisli Jenkins[2], Sally Singh[33], William D-C Man[2,22,33], Christopher E Brightling[4,15], Louise V Wain[4,25], Joanna C Porter[46], A A Roger Thompson[42,47], Alex Horsley[5,39], Philip L Molyneaux[2], Rachael A Evans[4,15], Samuel E Jones[48], Martin K Rutter[34,49], John F Blaikley[5,40], on behalf of the PHOSP-COVID Study Collaborative Group[†]

Affiliations:

1. Department of Mathematics, The University of Manchester, Oxford Road, Manchester M13 9PL, United Kingdom
2. National Heart & Lung Institute, Imperial College London, London, UK
3. Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, LE5 4PW, UK
4. NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
5. Faculty of Biology, Medicine and Health, The University of Manchester, Oxford Road, Manchester M13 9PL United Kingdom
6. Manchester University NHS Foundation Trust
7. St Georges University Hospitals NHS Foundation Trust, London, UK
8. Nottingham University Hospitals NHS Trust & University of Nottingham
9. NIHR Nottingham BRC respiratory theme, Translational Medical Sciences, School of Medicine, University of Nottingham, Nottingham, UK
10. Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom
11. South London and Maudsley NHS Trust
12. University of Dundee, Ninewells Hospital and Medical School, Dundee, UK
13. University Hospital of South Manchester NHS Foundation Trust
14. Centre for Medical Informatics, The Usher Institute, University of Edinburgh, Edinburgh, UK
15. University Hospitals of Leicester NHS Trust & University of Leicester
16. Oxford University Hospitals NHS Foundation Trust & University of Oxford
17. MRC Human Immunology Unit, University of Oxford, Oxford, UK
18. Centre for Exercise and Rehabilitation Science, NIHR Leicester Biomedical Research Centre-Respiratory, University of Leicester, Leicester, UK
19. Department of Respiratory Sciences, University of Leicester, Leicester, UK
20. Therapy Department, University Hospitals of Leicester, NHS Trust, Leicester, UK
21. Hammersmith Hospital, Imperial College Healthcare NHS Trust, London
22. King's College Hospital NHS Foundation Trust & Kings College London
23. Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK
24. NIHR Southampton Biomedical Research Centre, University Hospitals Southampton, Southampton, UK
25. Department of Health Sciences, University of Leicester, Leicester, UK
26. Swansea University, Swansea Welsh Network, Hywel Dda University Health Board
27. Respiratory Innovation Wales, Wales, UK

28. Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
29. Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, United Kingdom
30. Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK
31. Hospital for Tropical Diseases, University College London Hospital, London, UK
32. Division of Infection and Immunity, University College London, London, UK
33. Royal Brompton and Harefield Clinical Group, Guy's and St Thomas' NHS Foundation trust
34. Division of Diabetes, Endocrinology & Gastroenterology, School of Medical Sciences, University of Manchester, Manchester, UK
35. Wellcome Centre for Cell-Matrix Research, Faculty of Biology, Medicine & Health, Manchester Academic Health Science Centre, University of Manchester, Oxford Road, Manchester, UK
36. Asthma UK and British Lung Foundation, London, UK
37. Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom
38. University of Leicester, University Rd, Leicester LE1 7RH, UK
39. Manchester University NHS Foundation Trust
40. Interstitial Lung Disease Unit, North West Lung Centre, Wythenshawe Hospital, Southmoor Rd, Wythenshawe, Manchester M23 9LT, UK
41. University of Sheffield, Sheffield, UK
42. Sheffield Teaching NHS Foundation Trust, Sheffield, UK
43. MRC - University of Glasgow Centre for Virus Research, Glasgow, UK
44. Liverpool University Hospitals NHS Foundation Trust & University of Liverpool
45. Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool
46. Department of Respiratory Medicine, University College London WC1E 2JF
47. Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield UK
48. Institute for Molecular Medicine Finland, FIMM, HiLIFE, University of Helsinki, Helsinki, Finland
49. Diabetes, Endocrinology and Metabolism Centre, NIHR Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, Manchester University Hospitals NHS Foundation Trust, Manchester, UK

What is Known:

We systematically searched PubMed databases for medium studies (>100 participants) reporting sleep disturbance for patients discharged from hospital after contracting COVID-19, published between Jan 1, 2020, and Nov 25, 2022, without language restrictions. Search terms related to COVID-19 ("COVID-19", "COVID-2019", "SARS-CoV-2", "2019-nCoV", "2019-SARS-CoV-2"), hospitalisation ("hospital*"), sleep ("sleep") and long-term follow-up ("survivor*", "recover*", "persistent", "follow up", "long term", "sequela*", "long Covid") were used. Studies reported that sleep disturbance is a common symptom following COVID-19 hospitalisation. Reported prevalence varied between 10-70% depending on which subjective method was used. One device-based study suggested that sleep regularity and efficiency are altered but did not report sleep quality. Most studies only reported prevalence of sleep disturbance, but two studies also identified an association between sleep disturbance and anxiety. No other clinical associations have been reported, despite COVID-19 symptom studies suggesting sleep disruption could be part of a cluster of symptoms.

What this study adds:

This UK multi-centre cohort study used multiple measures to assess sleep disturbance following COVID-19 hospitalisation. Study findings were consistent regardless of the measure used revealing a high prevalence of sleep disturbance. Sleep disturbance was associated with dyspnoea, reduced lung function, anxiety, and muscle weakness. Further analysis revealed that both anxiety and muscle weakness could partially mediate some of these relationships.

Implications of this study:

Our findings suggest that sleep disturbance is a common problem after hospitalisation for COVID-19 and is associated with dyspnoea. Future research should assess whether interventions targeting sleep disturbance can improve dyspnoea through reducing anxiety and improving muscle strength.

Abstract

Background

Sleep disturbance is common following hospitalisation both for COVID-19 and other causes. The clinical associations are poorly understood despite sleep disturbance contributing to morbidity in other scenarios. Therefore, we investigated the prevalence and nature of sleep disturbance after COVID-19 hospitalisation and whether this was associated with dyspnoea.

Methods

Sleep parameters were assessed in a prospective multi-centre cohort of patients (n=2,468) hospitalised for COVID-19 in the United Kingdom using both subjective (n=638) and device-based (n=729) measures. Results were compared to a matched UK Biobank cohort. Multivariable linear regression was used to define associations.

Findings

The majority (62% (396/638)) of participants reported poor sleep quality. A comparable proportion (53% (338/638)) felt their sleep quality had deteriorated for at least 1-year following hospitalisation. Compared to a non-hospitalised matched cohort, both sleep regularity (44·5 vs 56·5) and sleep efficiency (85·4% vs 89·0%) were lower as opposed to sleep period duration which was longer (8·25h vs 7·17h). Overall sleep quality (effect estimate 3·9, 95%CI (2·8–5·1)), deterioration in sleep quality following hospitalisation (effect estimate 3·0, 95%CI (1·8–4·3)), and sleep regularity (effect estimate 4·4, 95%CI (2·1–6·7)) were associated with dyspnoea and impaired lung function (FEV_1 and FVC). Depending on the sleep metric, anxiety mediated 18–39% of the effect of sleep disturbance on dyspnoea and muscle weakness mediated 27-41% of this effect.

Interpretation

Sleep disturbance is associated with dyspnoea, anxiety, and muscle weakness following COVID-19 hospitalisation. Targeting sleep disturbance may be beneficial in treating the post-COVID-19 condition.

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Introduction

It has been recognised that delayed recovery and persistent illness following hospitalisation for COVID-19 constitutes "post-COVID-19 syndrome"[1]. Dyspnoea is a frequent symptom of this syndrome, with a recent study suggesting that 48% of patients hospitalised with COVID-19 in the UK[2] experience it. Dyspnoea can arise from conditions which affect the respiratory, neurological, cardiovascular, and mental health systems[3]. These systems are also affected by sleep disturbance[4], another symptom that has been frequently reported after COVID-19[5-14]. The association between sleep disturbance and dyspnoea, however, has not been widely studied.

Sleep disturbance following hospitalization is common[15] regardless of the original reason for admission. Despite its prevalence, the clinical implications of sleep disturbance during recovery from an acute illness are not well understood. In experimental settings, sleep disturbance is causally associated with two recognised causes of dyspnoea: anxiety[16] and muscle weakness[17]. Furthermore, epidemiological studies have suggested that sleep disturbance is associated with respiratory disease[18] which can cause dyspnoea. Whether these associations persist following acute sleep disturbance, for example after hospitalisation, has still to be established.

An accurate assessment of sleep disturbance is best carried out using a multi-modal approach. Subjective assessments provide an overall score of sleep quality but may be affected by recall (reporting) bias[19], as well as questionnaire language. Subjective assessments also provide only limited insights into specific types of sleep disturbance. In contrast, device-based assessments of sleep quality e.g., actigraphy[20], measure sleep disturbance subtypes but they do not assess overall sleep quality[21]. Combining both subjective and device-based measures into a multi-modal approach[21] can provide valuable insights into sleep disruption partially overcoming the limitation of individual approaches.

A limited number of studies[5-14] have already reported altered sleep quality following COVID-19 hospitalisation. The majority of these have been single-centre, modest in size and only used subjective measures. Two studies to date have employed a multi-modal approach[22,23]. In these studies, an association with anxiety was reported only with subjective but not device-based measures. Furthermore, no other clinical associations were reported. The studies also only used participants who had been admitted to critical care, limiting generalisation to the broader hospital cohort.

The aim of this study was, therefore, to characterise the prevalence, type, and impact of sleep disturbance in a broad cohort of patients that had been hospitalised for COVID-19 using a multi-modal approach. We hypothesised

that sleep disturbance would be associated with dyspnoea and that this relationship would be mediated by anxiety and muscle weakness.

Methods

Participants

Subjects were recruited from the PHOSP-COVID study. All participants were ≥18 years of age, admitted to hospital with either PCR confirmed or clinically diagnosed COVID-19 and discharged between March 2020 – October 2021. The demographics and recruitment of participants into PHOSP-COVID have been described elsewhere[2] and are briefly described in the supplementary methods. COVID-19 severity during admission was assessed using the WHO clinical progression scale[24]. Participants were excluded from the analysis based on pre-existing conditions linked to sleep disturbance, medication, and nosocomial infections (**Supplementary Methods**).

Subjective assessment of sleep quality:

Two different methods assessed this a median of 5 months (IQR 4-6) post-hospitalisation.

(i) **Pittsburgh Sleep Quality Index (PSQI) questionnaire[25]:** This questionnaire assesses sleep quality across seven components. A total score greater than 5 was defined as poor sleep quality and a score ≤ 5 was defined as good sleep quality[25]. Unless specified elsewhere, participants with good sleep were compared to participants with poor sleep.

(ii) **Numerical rating scale (NRS) assessment of sleep quality:** Patients were asked to rate their sleep quality on a numerical rating scale (0-10; zero being the worst sleep quality, **Supplementary Methods**). Unless specified elsewhere, participants whose sleep had deteriorated (i.e., sleep score decreased by at least 1 compared to their pre-COVID-19 baseline) were compared to those whose sleep was unaffected by COVID-19.

Device-based assessment of sleep quality

Participants were invited to wear a wrist-worn accelerometer (GENEActiv Original, ActivInsights, Kimbolton, UK) on their non-dominant wrist 24h/day for 14 days a median of 7 months (IQR 5-8) post-discharge. Details of the data cleaning, analysis, and variable definitions are given in the supplementary methods. The top and bottom quintiles were compared for sleep regularity, sleep efficiency, and sleep period duration in the main manuscript as has been reported elsewhere[27,28]. Sleep regularity was also analysed as a continuous measure with the results being reported in the supplement.

UK Biobank cohorts

The UK Biobank[26] was used as a pre-pandemic comparator cohort. The UK Biobank recruited 502,540 participants aged 40 – 69 years who were invited to a baseline visit at one of 22 assessment centres between 2006 and 2010 during which their phenotypes were established using questionnaires, physical examination, and collection of biological samples. From this data set, three sub-cohorts (non-hospitalised, hospitalised and pneumonia) were created for analysis, and these are defined in the **Supplementary Methods**.

Symptom assessment

All symptoms were assessed at the first clinical visit a median of 5 months (IQR 4 – 6) post-hospitalisation. Details of each assessment are given in the supplementary methods.

Statistical analysis

Continuous values are presented as mean (95% CI) and ordinal values are presented as median (IQR). All univariable and multivariable analyses of continuous data were analysed using ordinary least squares linear regression or multinomial logistic regression. The multivariable analyses adjusted for a minimally sufficient set of covariates: age, sex, body mass index (BMI), number of days into the pandemic, number of days since discharge, pre-COVID comorbidities, COVID-19 severity, and length of stay; participants with missing values for any variable were excluded. This set was identified based on a Directed Acyclic Graph (DAG; www.dagitty.net, **Supplementary Methods**). Multinomial logistic regression was used for modelling anxiety. The 95% confidence intervals for regression coefficients were calculated from a residual bootstrap approach with 1,999 resamples (**Supplementary Methods**). Chi-square tests compared the proportions of categorical variables. Mediation was evaluated using linear regression with the product of coefficients method[27] to estimate the direct and indirect effects of the relationship, performed using the R package *lavaan* version 0·6-12 (**Supplementary Methods**). All data were analysed using R (version 4·2·0) within the Scottish National Safe Haven Trusted Research Environment. A p-value < 0·05 was considered significant.

Ethics

The study was ethically approved (Ref: 20/YH/0225)

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 2,468 participants were enrolled in the PHOSP-COVID study, of which 2,320 attended an early time point research visit a median of 5 months (IQR 4-6) following discharge across 83 hospitals in the United Kingdom. Subjective sleep quality was measured using both the Pittsburgh sleep quality index questionnaire and a numerical rating scale. Only 51% (1,179/2,320) of participants attended an early follow-up at a centre offering the Pittsburgh sleep quality index questionnaire (**Figure 1**). Of these, 61% (714/1,179) completed the Pittsburgh sleep quality index questionnaire and numerical rating scale at the early time point. A further 11% (76/714) were excluded due to suspected nosocomial infection or pre-COVID sleep problems. At the late time point, 39% (248/638) of participants also completed the numerical rating scale (**Figure 1**), a median of 12 months (IQR 11-13) after discharge. Device-based sleep quality was assessed using actigraphy in 38% (829/2,157) of eligible participants a median of 7 months (IQR 5-8) after discharge. Nosocomial infection or suspected pre-existing sleep disorder excluded a further 12% (100/829) of the cohort (**Figure 1**).

Overall, 45% (285/638) of participants completed both subjective and device-based assessments of sleep quality. When both subjective and device-based groups were compared to each other, and to the broader cohort of participants who consented to research, small differences were observed for when their admission occurred during the pandemic, COVID-19 severity, age, BMI, ethnicity, Townsend deprivation index, days since discharge and pre-morbid depression/anxiety (**Supplementary Table 1**).

Participants with poor sleep quality (Pittsburgh sleep quality index) tended to be female, younger, have a higher BMI, have previous depression/anxiety, have previous dyspnoea, have previous poor sleep, and have lower alcohol consumption (**Table 1**). Similar demographic differences were reported for those who experienced a deterioration in sleep quality (numerical rating scale) except these participants tended to have good quality sleep rather than poor quality sleep before COVID-19 (**Supplementary Table 2**). Participants with the greatest sleep irregularity following COVID-19 hospitalisation tended to have a lower Townsend deprivation index, smoke, and have premorbid depression/ anxiety, diabetes, hypertension, and kidney disease (**Supplementary Table 3**).

Prevalence of sleep disturbance following hospitalisation

Subjective assessment of sleep quality revealed that 62% (396/638) of participants reported poor sleep quality (Pittsburgh sleep quality index). Analysis of temporal changes in sleep quality by the numerical rating scale

revealed that sleep quality deteriorated following hospital admission for COVID-19 in 53% (338/638) of participants. At the early time point, sleep quality fell by a median of 3 points and at the late time point sleep quality fell by a median of 2 points (**Figure 2A**) compared to their pre-COVID-19 scores.

The actigraphy traces of this cohort were then compared to two UK Biobank cohorts (non-hospitalised vs recently hospitalised), dependent on whether participants had been admitted into hospital for at least one night (**Supplementary Methods**). Cohorts were matched for age, sex, BMI, and, if applicable, time from hospital discharge (**Supplementary Table 4**). Participants hospitalised for COVID-19, slept on average 69 minutes longer (**Figure 2B**), had a lower (-19%) sleep regularity index (**Figure 2C**) and a lower (3.6 percentage points) sleep efficiency (**Figure 2D**) compared to UK Biobank participants who had not been hospitalised. Compared to UK Biobank participants that had been recently hospitalised, participants hospitalised with COVID-19 slept on average 66 minutes longer (**Figure 2B**), had a lower (-18%) sleep regularity index (**Figure 2C**) and a lower (3.6 percentage points) sleep efficiency (**Figure 2D**).

Actigraphy traces of participants in the UK Biobank who had been recently (2-11 months before actigraphy, n=91, **Supplementary Methods**) hospitalised with pneumonia were also compared to both UK Biobank cohorts defined above. No significant differences were observed for sleep duration or efficiency compared to either the non-hospitalised or recently hospitalised UK Biobank cohorts (**Supplementary Figure 1A, B**). Participants recently hospitalised with pneumonia did have a lower sleep regularity index (-7%) compared to the non-hospitalised UK Biobank cohort (**Supplementary Figure 1C**). The small size of this cohort precluded matching to patients hospitalised for COVID-19.

Relationship of sleep disturbance with dyspnoea

Participants with poor sleep quality (Pittsburgh sleep quality index), scored 3·9 (95%CI 2·8 to 5·1) points higher on the dyspnoea-12 questionnaire compared to those with good sleep quality (**Figure 3A**). Sleep deterioration (numerical rating scale) was also associated with dyspnoea. Those reporting a deterioration in their sleep quality scored 3·0 (95%CI 1·8 to 4·3) points higher on the dyspnoea-12 questionnaire compared to those who did not experience a deterioration (**Figure 3A**). Associations were consistent following adjustments for a minimum set of covariates (age, sex, body mass index (BMI), period into the pandemic, time since discharge, comorbidities, COVID-19 severity, and length of stay).

Device-based measurements of sleep were then assessed; participants with the lowest sleep regularity scored 4·4 (95%CI 2·1 to 6·7) points higher on the dyspnoea-12 score compared to participants with the best sleep regularity (**Figure 3A, Supplementary Table 5**). This association was unaffected following adjustment for a minimum set of covariates. No association was observed between dyspnoea and either sleep efficiency or sleep period duration in both unadjusted and adjusted models (**Figure 3A)**. Therefore, these measures were not investigated further.

Relationship of sleep disturbance with lower lung function (FEV_1 and FVC)

Individuals with poor quality sleep (Pittsburgh sleep quality index) had a lower predicted forced expiratory volume in one second (FEV_1) of -7·1% (95%CI -13·4 to -2·2%, **Supplementary Figure 2A**) and a lower predicted forced vital capacity (FVC) of -9·0% (95%CI -15·3 to -4·3%, **Figure 3B**) compared to those who reported good quality sleep. The associations were consistent following adjustment for a minimum set of covariates for both FEV_1 (**Supplementary Figure 2A, Supplementary Table 5**), and FVC (**Figure 3B, Supplementary Table 5**). Participants who experienced a deterioration in their sleep quality (numerical rating scale) following COVID-19 hospitalisation had a lower percent predicted FEV_1 (-8·8%, 95%CI -14·9% to -3·8%) and a lower percent predicted FVC (-8·3%, 95%CI -14·4% to -3·6%) compared to participants whose sleep quality had remained the same or improved. Associations were consistent following adjustments for the minimal set of covariates (**Figure 3B, Supplementary Figure 2A, Supplementary Table 5**).

Sleep regularity was then assessed. Participants with the lowest sleep regularity had a lower percent predicted FEV_1 (-13·6%; 95%CI -24·7% to -4·8% **Supplementary Figure 1A**) and a lower percent predicted FVC percent predicted (-14·2%; 95%CI -24·2% to -4·3%; **Figure 3B)** compared to participants with the highest sleep regularity. This association was also consistent following adjustment for a minimal set of covariates (**Figure 3B, Supplementary Figure 2A, Supplementary Table 5**).

Participants' diffusion capacity was also evaluated. No associations were observed between these measures (KCO, DLCO) and either of the three-sleep metrics for both unadjusted and adjusted models (**Supplementary Figure 2B, C, Supplementary Table 5**).

Relationship of sleep disturbance with respiratory pressures

Participants with the lowest sleep regularity had a lower MEP (-31·6 cmH_2O, 95%CI -58·5 to -3·3; **Supplementary Figure 3A**) compared to those participants with the highest sleep regularity. No similar association was observed with MIP. The small sample size (n=55) of this cohort precluded adjustment for a minimal set of covariates.

No associations were observed for either MIP or MEP and the subjective measures of sleep quality following COVID-19 hospitalisation (**Supplementary Figure 3A, B, Supplementary Table 5**).

Relationship of sleep disturbance with muscle function

Participants with poor sleep quality (Pittsburgh sleep quality index) had a higher score on the SARC-F questionnaire (1·0, 95%CI 0·7 to 1·3; **Figure 3C**) compared to participants with good quality sleep. Those who reported sleep deterioration (numerical rating scale) following COVID-19 hospitalisation also reported higher scores on the SARC-F questionnaire (0·5, 95%CI 0·2 to 0·9 **Figure 3C**) compared to those participants whose sleep had not deteriorated. Associations were consistent following adjustments for a minimal set of covariates (**Figure 3C, Supplementary Table 5**). This association was also observed for sleep irregularity. Participants with the most irregular sleep had a higher SARC-F (1·3, 95%CI 0·7 to 1·8 **Figure 3C, Supplementary Table 5**) score compared to participants with the best sleep regularity with similar results following adjustment.

Relationship of sleep disturbance with anxiety

Participants with poor sleep quality (Pittsburgh sleep quality index) were more likely to have *mild* (Relative Risk (RR) 2·5, 95%CI 1·6 to 3·9), *moderate* (RR 7·9, 95%CI 3·5 to 17·7) or *severe* (RR 19·9, 95%CI 4·7 to 84·5) anxiety compared to participants who reported good quality sleep (**Figure 4A-C, Supplementary Table 5**).

A similar association was also observed between anxiety and participants who experienced sleep deterioration (numerical rating scale) after COVID-19. Participants who experienced sleep deterioration had a higher relative risk of *mild* (RR 3·0, 95%CI 1·9 to 4·6), *moderate* (RR 2·2, 95%CI 1·3 to 3·9) and *severe* (RR 3·7, 95%CI 1·8 to 7·7) anxiety (**Figure 4A-C, Supplementary Table 5)** compared to participants who did not experience deterioration in their sleep quality. Following adjustment for the minimal sufficient set of covariates the association was attenuated for *severe* anxiety, but the other associations remained unchanged.

Participants with the lowest sleep regularity were more likely to report *moderate* anxiety (RR 3·3, 1·4 to 8·0 95%CI)) compared to participants with the highest sleep regularity (**Figure 4B, Supplementary Table 5**). In contrast, there was no association with *mild* (RR 1·0, 95%CI 0·5 to 2·0) or *severe* (RR 2.5; 95%CI 0.8 to 7.1) anxiety. Adjustment for the minimal sufficient set of covariates attenuated the effect with *moderate* anxiety.

Mediation analysis for the relationship between sleep disturbance and dyspnoea

Anxiety and altered muscle function are recognised causes of dyspnoea. Mediation analysis was performed (**Supplementary Figure 4**) to investigate their contribution to mediating the effect between sleep and dyspnoea. Anxiety following COVID-19 mediated the effect of poor sleep quality on dyspnoea by 38·7% (95%CI 22·7 to 57·2%) and reduced muscle function had a similar mediation effect (36·2% (95%CI 21·2 to 55·7%) **Figure 5A, Supplementary Table 6**).

For the relationship between sleep quality deterioration and dyspnoea, anxiety mediated the effect by 35·6% (95%CI 16·1 to 59·3%) and reduced muscle function mediated the effect by 26·8% (95%CI 3·9 to 52·3%, **Figure 5B**, **Supplementary Table 7**). The relationship between sleep irregularity and dyspnoea was also mediated by both anxiety 17·7% (95%CI 1·4 to 42·3%) and reduced muscle function 40·6% (95%CI 15·1 to 72·3%; **Figure 5C**, **Supplementary Table 8**).

Discussion

Using multi-modal sleep evaluation conducted in a nationwide UK cohort, we have demonstrated that sleep disturbance is prevalent following hospitalisation for COVID-19. This is likely to persist for at least 12 months as subjective sleep quality did not change between early (5 months) and late (12 months) follow-up visits. Multi-modal assessment of sleep disturbance revealed that three factors (sleep quality, degradation of sleep quality compared to baseline, and sleep regularity) were associated with dyspnoea and lower lung function. Mediation analysis identified that reduced muscle function and anxiety, both recognised causes of dyspnoea[3], could partially mediate the association between sleep disturbance and dyspnoea.

Three different complementary methods (Pittsburgh sleep quality index, numerical rating scale and device-based)[21] were used to define sleep disturbance in our study. The Pittsburgh sleep quality index is a well-validated assessment tool[28] that evaluates sleep quality at the time of administration. Additional evaluation of sleep quality using the numerical rating scale confirmed these associations occurred due to a deterioration of sleep quality as a result of COVID-19 hospitalisation, complementing the Pittsburgh sleep quality index evaluation. Device-based metrics were then used to investigate specific aspects of sleep quality revealing clinical associations with sleep irregularity. The gold standard device-based metric is polysomnography. However, this can be technically challenging and samples sleep quality over shorter timeframes. Instead, actigraphy was used which accurately identifies many of the sleep traits captured by polysomnography[21]. Analysis of the actigraphy traces revealed an association between dyspnoea and sleep regularity index. Although this association has not previously been widely reported, sleep regularity index has been associated with morbidity in other studies[29-31].

Device-based sleep metrics following hospitalisation for COVID-19 have predominantly been measured in participants who had been admitted to critical care[22,23]. Our cohort extends these findings, revealing altered sleep-based metrics in all participants who had been hospitalised regardless of critical care admission. Comparison with UK Biobank participants hospitalised for other causes suggested this could be partially due to COVID-19, due to the modest effects seen with hospitalisation for other causes. Both previous device-based studies in the setting of COVID-19 revealed clinical associations between anxiety and subjective but not device-based assessments of sleep quality. These limited clinical effects are an apparent contradiction both with experimental models where sleep disturbance has broad effects[32] and clinical studies outside the context of hospitalisation[33]. In this study, we found broadly consistent clinical associations between device-based and subjective measures of sleep disturbance. These multiple associations suggest sleep disturbance could have broad clinical effects. This is exemplified by

investigating the association between sleep disturbance and dyspnoea where mediation analysis revealed it could only be partially explained by the effect of sleep disturbance on anxiety and muscle function. Therefore, other unidentified clinical or behavioural effects are likely to be involved or, alternatively, sleep disturbance directly affects dyspnoea[34]. Further studies will be needed to define this since the association between sleep disturbance and dyspnoea is likely to be relevant to other respiratory diseases.

Strengths of our study include its size, multi-centre nature, and the use of different complementary assessment measures to evaluate sleep disturbance. Consistent clinical associations were also observed across each evaluation method. This study does have some limitations which should be considered when interpreting the results. Firstly, the hypothesised directionality of effects in the DAG cannot be confirmed in this study. Whilst other studies do support these directions[35,36], bidirectionality of effects has been reported in other settings[16]. Numerical rating scale quantification of sleep deterioration relied upon participant recall and therefore could be affected by recall bias, also known as reporting bias[19]. Selection bias could also affect the results. However, we have minimised this by using bootstrapping combined with cohort matching.

This study provides insight into the prevalence and wider consequences of sleep disturbance following hospitalisation for COVID-19. The associations described in this study between sleep disturbance and reduced muscle function, anxiety and dyspnoea suggest that sleep disturbance could be an important driver of the post-COVID-19 condition. If this is the case, then interventions targeting poor sleep quality[37] might be used to manage multi-morbidity and convalescence following COVID-19 hospitalisation potentially improving patient outcomes.

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Data sharing: The protocol, consent form, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, information about requests for data access, and other relevant study materials are available online (https://www.phosp.org/). UK Biobank information can be released once necessary approvals have been obtained. Other data (e.g., R code/protocol) will be made available on reasonable request.

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Figure Legends:

Figure 1: Consort diagram revealing the number of participants used in the analysis: Participants were recruited from the PHOSP-COVID study who were evaluated at the early time point and gave their consent for research. Sleep disturbance was evaluated using two types of measures (subjective and device-based). PSQI=Pittsburgh Sleep Quality Index. NRS=Numerical Rating Scale. FEV_1=Forced Expiratory Volume in one second. FVC=Forced Vital Capacity. TLCO=gas transfer capacity. KCO=carbon monoxide transfer coefficient. MIP=Maximum Inspiratory Pressure. MEP=Maximum Expiratory Pressure. GAD7=Generalised Anxiety Disorder 7-item scale.

Figure 2: Sleep disturbance after COVID-19 hospitalisation: (**A)** Participants were asked to rate their sleep quality using a numerical rating scale (NRS) either at an early follow-up (median 5 months post COVID-19 admission for both before COVID and at this time point) as well as at late follow-up (median 12 months post COVID-19 admission). The red line indicates median change, the black lines show individual subjects. **= p<0.0001 Dunn's post-hoc test, Benjamini-Hochberg corrected *p*-value. Sleep was also quantified using a device-based approach. This was used to quantify **(B)** sleep period duration, **(C)** sleep regularity index, and **(D)** sleep efficiency. The post-COVID cohort (blue, lower) was matched (age, sex, BMI and, if applicable, time from discharge) to *non-hospitalised* UK Biobank participants (green, upper) or *recently hospitalised* UK Biobank participants (red, middle). Mean±95% confidence intervals are shown underneath the graphs (**=p<0.0001, t-test Benjamini-Hochberg corrected *p*-value).

Figure 3: Clinical associations with sleep disturbance: The associations between changes in sleep parameters Sleep quality (Pittsburgh Sleep Quality Index, black); Sleep deterioration (Numerical Rating Scale, Pink); Sleep regularity (Teal); Sleep efficiency (Purple, dyspnoea only); Sleep Period Duration (Lilac, dyspnoea only) were investigated for various clinical characteristics. **(A)** Shows the association with Dyspnoea-12 score. (**B)** Shows the association with predicted forced vital capacity (FVC) **(C)** Shows the association with SARC-F score. Both unadjusted (circles) or multivariable (squares) effect estimates are shown alongside 95% confidence intervals. In multivariable linear regression, the association was adjusted for age, sex, BMI, comorbidities, COVID-19 severity, length of stay, number of days into the pandemic and number of days since discharge. Light grey background indicates a subjective evaluation of sleep quality, and a dark-grey background indicates a device-based measurement of sleep. BMI=Body Mass Index. FVC=Forced Vital Capacity.

Figure 4: Subjective sleep disturbance is associated with anxiety The associations between changes in sleep parameters Sleep quality (Pittsburgh Sleep Quality Index, black); Sleep deterioration (Numerical Rating Scale, Pink); Sleep regularity (Teal) were investigated with symptoms of anxiety (GAD-7 scale). **(A)** Shows relative risk with *mild* anxiety **(B)** shows relative risk with *moderate* anxiety **(C)** shows relative risk with *severe* anxiety. Both unadjusted (circles) or multivariable (squares) multinomial logistic regression relative risks are shown alongside 95% confidence interval. In multivariable multinomial logistic regression, the association was adjusted for age, sex, BMI, comorbidities, COVID-19 severity, length of stay, number of days into the pandemic and number of days since discharge. Light grey background indicates a subjective evaluation of sleep quality, and a dark-grey background indicates a device-based measurement of sleep. Note the log2 scale on the horizontal axis. BMI=Body Mass Index.

Figure 5: The effect of anxiety or muscle weakness in mediating the effect of sleep on dyspnoea: Mediation models were used to investigate the effects of muscle weakness or anxiety, recognised causes of dyspnoea, in mediating the association between sleep disruption and dyspnoea. Exposures: **(A)** poor sleep quality **(B)** sleep deterioration or **(C)** sleep regularity are shown in orange.

Figure 1:

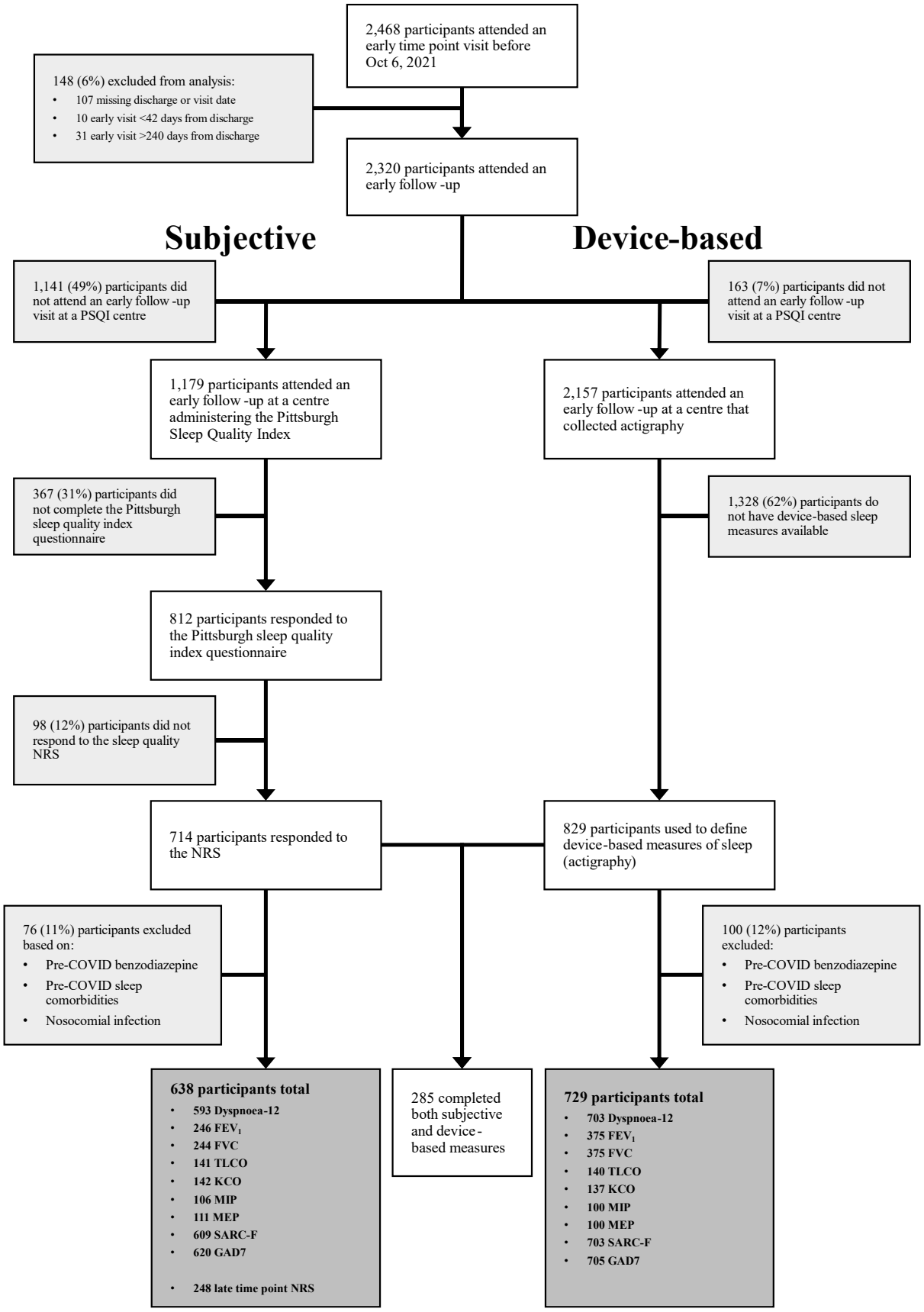
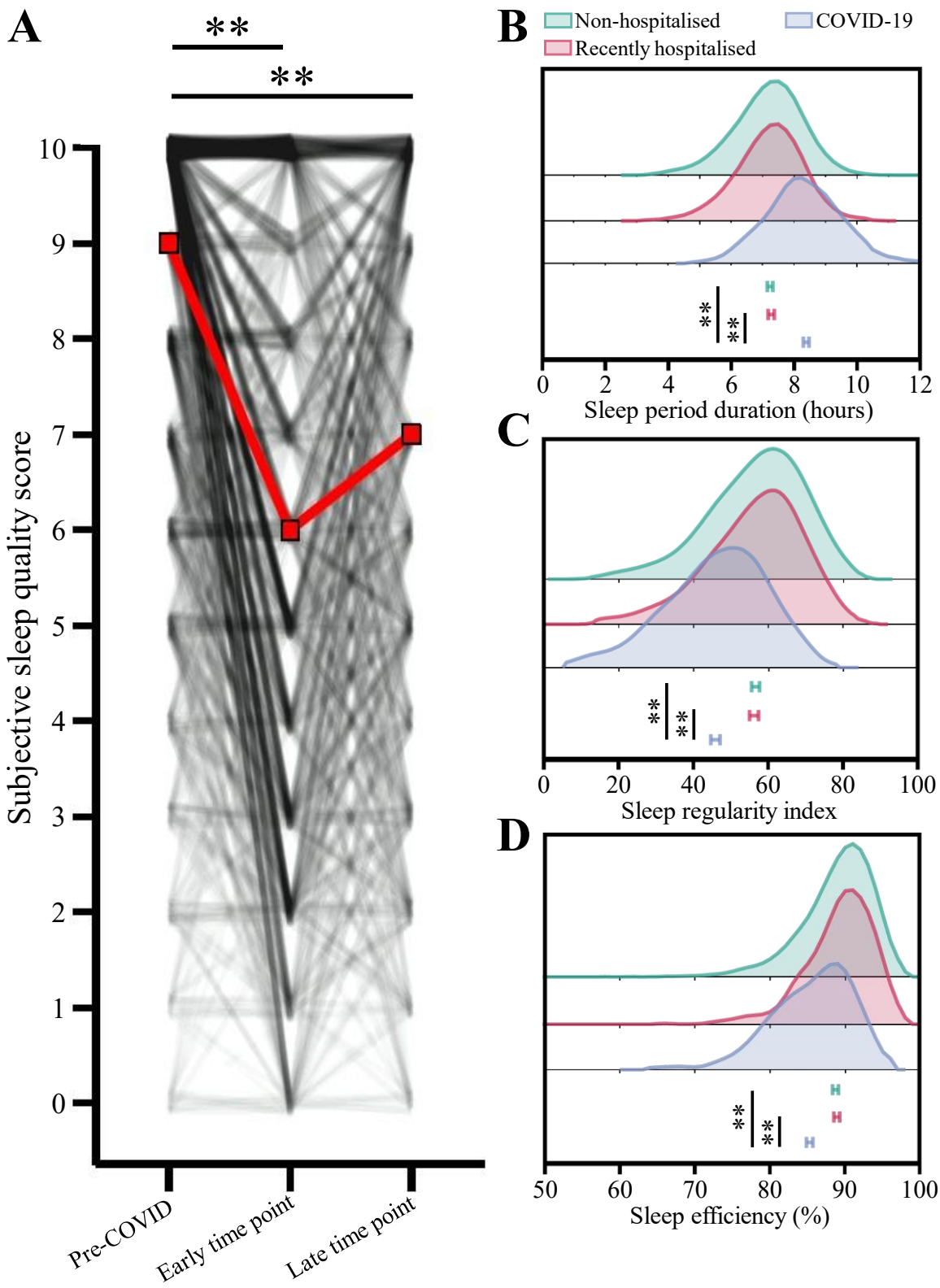
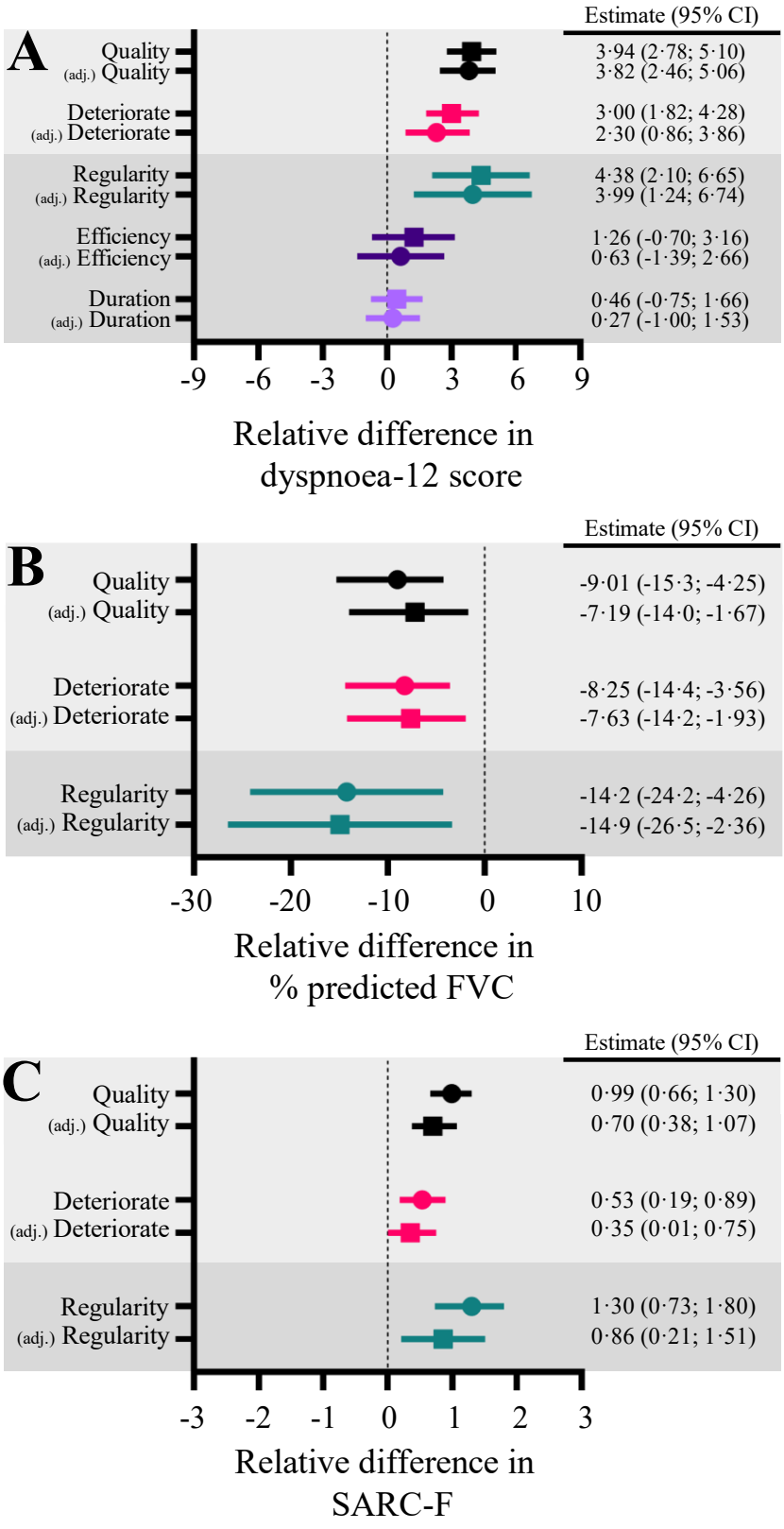

2,468 participants attended an early time point visit before Oct 6, 2021
148 (6%) excluded from analysis:
• 107 missing discharge or visit date
• 10 early visit <42 days from discharge
• 31 early visit >240 days from discharge
2,320 participants attended an early follow -up
Subjective
Device-based
1,141 (49%) participants did not attend an early follow -up visit at a PSQI centre
163 (7%) participants did not attend an early follow -up visit at a PSQI centre
1,179 participants attended an early follow -up at a centre administering the Pittsburgh Sleep Quality Index
2,157 participants attended an early follow -up at a centre that collected actigraphy
367 (31%) participants did not complete the Pittsburgh sleep quality index questionnaire
1,328 (62%) participants do not have device-based sleep measures available
812 participants responded to the Pittsburgh sleep quality index questionnaire
98 (12%) participants did not respond to the sleep quality NRS
714 participants responded to the NRS
829 participants used to define device-based measures of sleep (actigraphy)
76 (11%) participants excluded based on:
• Pre-COVID benzodiazepine
• Pre-COVID sleep comorbidities
• Nosocomial infection
100 (12%) participants excluded:
• Pre-COVID benzodiazepine
• Pre-COVID sleep comorbidities
• Nosocomial infection
638 participants total
• 593 Dyspnoea-12
• 246 FEV1
• 244 FVC
• 141 TLCO
• 142 KCO
• 106 MIP
• 111 MEP
• 609 SARC-F
• 620 GAD7
• 248 late time point NRS
285 completed both subjective and device-based measures
729 participants total
• 703 Dyspnoea-12
• 375 FEV1
• 375 FVC
• 140 TLCO
• 137 KCO
• 100 MIP
• 100 MEP
• 703 SARC-F
• 705 GAD7

Figure 2:

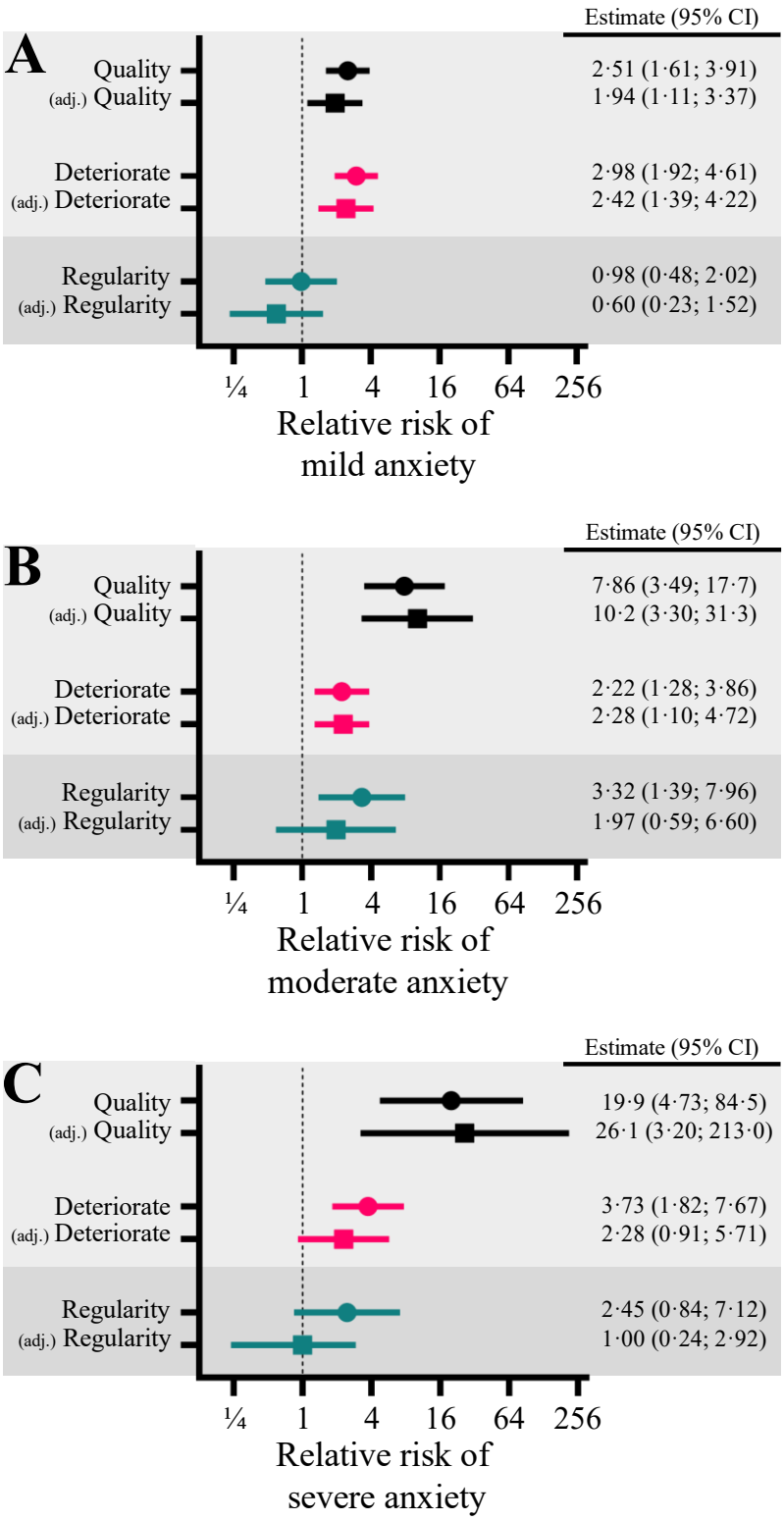

A
**
**
Subjective sleep quality score
10
9
8
7
6
5
4
3
2
1
0
Pre-COVID
Early time point
Late time point
B
Non-hospitalised
COVID-19
Recently hospitalised
H
H
H
0
2
4
6
8
10
12
Sleep period duration (hours)
C
H
H
H
0
20
40
60
80
100
Sleep regularity index
D
H
H
H
50
60
70
80
90
100
Sleep efficiency (%)

496 **Figure 3:**



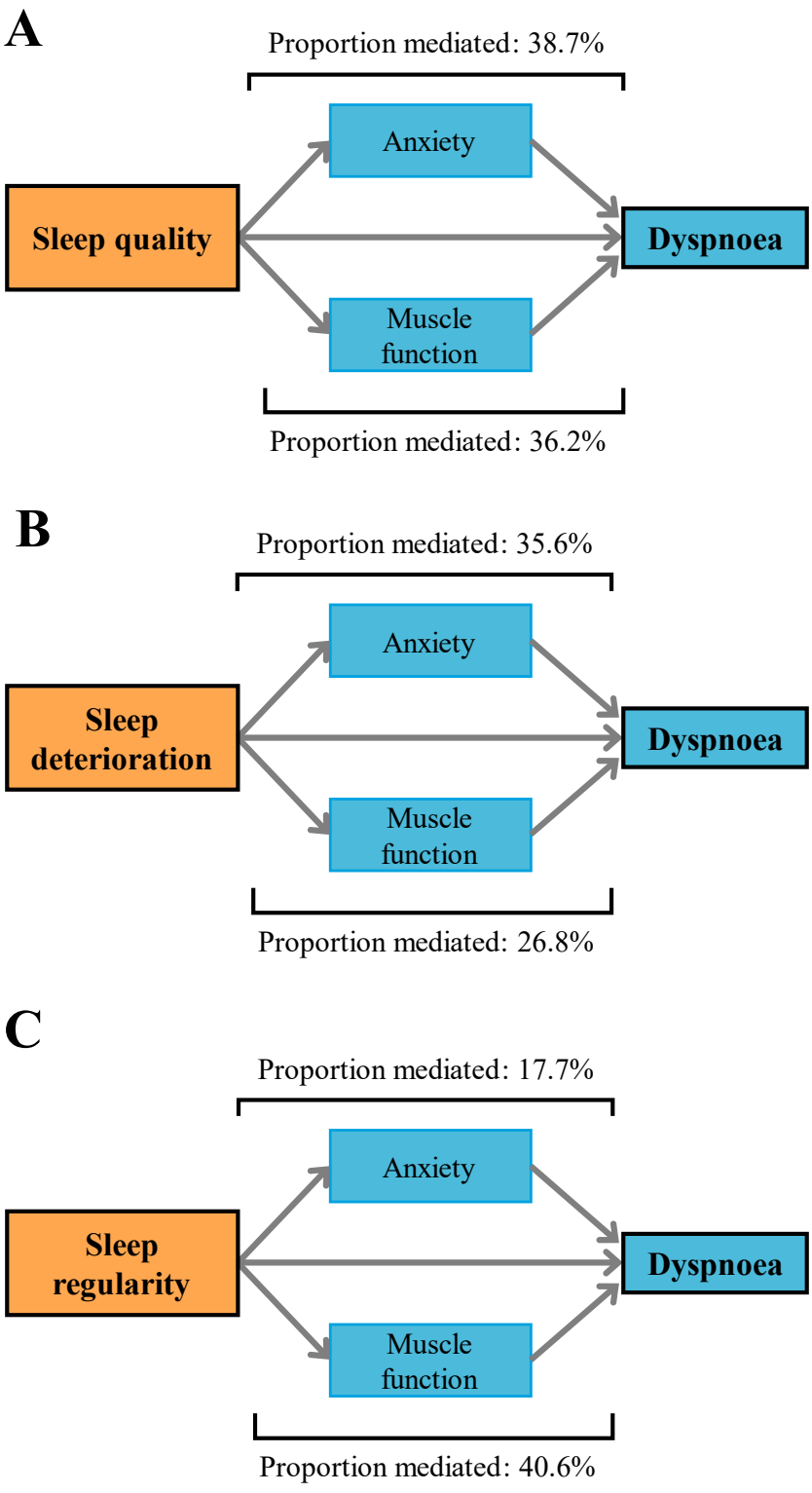
497

498 **Figure 4:**



499

Figure 5:


A
Proportion mediated: 38.7%
Anxiety
Sleep quality
Dyspnoea
Muscle function
Proportion mediated: 36.2%
B
Proportion mediated: 35.6%
Anxiety
Sleep deterioration
Dyspnoea
Muscle function
Proportion mediated: 26.8%
C
Proportion mediated: 17.7%
Anxiety
Sleep regularity
Dyspnoea
Muscle function
Proportion mediated: 40.6%

502

		N	Good sleep quality, N = 242	Poor sleep quality, N = 396
PSQI score		638	3·4 (1·4)	10·1 (3·4)
Age (years)		629	59·6 (13·9)	57·7 (12·4)
Sex (% male)		583	70% (154/221)	54% (196/232)
BMI (kg/m^2)		565	30·6% (6·7)	32·5 (6·6)
Ethnicity		619		
	White		68% (159/234)	73% (280/385)
	South Asian		20% (46/234)	15% (59/385)
	Black		6·4% (15/234)	6·2% (24/385)
	Mixed		3·0% (7/234)	2·3% (9/385)
	Other		3·0% (7/234)	3·4% (13/385)
Townsend IMD quintile		629		
	1 - most deprived		18% (44/239)	21% (83/390)
	2		19% (45/239)	19% (73/390)
	3		15% (37/239)	18% (71/390)
	4		22% (52/239)	22% (84/390)
	5 - least deprived		26% (61/239)	20% (79/390)
Smoking Status		631		
	Never		61% (146/239)	58% (22/392)
	Ex-smoker		38% (91/239)	41% (160/392)
	Current smoker		0·8% (2/239)	1·3% (5/392)
Average units of alcohol (per week)		605	5·8 (7·5)	4·3 (7·4)
Days admission was into pandemic		638	170 (119)	176 (118)
Days since discharge		638	161 (38)	162 (41)
Comorbidities				
Hypertension		576	33% (73/221)	40% (142/355)
Diabetes		571	19% (42/220)	23% (81/351)
Liver disease		571	3·2% (7/220)	2·3% (8/351)
Asthma		574	14% (31/220)	16% (57/354)
COPD		573	4·1% (9/220)	4·2% (15/353)
Chronic kidney disease		572	2·7% (6/221)	4·3% (15/351)
High cholesterol		572	24% (54/221)	22% (78/351)
Depression or anxiety		572	5·4% (12/221)	15% (51/351)
COVID-19 severity				
WHO clinical progression		626		

	WHO – class 3-4		19% (46/239)	22% (84/387)
	WHO – class 5		46% (110/239)	42% (163/387)
	WHO – class 6		17% (41/239)	16% (63/387)
	WHO – class 7-9		18% (42/239)	20% (77/387)
Length of stay (days)		635	13·5 (16·5)	14·2 (21·0)
ITU admission (% admitted)		631	32% (77/241)	32% (125/390)
Pre-COVID-19 symptoms				
Subjective sleep quality (10=best)		638	9·1 (1·8)	7·5 (2·7)
Subjective dyspnoea (0=best)		638	0·8 (1·8)	1·3 (2·1)
Post-COVID-19 symptoms				
Subjective sleep quality (10=best)		638	8·1 (2·5)	5·2 (2·8)
Subjective dyspnoea (0=best)		638	3·3 (2·8)	4·5 (2·7)
PHQ9 level		622		
	None		80% (189/236)	36% (140/386)
	Mild		15% (35/236)	25% (98/386)
	Moderate		3·8% (9/236)	20% (79/386)
	Moderately Severe		0·4% (1/236)	9·6% (37/386)
	Severe		0·8% (2/236)	8·3% (32/386)
GAD7 level		620		
	Minimal		79% (187/236)	49% (190/384)
	Mild		17% (40/236)	24% (93/384)
	Moderate		3·0% (7/236)	16% (60/384)
	Severe		0·8% (2/236)	11% (41/384)
Subjective sleep period duration (hours)		603	7·4 (1·7)	6·1 (2·0)

Table 1 Cohort demographics for Pittsburgh Sleep Quality Index participants: Participants were categorised by the Pittsburg Sleep Quality Index. Continuous values are presented as mean (SD) and were compared using a Wilcoxon rank-sum test. Categorical data are presented as % (n/N) and were compared using a Pearson Chi-squared test. PSQI=Pittsburgh sleep quality index. BMI=body mass index. IMD=Index of multiple deprivation. COPD=Chronic obstructive pulmonary disease. WHO=World health organisation. PHQ9=Patient Health Questionnaire. GAD7=Generalised Anxiety Disorder 7-item scale.

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