Pandemic-disordered sleep: longer illness and more fatigue but little SARS-CoV-2 effect

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Shareable abstract (@ERSpublications)
Sleep disturbance was extremely common in the pandemic, even after 2 years. Prior infection with SARS-CoV-2 does not increase risk of sleep disturbance but does increase risk of fatigue even a year later and after apparent recovery. https://bit.ly/3ZAGmQ2

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Abstract

Background The COVID-19 pandemic disturbed sleep globally in both infected and uninfected individuals. Prolonged symptoms (particularly fatigue) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (post-COVID 2019 syndrome (PCS)) remain a health issue. Whether there is a relationship between PCS and sleep disturbance is largely unknown, with most studies lacking uninfected controls. We assessed sleep behaviours in a large UK cohort, analysing sleep disruption, fatigue, SARS-CoV-2 infection and symptom duration.

Methods UK adults previously recruited from the King's College London ZOE COVID Symptom Study to the COVID Symptom Study Biobank, with prospective symptom logging and SARS-CoV-2 testing, were invited to complete online validated questionnaires for sleep (Pittsburgh Sleep Quality Index, Sleep Condition Indicator, the STOP-Bang Questionnaire and Epworth Sleepiness Scale), fatigue (Chalder Fatigue Scale) and mental health (Generalised Anxiety Disorder 2 scale and Patient Health Questionnaire 2). Data were analysed considering SARS-CoV-2 infection, symptom duration and co-morbidities, including mental health.

Results Questionnaires were completed by 3833 of 8355 participants (2089 infected, 1721 uninfected, 23 unknown). Individuals with longer (*versus* shorter) symptom duration had poorer sleep scores for multiple questionnaires, but SARS-CoV-2 infection had no independent effect on sleep. However, previously infected (*versus* uninfected) individuals had greater fatigue, over a year since infection. Longer symptom duration, poorer sleep scores and greater fatigue were also associated with higher contemporaneous levels of anxiety and depression; however, an independent effect of prior SARS-CoV-2 infection on fatigue remained after adjustment. Higher body mass index, greater age and prior co-morbidities also independently worsened sleep scores.

Conclusions Sleep disturbance contributes to prolonged symptom reporting, irrespective of SARS-CoV-2 infection. Proven sleep interventions may help individuals with post-pandemic fatigue, including PCS.

Introduction

Prolonged symptoms after acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection became evident early in the pandemic [1], with subsequent delineation of ongoing symptomatic COVID-19 (OSC) and post-COVID-19 syndrome (PCS) (long COVID) [2]. Prevalence estimates vary internationally, with many studies focused on hospitalised individuals [3] and early studies of both hospitalised and community-managed cases suggested an overall PCS prevalence of 6.2% [4]. The most recent UK data found 2.9% of the population self-report symptoms for ⩾4 weeks after likely COVID-19, of whom 92% had symptoms for ⩾12 weeks [5]. However, potential biases here include self-reported symptoms, unconfirmed infection and no uninfected population data to control for physical and psychosocial effects of the pandemic *per se*, which affect many observational PCS studies similarly [6]. In contrast, a community study of nearly 2 million participants (a quarter of whom (486 149) had confirmed SARS-CoV-2 infection) reported extended symptom duration in 5.4% of infected *versus* 4.3% in uninfected individuals [7].

Fatigue and unrefreshing sleep are prominent symptoms in post-acute infection syndromes, including PCS [8–10]. However, pandemic-related increases in fatigue, sleep disturbance and mood disorders were common in both infected and uninfected individuals (reviewed in [11–14]). Fatigue occurs commonly with sleep disorders [15, 16]. In addition, sleep abnormalities, sleep disturbance and daytime fatigue frequently co-occur with mood disorders including anxiety and depression [17, 18]. Although many early pandemic studies assessed sleep in infected individuals, few used validated sleep questionnaires or compared infected *versus* uninfected individuals [19]. Thus, the extent to which sleep difficulties, from the pandemic *per se* or from direct SARS-CoV-2 effects, contribute to OSC/PCS [10], the contribution of comorbidities including prior sleep and mood disorders upon symptom presentation [20, 21], and whether SARS-CoV-2 causes long-term sleep disturbance remain challenging questions. Improved sleep health can improve symptoms in many illnesses (*e.g.*, depression [22], chronic pain [23] and fibromyalgia [24]) and proven sleep interventions might also help symptoms for individuals with OSC/PSC.

Here we deployed multiple validated questionnaires to assess sleep, fatigue, sleepiness, sleep apnoea, insomnia, anxiety and depression in a large volunteer cohort of UK adults, including individuals with and without SARS-CoV-2 infection, with varying symptom duration. Our aims included the following:

1) describe sleep quality during the pandemic,
2) determine whether sleep disturbance was associated with SARS-CoV-2 infection,
3) assess the relationship between sleep disturbance and fatigue in infected and uninfected individuals, and
4) assess the contribution of prior co-morbidities, including a mental health diagnosis, on sleep symptoms and fatigue.

Methods

Participants

The COVID Symptom Study Biobank (CSSB) (Yorkshire and Humber NHS Research Ethics Committee Approval Ref: 20/YH/0298) was drawn from volunteers participating in the King's College London (KCL)-COVID Symptom Study (KCL-CSS)/ZOE study (KCL Ethics Committee Approval LRS-19/20-18210) (supplementary table S2). Both cohorts have been described previously and see supplementary methods for details [25, 26]. The current study was approved by the CSSB Governance Committee (CSSB ID 0070).

Personalised invitations were emailed to CSSB participants from 2 weeks after the Autumn equinox (22 September 2020), with study information and links for online participation including consent. Validated questionnaires were used to assess sleep and fatigue (supplementary table S3), including common sleep disorders, subjective sleep quality, daytime sleepiness and fatigue, likelihood of obstructive sleep apnoea (OSA), and for comorbid mood disturbance and anxiety. The questionnaires included the following: the Pittsburgh Sleep Quality Index (PSQI) [27], the Sleep Condition Indicator (SCI) [28], the STOP-Bang [29] Questionnaire, a restless leg syndrome question [30], the Epworth Sleepiness Scale [31], the Chalder Fatigue Scale (CFS) [32, 33] and shortened versions of the Generalised Anxiety Disorder scale (GAD-2) [34] and the Patient Health Questionnaire (PHQ-2) [35]. Written approval to use each questionnaire was obtained from relevant researchers/institutions (private correspondence). Questionnaires were administered electronically *via* secure link, using REDCap [36]. Two reminder emails were sent and data collection closed after 3 weeks.

Statistical analyses

As previously described [26], CSSB participant groups were considered by infection status (including after CSSB recruitment) and symptom duration. Infection status was initially determined at time of recruitment to CSSB (prior to the UK SARS-CoV-2 vaccination campaign). All individuals had previously self-reported

SARS-CoV-2 testing (either lateral flow antigen testing (LFAT) or PCR, per UK population access) through the ZOE app and all individuals were tested in-house for antispike and antinucleocapsid antibodies with infection status refined according to results. Later UK SARS-CoV-2 infection waves meant infection status and symptom duration might alter; thus, group data were recalculated according to any subsequent LFAT/PCR test results (without further in-house antibody testing), per individual logging through the app. Symptom duration relative to time of testing was as previously described [26].

Final groupings comprised the following:

1) confirmed positive SARS-CoV-2 infection:
   a) asymptomatic (Pos_Asx)
   b) symptoms <4 weeks (Pos_0–4w)
   c) symptoms 4–12 weeks, fulfilling OSC criteria (Pos_4–12w)
   d) symptoms ⩾12 weeks, fulfilling PCS criteria (Pos⩾12w)
2) confirmed negative SARS-CoV-2 infection:
   a) asymptomatic (Neg_Asx)
   b) symptoms <4 weeks (Neg_0–4w)
   c) symptoms 4–12 weeks (Neg_4–12w)
   d) symptoms ⩾12 weeks (Neg_12w)

Permissible logging frequency gaps were limited to 7 days; a sensitivity analysis with case definition per relaxed logging frequency (to 14 days) was performed.

Analyses were performed using IBM SPSS Statistics Version 27, GraphPad Prism Version 9 and Stata Version 17. Data are presented as mean±SD for continuous variables and frequencies and percentages for categorical data. Between-group differences were compared using chi-square tests, independent sample *t*-tests or one-way ANOVA, as appropriate. False discovery rate adjustment using the Benjamini–Hochberg procedure was applied for multiple comparisons. As described in the results, inverse probability weighting (IPW) was used to adjust for participation bias.

For univariate analyses, we compared:

1) symptom duration groups within infection status groups, using asymptomatic groups as reference (*i.e.*, Neg_Asx compared with Neg_0–4w, Neg_4–12w and Neg⩾12w, and similarly for positive individuals)
2) infection status groups within symptom duration groups, using negative individuals as reference category (Neg_0–4w *versus* Pos_0–4w, *etc.*).

Multiple regression was performed to identify significant independent predictors of outcome variables and contribution of SARS-COV-2 infection and symptom duration, with two models, as follows:

1) Model 1: covariates age, sex, body mass index (BMI) and presence of medical comorbidities
2) Model 2: as above, with additional covariate GAD2 and PHQ2 scores.

We considered quantitative analytical approaches; however, a lack of linearity between symptom duration and outcome variables precluded linear regression. We also considered approaches for missing data (*e.g.*, imputation); this was not pursued due to implications for IPW (discussed below).

Results

Cohort

Of 8355 CSSB participants, 3833 (45.87%) consented to participate, 3053 (79.7%) fully and 713 (18.6%) partially completed questionnaires, and 67 (1.7%) did not complete any data. 23 participants did not have SARS-CoV-2 results and 437 had insufficient logging for categorisation.

Supplemental figure S1 shows symptom profiles at time of illness, by infection status and symptom duration. Time between symptom onset and questionnaire administration (assessable in 2325 symptomatic individuals) was over a year (median 410 (IQR 153) days). By virtue of staggered recruitment (supplementary table S2), this differed across groups overall ($p<0.0001$) and within infection status groups with reverse relationships (in negative individuals: shorter time between symptom onset and questionnaires in individuals with short (*versus* long) symptom duration (Neg0–4w: 335 (180) days) *versus* Neg⩾12w: 389 (111) days, $p=0.0005$); in positive individuals: longer time between symptom onset and questionnaires in individuals with short (*versus* long) symptom duration (Pos_0–4w: 473 (137) days *versus* Pos⩾12w: 398 (101) days), $p<0.0001$)).

Table 1 presents demographic information for the cohort overall and by SARS-CoV-2 infection status (data by individual duration and infection groups shown in supplementary table S4). Participants differed by age, sex, index of multiple deprivation, comorbidities, vaccination status, smoking history and prior mental health diagnosis, between positive and negative individuals, and between illness duration categories (table 1, supplementary table S4, supplementary figures S2a–e). Further, systematic biases were evident in study participation (supplementary figure S3). Thus, IPW was used to adjust for participation bias for subsequent analyses (thus precluding capacity to impute missing data robustly). Post-IPW, differences remained between groups (supplementary table S5), informing subsequent multivariate analyses, noting the predictive performance of the model generating the weighting was relatively low (area under the curve – receiver operating characteristic 0.63).

Univariate analyses

Sleep scores are shown in table 2 for the cohort overall and by SARS-CoV-2 infection status (data by individual duration and infection groups shown in supplementary table S6), showing clinically relevant sleep disturbance (PSQI scores) across the cohort.

When analysed within infection groups(figure 1a), incrementally more adverse scores were seen with each incremental symptom duration category for multiple sleep questionnaires (PSQI, SCI and ESS), in both positive and negative groups. Incrementally more adverse scores were also seen for STOP-Bang in negative individuals.

TABLE 1 Participant demographic data

Characteristic		Cohort	SARS-CoV-2 test result (n=3810)[#]		
		All participants (n=3833)	Negative (n=1721)	Positive (n=2089)	p-value[¶]
Mean±SD age (years)		56.1±10.8	56.3±10.8	56.0±10.9	0.275
Sex, n (%)	Male	761 (19.9)	325 (18.9)	431 (20.6)	0.185
	Female	3067 (80.0)	1393 (80.9)	1657 (79.3)	
	Missing	5 (0.1)	3 (0.2)	1 (0)	
Mean±SD BMI (kg·m^{-2})		27.1±6.0	27.0±6.3	27.1±5.9	0.839
IMD quintile, n (%)	1	239 (6.2)	103 (6)	136 (6.5)	0.889
	2	481 (12.5)	209 (12.1)	270 (12.9)	
	3	764 (19.9)	345 (20)	414 (19.8)	
	4	1053 (27.5)	479 (27.8)	568 (27.2)	
	5	1293 (33.7)	585 (34)	698 (33.4)	
Missing	3 (0.1)	0 (0)	3 (0.1)		
Ethnicity, n (%)	White	3684 (96.1)	1658 (96.3)	2003 (95.9)	0.463
	Other	140 (3.7)	59 (3.4)	81 (3.9)	
	Missing	9 (0.2)	4 (0.2)	5 (0.2)	
Smoker status, n (%)	Never	1297 (33.8)	532 (30.9)	755 (36.1)	0.040
	Ex-smoker	457 (11.9)	185 (10.7)	270 (12.9)	
	Current	63 (1.6)	36 (2.1)	27 (1.3)	
	Missing	2016 (52.6)	968 (56.2)	1037 (49.6)	
Prior chronic medical comorbidity, n (%)	No	2957 (77.1)	1325 (77)	1611 (77.1)	0.925
	Yes	876 (22.9)	396 (23)	478 (22.9)	
Prior mental health diagnosis, n (%)	No	2328 (60.7)	1070 (62.2)	1241 (59.4)	0.034
	Yes	824 (21.5)	416 (24.2)	406 (19.4)	
	Missing	681 (17.8)	235 (13.7)	442 (21.2)	
Presence of baseline symptoms, n (%)[+]	No	2268 (59.2)	1230 (71.5)	1038 (49.7)	0.437
	Yes	223 (5.8)	127 (7.4)	96 (4.6)	
	Missing	1342 (35)	364 (21.2)	955 (45.7)	
Number of SARS-CoV-2 vaccinations, n (%)	1–2	370 (9.7)	120 (7)	249 (11.9)	<0.001
	3 or more	3320 (86.6)	1558 (90.5)	1745 (83.5)	
	Missing	143 (3.7)	43 (2.5)	95 (4.5)	

Baseline symptoms: symptoms recorded prior to date of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing. [#]: COVID-19 test result not available for 23 participants. [¶]: By independent samples *t*-test for continuous variables or Chi-Square test for categorical variable. [+]: Excludes asymptomatic cases. BMI: body mass index. IMD: index of multiple deprivation.

TABLE 2 Sleep questionnaire scores for the cohort overall, in individuals with and without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and by symptom duration group

		SARS-CoV-2 test result		
	All participants	Negative	Positive	p-value[#]
Mean±SD PSQI score	6.9±3.7	7.0±3.7	6.8±3.7	0.323
Mean±SD CFS score	15.0±5.3	14.5±4.9	15.5±5.6	<0.001
Mean±SD SCI score	19.5±8.0	19.3±8.1	19.6±8.0	0.257
Mean±SD STOP-Bang score	2.1±1.5	2.0±1.4	2.1±1.5	0.623
Mean±SD ESS score	6.3±4.2	6.2±4.0	6.5±4.4	0.061
Single question for RLS answer, n (%)				0.404
No	1871 (68.8)	864 (69.6)	1007 (68.1)	
Yes	848 (31.2)	377 (30.4)	471 (31.9)	
Mean±SD PHQ2 score	1.2±1.5	1.2±1.5	1.1±1.6	0.008
Mean±SD GAD2 score	1.3±1.6	1.3±1.6	1.3±1.6	0.314

[#]: By independent sample *t*-test for continuous variables or Chi-square test for categorical variables. Symptom duration categories are as described in the methods. Results are adjusted for inverse probability weighting. Clinical context is as follows: Pittsburgh Sleep Quality Index (PSQI) score ⩾5 (out of 21) is consistent with significant sleep disturbance; Sleep Condition Indicator (SCI) score ⩽16 (out of 32) represents significant sleep disturbance and possible insomnia disorder; Epworth Sleepiness Scale (ESS) score ⩾10 (out of 24) indicates excess sleepiness; Stop-BANG score ⩾3 is clinically significant and suggestive of moderate to high obstructive sleep apnoea risk; Patient Health Questionnaire (PHQ2) score ⩾3 (out of 6) is consistent with depression; and Generalised Anxiety Disorder 2 (GAD-2) score ⩾3 (out of 6) is consistent with generalised anxiety. For the Chalder Fatigue Scale (CFS) using the Likert scoring system (out of 33), scores ⩾20 are generally considered to indicate clinically significant fatigue with ⩾29 consistent with severe fatigue and possible chronic fatigue syndrome. Restless legs syndrome (RLS) prevalence is typically 5–10% of the population.

Considered within symptom duration groups (figure 2a), sleep scores did not differ between positive and negative individuals. Indeed, negative individuals with a short (<4 weeks) symptom duration had more adverse SCI scores than their positive counterparts.

Considering fatigue within infection (figure 1b) and duration (figure 2b) groups, positive (*versus* negative) individuals had more adverse CFS scores overall (table 2: 15.5 (5.6) *versus* 14.5 (4.9), p<0.001), particularly individuals with longer symptom duration, corresponding to OSC and PCS (figure 2b). Scores ⩾29 are considered to indicate severe fatigue and likely chronic fatigue syndrome [33]; more positive (*versus* negative) individuals had severe fatigue (3.6% *versus* 1.9%, p=0.008).

We considered circularity here (*viz*. if fatigue were the main symptom driving illness duration, then individuals with longer duration would be more likely to have fatigue). However, most individuals had reported full recovery months earlier. We considered prospectively logged fatigue prior to illness presentation [21], where data were available (supplementary table S7). Fatigue was common (60–98%), with prevalence differing significantly by subsequent illness groupings (highest in those with subsequent long (⩾12 week) symptom duration, in both positive and negative individuals). However, baseline fatigue prevalence did not differ between positive and negative individuals with subsequent long illness duration (98% *versus* 85%, p=0.36).

Considering symptoms of depression, anhedonia and anxiety (table 2, supplementary table S6) within infection (figure 1c) and duration (figure 2c) groups: PHQ2 scores were slightly worse (*i.e.*, higher) in negative (*versus* positive) individuals overall (1.2 (1.5) *versus* 1.1 (1.6), p=0.008), most evidently in negative (*versus* positive) individuals with short (0–4 weeks) symptom duration. GAD2 scores did not differ by infection status overall (1.3 (1.6) *versus* 1.3 (1.6); p=0.314); but were again slightly worse (*i.e.*, higher) in negative (*versus* positive) individuals with short symptom duration.

Multivariate analyses

Regardless of infection, longer symptom duration was associated with poorer sleep quality (PSQI) (table 3), more severe symptoms of insomnia (SCI) (supplementary table S8) and worsening fatigue (CFS) (table 4).

Considering sleep quality, with covariates of age, sex, BMI and presence of comorbidities (model 1): incrementally more adverse (*i.e.*, higher) PSQI scores were observed for each symptom duration increment, a

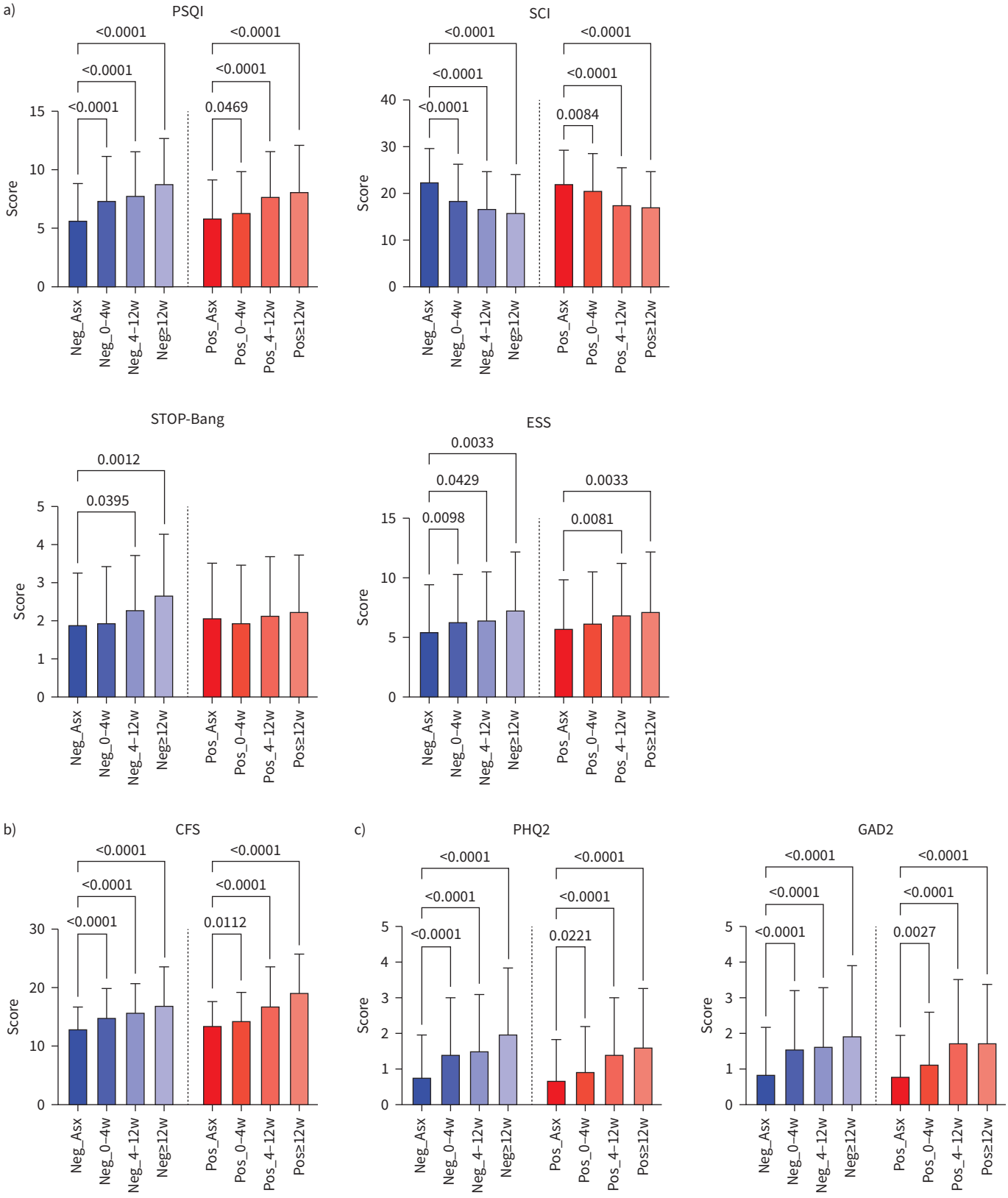

FIGURE 1 Validated questionnaire scores for sleep in individuals with differing symptom duration, considered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection status. a) Pittsburgh Sleep Quality Index (PSQI), Sleep Condition Indicator (SCI), STOP-Bang and Epworth Sleepiness Scale (ESS) scores by symptom duration. b) Chalder Fatigue Scale (CFS) score by symptom duration. c) Patient Health Questionnaire 2 (PHQ2) and Generalised Anxiety Disorder 2 (GAD2) scores by symptom duration. Red: test-positive individuals. Blue: test-negative individuals.

Symptom duration categories (per methods) are: Neg_Asx: SARS-CoV-2 negative and asymptomatic; Neg_0–4: SARS-CoV-2 negative and symptom duration 0–4 weeks; Neg_4–12: SARS-CoV-2 negative and symptom duration 4–12 weeks; Neg⩾12w: SARS-CoV-2 negative and symptom duration 12 weeks or longer; Pos_Asx: SARS-CoV-2 positive and asymptomatic; Pos_0–4: SARS-CoV-2 positive and symptom duration 0–4 weeks; Pos_4–12w: SARS-CoV-2 positive and symptom duration 4–12 weeks; Pos⩾12w: SARS-CoV-2 positive and symptom duration 12 weeks or longer. Statistically significant differences are shown with p-values.

finding that remained significant after including contemporaneous mental health scores (model 2). Similarly, SCI scores were serially more adverse (*i.e.*, lower) at each symptom duration increment. This was not evident for daytime sleepiness (ESS) or OSA risk (STOP-Bang) (supplementary table S6).

However, SARS-CoV-2 infection did not have an independent effect on sleep quality. Indeed, positive individuals with short (0–4 weeks) symptom duration had slightly *lower* (*i.e.*, better) PSQI scores in model 1 ($p<0.001$) and model 2 ($p=0.047$). There was also no association between SARS-CoV-2 test result and severity of insomnia (SCI), daytime sleepiness (ESS) or OSA risk (STOP-Bang).

In contrast, an independent effect of SARS-CoV-2 infection upon fatigue was evident ($p=0.024$) (model 1), the significance of which increased when including contemporaneous mental health scores ($p=0.002$) (model 2). Testing for interaction showed direction of this effect varied according to symptom duration. In model 1, positive status was associated with *less* fatigue in individuals with short (0–4 weeks) illness but *more* fatigue in individuals with long (⩾12 weeks) duration (both compared with the asymptomatic group). In model 2, positive status was associated with more fatigue only in individuals with long symptom duration. Missing data (>25%) precluded incorporation of baseline fatigue reporting into the model (supplementary table S5).

Mental health distress

PHQ2 and GAD2 scores were independently associated with sleep scores for each questionnaire (more adverse scores with poorer sleep), with magnitude of effect highest for insomnia severity (SCI) sleep quality (PSQI), and daytime sleepiness (ESS) (table 3 and supplementary table S6). Additionally, both PHQ2 and GAD2 were independently associated with fatigue (CFS) (more adverse scores with greater fatigue) (table 4).

Other covariates

Higher BMI and the presence of comorbidities independently contributed to poorer sleep quality (PSQI) in both models (table 3). The effect of sex differed between models. Female sex was associated with *poorer* sleep quality in model 1 but *better* sleep quality in model 2. Age had a small residual effect (higher age associated with poorer sleep scores) only in model 2.

For other sleep scores, residual effects are shown in supplementary table S8 and were broadly similar. Female sex was independently associated with poorer PSQI, SCI and ESS scores but lower OSA risk, noting that male sex contributes to STOP-Bang scoring.

In terms of CFS score (table 4), residual effects of higher BMI, presence of comorbidities and female sex (all contributing to more fatigue) were evident in both models. A small protective effect of younger age was evident in model 1.

Sensitivity analyses

Relaxing symptom logging frequency tolerance from 7 to 14 days made little difference to the results (see supplementary results**,** section 3.9).

Discussion

Nearly 2 years into the pandemic, sleep disturbance was common in our large volunteer cohort, with sleep quality scores above a clinically significant threshold for all groups. However, SARS-CoV-2 infection *per se* was not associated with sleep disturbance, whether sleep quality, insomnia or daytime sleepiness, even in individuals with long symptom duration. Individuals with long (*versus* short) symptom duration had poorer sleep scores, irrespective of prior infection; but absolute clinical differences were small.

However, to our knowledge this is the first prospective study demonstrating a long-term association of SARS-CoV-2 infection with fatigue, controlling for anxiety, depression and population lockdown. Greater fatigue was evident despite considerable time since infection and reported recovery. Nonetheless, the

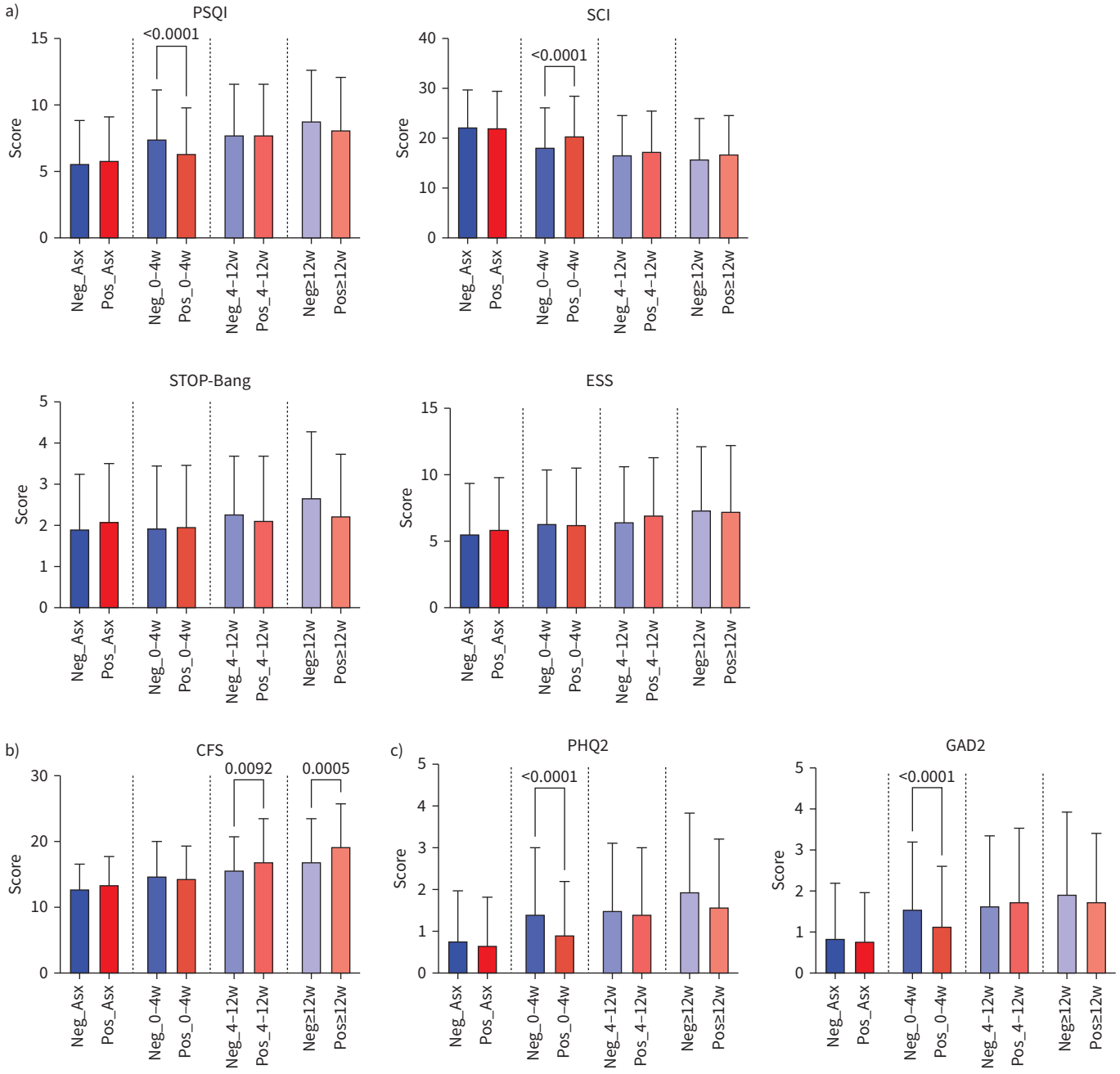

FIGURE 2 Validated questionnaire scores for sleep in individuals with and without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, by symptom duration. a) Pittsburgh Sleep Quality Index (PSQI), Sleep Condition Indicator (SCI), STOP-Bang and Epworth Sleepiness Scale (ESS) scores by COVID status. b) Chalder Fatigue Scale (CFS) score by COVID status. c) Patient Health Questionnaire 2 (PHQ2) and Generalised Anxiety Disorder 2 (GAD2) scores by COVID status. Red: test-positive individuals. Blue: test-negative individuals. Symptom duration categories (per methods) are: Neg_Asx: SARS-CoV-2 negative and asymptomatic; Neg_0–4: SARS-CoV-2 negative and symptom duration 0–4 weeks; Neg_4–12: SARS-CoV-2 negative and symptom duration 4–12 weeks; Neg⩾12w: SARS-CoV-2 negative and symptom duration 12 weeks or longer; Pos_Asx: SARS-CoV-2 positive and asymptomatic; Pos_0–4: SARS-CoV-2 positive and symptom duration 0–4 weeks; Pos_4–12w: SARS-CoV-2 positive and symptom duration 4–12 weeks; Pos⩾12w: SARS-CoV-2 positive and symptom duration 12 weeks or longer. Significant differences are shown with p-values.

absolute difference in fatigue in individuals with *versus* without SARS-CoV-2 infection was small. Poorer sleep and greater fatigue were also independently associated with poorer mental health scores, prior comorbidities and higher BMI.

TABLE 3 Multiple regression analysis of factors affecting sleep quality assessed using the Pittsburgh Sleep Quality Index

	Model 1			Model 2		
	b (95% CI)	SE	p-value	b (95% CI)	SE	p-value
Intercept (constant)	1.66 (0.62–2.7)	0.53	0.002	0.25 (−0.7–1.2)	0.48	0.6
Symptom duration			<0.001			<0.001
Asymptomatic (reference)	NA	NA	NA	NA	NA	NA
0–4 weeks	1.62 (1.23–2.02)	0.20	<0.001	0.89 (0.53–1.26)	0.19	<0.001
4–12 weeks	1.95 (1.38–2.52)	0.29	<0.001	1.08 (0.54–1.61)	0.27	<0.001
⩾12 weeks	2.98 (2.18–3.79)	0.41	<0.001	1.72 (0.94–2.49)	0.40	<0.001
SARS-CoV-2 test result			0.042			0.485
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	0.22 (−0.3–0.72)	0.26	0.409	0.14 (−0.34–0.62)	0.24	0.565
Symptom duration×SARS-CoV-2 test result interaction			0.002			0.154
Asymptomatic (reference)						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive (reference)	NA	NA	NA	NA	NA	NA
0–4 weeks						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	−1.15 (−1.8–−0.5)	0.33	<0.001	−0.61 (−1.21–−0.01)	0.31	0.047
4–12 weeks						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	−0.14 (−0.97–0.68)	0.42	0.73	0.01 (−0.77–0.79)	0.40	0.98
⩾12 weeks						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	−0.88 (−1.9–0.14)	0.52	0.091	−0.39 (−1.35–0.57)	0.49	0.425
PHQ2 score				0.62 (0.5–0.74)	0.06	<0.001
GAD2 score				0.55 (0.44–0.66)	0.06	<0.001
Age	0.01 (−0.01–0.02)	0.01	0.45	0.03 (0.02–0.04)	0.01	<0.001
Sex			<0.001			<0.001
Male (reference)	NA	NA	NA	NA	NA	NA
Female	1.04 (0.72–1.37)	0.17	<0.001	0.88 (0.58–1.17)	0.15	<0.001
BMI	0.11 (0.08–0.13)	0.01	<0.001	0.07 (0.05–0.09)	0.01	<0.001
Comorbidities			<0.001			<0.001
No (reference)	NA	NA	NA	NA	NA	NA
Yes	0.64 (0.31–0.96)	0.17	<0.001	0.54 (0.23–0.84)	0.15	<0.001

Model 1: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test outcome effect on symptom duration and sleep quality, considering age, sex, body mass index (BMI) and medical comorbidities. Model 2: as per model 1, with additional prior mental health diagnosis. GAD2: Generalised Anxiety Disorder-2; NA: not applicable/available; PHQ2: Patient Health Questionnaire.

Early pandemic studies showed poorer sleep globally, compared to pre-pandemic data. In mid-2020, a large international bespoke survey (25 484 individuals from 14 countries, of whom 3% had prior COVID-19) reported globally increased sleep-related problems across multiple parameters, including poorer sleep quality, difficulties with sleep onset and sleep maintenance, fatigue, and excessive sleepiness [14]. Univariate analysis suggested SARS-CoV-2 infection was associated with worsening of multiple sleep components and greater fatigue, though this moderated in the fully adjusted model; pertinently, a very similar picture was seen for confinement and financial difficulties, and analyses did not adjust for depression or anxiety [14]. The same group reported in late 2021 (15 813 volunteers from 16 countries, including now 19.8% with prior COVID-19). Although fatigue, insomnia and excessive daytime sleepiness were common PSC symptoms, particularly in individuals with prior moderate to severe COVID-19, little difference was evident (*versus* controls) when considering mild or asymptomatic SARS-CoV-2 infection. Again, mental health was not included in multivariate analysis [37].

A systematic review and meta-analysis of 44 early pandemic cross-sectional studies that used validated sleep questionnaires (54 231 individuals, 13 countries) showed an overall prevalence of sleep problems of 35.7% in the general population and 74.8% in individuals with COVID-19, although this latter figure was based on only three studies (1884 individuals) [12]. The authors later published a larger systematic review of 250 observational studies (493 475 participants, 49 countries) showing that sleep disturbance increased from 2020 to 2021, with global prevalence now 40.5%. Sub-analyses again showed higher prevalence in individuals with prior (*versus* no) COVID-19 (52.49%), although lower than previously reported - but also

TABLE 4 Multiple regression analysis of factors affecting sleep quality assessed using the Chalder Fatigue Scale

	Model 1			Model 2		
	b (95% CI)	SE	p-value	b (95% CI)	SE	p-value
Intercept (constant)	10.71 (9.14–12.28)	0.8	<0.001	8.85 (7.53–10.17)	0.68	<0.001
Symptom duration			<0.001			<0.001
Asymptomatic (reference)	NA	NA	NA	NA	NA	NA
0–4 weeks	1.7 (1.15–2.24)	0.28	<0.001	0.57 (0.12–1.02)	0.23	0.014
4–12 weeks	2.52 (1.72–3.32)	0.41	<0.001	1.16 (0.44–1.87)	0.37	0.002
⩾12 weeks	3.69 (2.32–5.07)	0.70	<0.001	1.51 (0.27–2.75)	0.63	0.017
SARS-CoV-2 test result			<0.001			<0.001
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	0.74 (0.1–1.38)	0.33	0.024	0.81 (0.29–1.32)	0.26	0.002
Symptom duration×SARS-CoV-2 test result interaction			<0.001			0.004
Asymptomatic (reference)						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive (reference)	NA	NA	NA	NA	NA	NA
0–4 weeks						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	−0.99 (−1.86–−0.12)	0.44	0.025	−0.23 (−0.94–0.48)	0.36	0.532
4–12 weeks						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	0.62 (−0.59–1.82)	0.61	0.317	0.67 (−0.37–1.71)	0.53	0.206
⩾12 weeks						
Negative (reference)	NA	NA	NA	NA	NA	NA
Positive	1.72 (0.07–3.38)	0.84	0.041	2.32 (0.86–3.77)	0.74	0.002
PHQ2 score				1.43 (1.25–1.6)	0.09	<0.001
GAD2 score				0.55 (0.39–0.71)	0.08	<0.001
Age	−0.04 (−0.06–−0.02)	0.01	<0.001	0 (−0.02–0.01)	0.01	0.592
Sex			<0.001			<0.001
Male (reference)	NA	NA	NA	NA	NA	NA
Female	0.99 (0.54–1.43)	0.23	<0.001	0.79 (0.42–1.16)	0.19	<0.001
BMI	0.14 (0.1–0.17)	0.02	<0.001	0.08 (0.05–0.1)	0.01	<0.001
Comorbidities			<0.001			0.003
No (reference)	NA	NA	NA	NA	NA	NA
Yes	0.91 (0.4–1.41)	0.26	<0.001	0.64 (0.22–1.07)	0.22	0.003

Model 1: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test outcome effect on symptom duration and sleep quality, considering age, sex, body mass index (BMI) and medical comorbidities. Model 2: as per model 1, with additional prior mental health diagnosis. GAD2: Generalised Anxiety Disorder-2; NA: not applicable/available; PHQ2: Patient Health Questionnaire.

an effect of lockdown (42.49% during lockdown *versus* 37.97% no lockdown) [13]. In both meta-analyses, high heterogeneity (I^2 99% and 98%) and country-specific results limited interpretation and generalisability.

Multiple other studies have assessed sleep, in the general community (*e.g.*, reviewed in [38]) or in PCS cohorts (*e.g.*, reviewed in [12]), but not usually both. Thus, prevalence figures for sleep disturbance in PCS are often "floating numerators". Further, few pandemic studies have assessed mental health alongside sleep measures. A large 2020 UK primary care study (11 923 105 individuals) illustrates the difficulties here [19]. This study found increased *de novo* psychiatric morbidity in 232 780 individuals (3%) with a positive SARS-CoV-2 test, with six-fold (hazard ratio 5.98) increase in fatigue and three-fold (3.16) increase in sleep problems, and a positive result in individuals with prior mental health diagnoses doubled risk of subsequent fatigue (2.24) and increased rates of depression and anxiety (1.3–1.4) in individuals with prior sleep problems. However, very similar rates of *de novo* psychiatric morbidity, fatigue and sleep problems were seen in negatively testing individuals (*versus* the untested population) and in individuals with influenza.

Post-viral fatigue is the commonest PSC symptom [1, 39] and pre-infection fatigue increases the odds of post-infection fatigue [21]. Whilst lacking baseline data on all participants, we did not observe differences in baseline fatigue between positive and negative individuals with long symptom duration (supplementary table S5). However, we did observe an independent effect of SARS-CoV-2 on fatigue, including after adjustment for mental distress scores.

Prior mental health diagnoses also influence post-infection symptoms [21]. A recent large study (1 180 948 individuals with SARS-CoV-2 infection; 17 990 (1.52%) diagnosed with PCS) showed pre-existing psychiatric disorders increased PSC risk, particularly pre-existing anxiety (relative risk 1.64), mood disorders (1.65) and depression (1.69) [40]. Whilst our data also show that anxiety and depression contribute to fatigue, an independent effect of SARS-CoV-2 was still evident. Our data emphasise the importance of considering individuals holistically and managing mental distress where appropriate. However, whether managing anxiety and depression can improve PCS *per se* is unknown. To date, no specific SARS-CoV-2-management approaches in PCS have proven effective.

Our cohort had higher prevalence of mental health diagnoses in negative (*versus* positive) symptomatic individuals, also observed previously [19]. Importantly, here we did not observe participation bias by mental health diagnosis (supplementary table S3). The cause of symptoms in our test-negative individuals is unknown. Anxious individuals might have lower thresholds for symptom-reporting and, consequently, higher testing rates with proportionally lower likelihood of positive results; this, however, is speculative.

Other independent factors associated with poorer sleep and greater fatigue included prior comorbidities and higher BMI. The effect of sex was more complex and varied according to inclusion of mental health measures. Nonetheless, with the exception of STOP-Bang (noting the obvious effect on scores from male sex inclusion as a criterion), female sex was associated with more adverse sleep across multiple models. Female sex has been extensively associated with multiple parameters of poorer sleep quality and insomnia across the lifespan (recently reviewed [41]) and with post-acute infection syndromes [8]. Our cohort was predominantly female, across all groups (table 1, supplementary table S4), and sex was included as a covariate in all analyses.

Our findings highlight the prevalence of sleep disturbance in individuals with prolonged symptoms. Established sleep interventions, which improve symptoms in other diseases, might benefit individuals with PCS and fatigue, as well as uninfected individuals with pandemic-related fatigue. Indeed, our data caution against diagnosing PCS in individuals with ongoing symptoms (particularly fatigue) without evidence of prior SARS-CoV-2 infection; rather, it illustrates the commonality of fatigue and high prevalence of sleep disturbance during the pandemic, irrespective of infection, and, where sleep disturbances are present, these should be managed appropriately.

Strengths of our study include large sample size, prospective contemporaneous symptom tracking, granular detail regarding SARS-CoV-2 status and use of previously validated sleep questionnaires at an individual level, administered at the Autumn equinox (22 September 2020) to ensure uniform participant light exposure. Our negative individuals served as a control for the impact of lockdown and social isolation on symptoms and sleep behaviours. By using individual-level data from participants across the range of symptoms and symptom duration, we avoided bias from differential healthcare interaction arising from those symptoms *per se*, as can occur with case note-level datasets. Recruitment following three COVID-19 waves enabled contributions from numerous participants who had experienced PCS. Unlike earlier studies, this allowed us to assess the long-lasting effects of SARS-CoV-2 on sleep quality and fatigue. Mental health screening questionnaires also allowed the assessment for an independent effect of mental distress upon symptom duration, sleep quality, and fatigue.

However, our disproportionately female (76%) and Caucasian (96%) cohort was a sample of convenience and unrepresentative of the UK population [1]. Our data may not be generalisable internationally given differing government responses (including lockdown) to COVID-19 and comorbid physical and mental illness prevalences. Indeed, differing regional SARS-CoV-2 transmission rates, population control measures and media coverage all affected the prevalence of sleep disturbance [13]. Although peri-testing symptoms were tracked prospectively, sleep surveys were administered much later, preventing comment on any acute SARS-CoV-2-related sleep disturbance. Pre-test symptom reporting was missing for some individuals and missing data could not be imputed without affecting IPW robustness. We acknowledge that the CFS is only one of several tools to measure fatigue [42] and has potential for a “ceiling” effect. However, this scale was chosen due to its simplicity to administer and complete, its prior validation within a UK cohort and its capacity to assess fatigue symptom severity reliably; further, our cohort’s scores were, in general, well short of the maximal score. In addition, our cohort’s high prevalence of sleep disorders could represent high pre-pandemic sleep disturbance. Our cross-sectional study design means we cannot differentiate as to whether prior illness (COVID-19 or otherwise) caused poorer sleep or whether poorer sleep caused prolonged symptoms including fatigue.

Conclusion

Prolonged symptoms, regardless of SARS-CoV-2 infection, are associated with poorer sleep quality and increasing fatigue. SARS-CoV-2 infection independently increases fatigue, even months after initial infection, but does not worsen sleep, even in individuals with OSC/PCS. Neither baseline mental health diagnosis nor concomitant mental health distress fully explain poor sleep quality and increased fatigue in individuals with long symptom duration, although they do contribute independently. Sleep health interventions may benefit individuals with prolonged symptoms; and assessing sleep in individuals with PCS may meaningfully contribute to management of their ongoing symptomatology. Lastly, rehabilitative services should be equipped to manage a heavy population burden of fatigue in the post-pandemic era.

Provenance: Submitted article, peer reviewed.

Ethics statement: The COVID Symptom Study Biobank (CSSB) (Yorkshire and Humber NHS Research Ethics Committee approval ref. 20/YH/0298) was drawn from volunteers participating in King's College London COVID Symptom Study/ZOE study (Kings College London Ethics Committee approval LRS-19/20-18210) (table S2). Both cohorts have been described previously [25, 26]; please see supplementary methods for details. The current study was approved by the CSSB Governance Committee (CSSB ID 0070).

Author contributions: The CSSB was conceived with funding obtained by C.J. Steves and E.L. Duncan. Recruitment strategy for CSSB was by C.J. Steves and E.L. Duncan. This particular study was conceived by S. Mukherjee and E.L. Duncan. Data collection was organised by J.R.B. Brown and V. Bowyer. Data management was by V. Bowyer, J.R.B. Brown and N.J. Cheetham. Analysis was by S. Proctor, N.J. Cheetham, C.J. Steves and B. Toson. The first draft was by S. Proctor and E.L. Duncan. All authors critically reviewed the manuscript.

Conflict of interest: C.J. Steves has consulted for ZOE Ltd. All other authors declare no conflict of interest.

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