



Blood biomarker levels by total sleep duration: cross-sectional analyses in UK Biobank

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ABSTRACT

Background: Short or long sleep duration has been associated with some major chronic diseases, but whether disease-related blood biomarkers vary according to habitual sleep duration is unclear. This cross-sectional study aimed to assess blood biomarker levels in relation to total sleep duration.

Methods: The analysis includes 459,796 white British adults aged 40–69 during 2006–2010 in UK Biobank. At recruitment, blood samples and self-reported information on total sleep duration were collected from participants. A panel of blood biomarkers were measured. Using linear regression, we estimated geometric mean concentrations of blood biomarkers and mean ratio of ApoB/ApoA1 by sleep duration adjusted for sex, age at data collection, time of blood collection, and lifestyle covariates.

Results: Percentage differences in the concentrations of most biomarkers by sleep duration were modest. The largest differences were for C-reactive protein (CRP, an inflammatory biomarker) and gamma glutamyltransferase (GGT, a liver function biomarker), and the differences were markedly attenuated after multivariable-adjustment. The multivariable-adjusted geometric means of CRP and of GGT were 14% and 14% higher in <6 h vs 7–8 h of sleep; and 22% and 12% higher in >9 h vs 7–8 h of sleep, respectively.

Conclusion: In white British adults, most blood biomarker levels varied only modestly with sleep duration and the remaining associations may be due to residual confounding.

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1. Introduction

The associations of sleep duration with risks of cardiovascular diseases [1], diabetes [2], and mortality [3] have been investigated in some meta-analyses, in which short sleep duration and long sleep duration have been suggested to be associated with higher disease or mortality risks [1–3]. It remains unclear if habitual sleep duration influences long-term blood concentrations of disease-related biomarkers, and thus alters the risks of chronic diseases via such pathways. Previous observational studies assessing blood biomarkers in relation to sleep duration generally have had small sample sizes [4].

The UK Biobank has measurements on a wide range of blood biomarkers related to cardiovascular, bone and joint, cancer, diabetes, renal, and liver diseases. Using this data source, the current study explores whether these disease related blood biomarkers vary according to total sleep duration, independent of the personal

characteristics that are known to vary by sleep duration and are also related to the blood biomarkers.

2. Materials and methods

2.1. Study

UK Biobank is a prospective cohort of ~500,000 UK individuals aged 40–69 recruited from 22 assessment centres during 2006–2010, with a response rate of 5.5% [5]. The Study aims to assess the associations of genetic and lifestyle factors with disease risks in individuals in middle and old age [5]. Details of the study design and method can be found online at <https://www.ukbiobank.ac.uk> and in a previously published article [6]. The protocol and operational procedures were approved by the North West Multicentre Research Ethics Committee, the National Information Governance Board for Health and Social Care (in England and Wales), and the Community

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Health Index Advisory Group (in Scotland). All participants provided an electronically signed consent.

At the assessment visit, participants were asked to complete a touchscreen questionnaire which asked questions about socio-demographic (including ethnicity), lifestyles (including sleep characteristics), medical history, and other health and personal information. For total sleep duration, participants were asked “About how many hours sleep do you get in every 24 h? (please include naps)”, and possible answers were 1–23 h. Total sleep duration was classified into six groups as <5, 5, 6, 7–8 (reference), 9, and >9 h.

Participants also reported their current use of medications at recruitment to the nurses. Physical measurements, including height, weight, and blood pressure, were taken by trained staff. About 45 ml non-fasting blood samples were taken from participants by either a phlebotomist or a nurse, using a set of six separate barcoded vacutainers with specific preservatives. Descriptions of sample processing can be found in the protocol published by the UK Biobank [6]. In brief, a unique barcode on each set of vacutainers was scanned into the IT system, which also initiated a timer for measuring clotting time. Following different clotting time allowances, blood in the plasma and serum separator tubes were centrifuged separately. All tubes were then maintained at 4 °C, with the exception of the acid citrate dextrose tubes that were kept at 18 °C, before being packed and dispatched to the central laboratory for further processing [6].

A panel of blood biomarkers were assayed centrally in UK Biobank using ten immunoassay analysers and four clinical chemistry analysers. All blood biomarkers were assayed using serum samples, except for glycated haemoglobin (HbA1c) that was measured using packed red blood cell samples. For details of the assay performance please refer to the report elsewhere [7]. In these analyses, rheumatoid factor and oestradiol were not included because of the large proportion of missing data for these biomarkers in the cohort (91% and 80% of the values of the respective biomarkers were below the reportable ranges), and lipoprotein(a) was not included as its serum concentration is largely genetically determined [8]. We selected 27 biomarkers out of the list. For women only, levels of testosterone for those values deemed too low were replaced by 0.2625 nmol/L (which is three quarters of the minimal reportable value of 0.35 nmol/L). For both men and women, concentrations of free testosterone was calculated following the law of mass action, with albumin and sex hormone binding globulin (SHBG) levels taken from the participants' measures [9]. A ratio of apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1) was derived as an additional biomarker.

In the current analyses, the biomarkers were grouped as follows: cardiovascular (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, ApoA1, ApoB, C-reactive protein [CRP], ratio of ApoB/ApoA1), bone and joint (vitamin D, alkaline phosphatase, calcium), cancer (SHBG, testosterone, calculated free testosterone, insulin-like growth factor I [IGF-1]), diabetes (glycated haemoglobin [HbA1c], glucose), renal (cystatin C, creatinine, total protein, urea, phosphate, urate), and liver (albumin, direct bilirubin, total bilirubin, gamma glutamyltransferase [GGT], alanine aminotransferase, aspartate aminotransferase) biomarkers.

2.2. Exclusion criteria

The current analysis restricted the sample to the self-identified white population as a way to minimise confounding by ethnicity, as there is some evidence suggesting that the distributions of serum biomarker levels, such as vitamin D and HbA1c, differed across ethnic groups [10–12]. Participants were included for the analyses

if they had data on at least one analysed biomarker. The total analysed sample included 459,796 individuals (249,426 [54%] women and 210,370 [46%] men).

2.3. Statistical analyses

Summary statistics of baseline characteristics by total sleep duration were presented in Table 1. We applied a uniform approach to analysing all biomarkers: all biomarkers except for the ApoB/ApoA1 ratio were logarithmically transformed to approximate a normal distribution. Geometric means of biomarkers or mean for the ratio with 95% confidence intervals of each biomarker across sleep duration groups were estimated from the following adjusted linear regression models: (i) the minimally-adjusted model was adjusted for sex (men, women) and age at recruitment (<50, 50–54, 55–59, 60–64, 65+ years) (note: in the case of vitamin D, the minimally-adjusted model was also adjusted for month of blood collection [12 months, unknown]), (ii) the multivariable-adjusted model was additionally adjusted for physical activity (<10, 10–<20, 20–<30, 30–<60, 60+ metabolic equivalent-hours per week, unknown), alcohol intake (<1, 1–8, 9–16, 17+ grams per day, non-drinkers, unknown), smoking status (never, past, current, unknown), and time of blood collection (10 a.m. or earlier, 11 a.m., 12 noon, 1 p.m., 2 p.m., 3 p.m., 4 p.m., 5 p.m., 6 p.m. or later, unknown), and (iii) the main multivariable-adjusted model was further adjusted for body mass index (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, 35.0+ kg/m², unknown). The percentages of missing values was 21% in physical activity and were <1% in other covariates. In the main analyses, we analysed total/calculated free testosterone in relation to sleep duration separately by sex, while all other biomarkers were analysed in relation to sleep duration in men and women combined. The F test for sleep duration categories was conducted to test for difference in the distributions of biomarker concentrations between sleep duration groups.

Generally, analyses with a large sample size are more powered to detect smaller associations than smaller sized studies. While we prioritised the discussion of the results where the geometric/arithmetic means of blood biomarkers of any sleep duration groups, compared to 7–8 h, differed by >10% in the current analysis, we acknowledged that the biological relevance of the difference in the biomarker concentrations to disease risks varies individually. Hence, percentage differences in the geometric/arithmetic mean biomarker levels in each sleep duration group relative to 7–8 h of sleep were presented to assist readers' interpretation of the findings (Supplementary Tables 1a and 1b).

For sensitivity analyses, we restricted the analysis to participants who did not report current or regular use of any of the following medications: sedatives or hypnotics, psychotropic medications [13,14], diabetes medications, lipid-lowering medications, blood pressure lowering medications, oral contraceptives or menopausal hormones (the former four groups of medications were derived from data field 20003, while the latter three groups of medications were derived from data fields 6153 (women) and 6177 (men)). We further excluded participants who reported their health as poor or fair. Moreover, we tested for interaction between sleep duration and sex in the main multivariable-adjusted model, and reported the results stratified by sex (Supplementary Table 1b).

As blood pressure are known to affect some biomarkers, we additionally adjusted for systolic blood pressure (<125, 125–144, 145–164, 165+ mm Hg, unknown) and diastolic blood pressure (<75, 75–84, 85–94, 95+ mm Hg, unknown). As another sensitivity analysis, we additionally adjusted for time since last meals (0–1, 2, 3, 4, 5, 6–7, 8+ hours, unknown). As the observed association between sleep duration and serum CRP concentrations may be driven

Table 1
Personal characteristics by total sleep duration in 459,796 white British adults in UK Biobank.

Personal characteristics, % unless otherwise specified	Total sleep duration (hours)					
	<5	5	6	7–8 (ref.)	9	>9
No. of individuals	4734	19,212	86,602	313,905	27,151	8192
Demographic factors						
Women	56%	56%	52%	54%	57%	55%
Age at recruitment (years), mean (SD)	56.9 (7.7)	57.2 (7.7)	56.6 (7.8)	56.6 (8.1)	58.9 (7.9)	58.4 (8.0)
Lifestyle and anthropometric factors						
Body mass index (kg/m ²), mean (SD)	29.1 (6.0)	28.4 (5.3)	27.8 (5.0)	27.1 (4.6)	27.8 (4.9)	29.1 (5.7)
Physical activity (MET-hours), median (IQR)	30 (10, 76)	31 (12, 71)	30 (13, 64)	30 (14, 60)	30 (13, 62)	22 (7, 50)
Current smokers	20%	14%	12%	9%	11%	16%
Alcohol intake, 17+ g/day	28%	31%	34%	34%	34%	31%
Self-rated health and medications						
Self-rated health, poor or fair	59%	42%	29%	21%	30%	54%
Current or regular use of selected medications ^b	54%	44%	36%	34%	47%	64%
Sleep medications	7%	3%	1%	1%	1%	3%
Psychotropic medications	21%	11%	7%	7%	14%	31%
Blood pressuring lowering medications	28%	25%	21%	19%	27%	33%
Oral contraceptives ^a	1%	2%	2%	3%	2%	2%
Menopausal hormone therapy ^a	9%	8%	7%	7%	8%	9%
Diabetes medications	7%	5%	3%	3%	5%	9%
Lipid-lowering medications	24%	20%	17%	15%	23%	29%

^a Among women.

^b Any of the medications listed in this table.

by daytime napping [15], we separately run the analysis in participants who reported never/rarely napping. All of these results were consistent with the main findings (result not shown).

All statistical analyses were conducted in Stata version 16.0 (StataCorp, TX). A two-sided p-value <0.001 was considered significant (ie based on Bonferroni correction of 0.05/31 [27 biomarker analysis (including ApoB/ApoA1 ratio) for the whole sample plus four separate total and free testosterone analyses for men and for women]).

3. Results

3.1. Participant characteristics by sleep duration

Baseline characteristics of the participants according to their reported total sleep duration are presented in Table 1. Individuals who reported >9 h tended to be older. Individuals who reported shorter or longer sleep duration were more likely to have a higher body mass index and be current smokers, but they were less likely to report a high alcohol consumption. Individuals who reported >9 h of sleep were the least physically active compared to other participants. Individuals with <5 and with >9 h sleep were twice as likely to rate their health as being poor or fair as those with 7–8 h of sleep. Both participants with short and with long sleep were more likely to report use of lipid-lowering and diabetes medications and regular use of blood pressure lowering medications than those with average sleep duration. While short sleepers were more likely to report use of sleeping pills, long sleepers were more likely to report use of psychotropic medications.

3.2. Differences in biomarker levels by sleep duration

Geometric means of serum biomarkers and arithmetic means for the ApoB/ApoA1 ratio by sleep duration are presented in Supplementary Table 1 (results from all models). When minimally adjusted for age and sex, all biomarkers were statistically

associated ($P < 0.001$) with total sleep duration (Supplementary Table 1a). There were over 10% differences in geometric means in circulating triglycerides, CRP, vitamin D, alkaline phosphatase, and GGT among participants with the shortest/longest sleep duration versus 7–8 h of sleep (Table 2).

In the multivariable-adjusted models, concentrations/ratios of most biomarkers varied modestly by sleep duration. Comparing the minimally-adjusted models, the F statistics for the associations of CRP and of GGT were reduced from 555 to 120 (79% decrease in the F statistic) and from 422 to 178 (58% decrease in the F statistic), after adjusting for all covariates including body mass index (Table 2), respectively. The main multivariable-adjusted geometric means of CRP and of GGT were 14% and 14% higher in <6 h vs 7–8 h of sleep; and 22% and 12% higher in >9 h vs 7–8 h of sleep, respectively (Table 2). As a comparison among individuals with a body mass index of <22.5 vs 35+ kg/m², the adjusted geometric means of GGT were 23.8 (95% CI, 23.6–23.9) vs 39.3 (39.0–39.5) U/L (66% higher); the adjusted geometric means of CRP were 0.69 (0.68–0.70) vs 3.56 (3.52–3.60) mg/L (4-fold higher).

For the association of sleep duration with circulating GGT, restriction to individuals without use of pre-specified medications and to those who rated their health as being good or excellent produced similar findings, albeit with smaller relative differences in geometric means for women across sleep duration groups. For the sensitivity analyses of circulating CRP, only participants who reported longer, but not shorter, sleep, had a higher CRP concentration compared to those with 7–8 h of sleep (Supplementary Table 1).

Further, in the stratified analyses by sex, the shape of the associations was mostly consistent with the main analyses conducted in the whole sample. For vitamin D, men with the shortest and the longest sleep duration had on average 11% and 7% lower geometric mean concentrations than those with 7–8 h of sleep; whereas women with the shortest and the longest sleep duration had 5% and 1% lower geometric mean concentrations (Supplementary Table 1b).

Table 2

Geometric means (95% confidence intervals) of selected blood biomarkers across sleep duration categories.

	N	Minimally-adjusted				Multivariable-adjusted				Multivariable-adjusted + Body mass index (Main multivariable-adjusted model)			
		Geometric mean (95% CI) of biomarker	% difference (ref. 7-8h)	F statistic	P-value	Geometric mean (95% CI) of biomarker	% difference (ref. 7-8h)	F statistic	P-value	Geometric mean (95% CI) of biomarker	% difference (ref. 7-8h)	F statistic	P-value
Triglycerides, mmol/L													
<5 h sleep	4501	1.69 (1.67–1.72)	13			1.64 (1.62–1.66)	9			1.58 (1.56–1.60)	4		
5 h sleep	18,334	1.60 (1.59–1.61)	6			1.58 (1.57–1.59)	5			1.54 (1.53–1.55)	1		
6 h sleep	82,902	1.53 (1.53–1.54)	2			1.53 (1.52–1.53)	1			1.51 (1.51–1.52)	0		
7–8 h sleep	300,295	1.50 (1.50–1.51)	Ref.			1.51 (1.51–1.51)	Ref.			1.52 (1.52–1.52)	Ref.		
9 h sleep	25,950	1.61 (1.60–1.62)	7			1.60 (1.59–1.61)	6			1.58 (1.58–1.59)	4		
>9 h sleep	7786	1.76 (1.74–1.78)	17	322	<0.001	1.69 (1.67–1.71)	12	188	<0.001	1.63 (1.61–1.65)	7	81	<0.001
C-reactive protein, mg/L													
<5 h sleep	4492	1.92 (1.86–1.98)	44			1.75 (1.70–1.81)	31			1.56 (1.52–1.61)	14		
5 h sleep	18,300	1.62 (1.59–1.64)	22			1.55 (1.53–1.57)	15			1.44 (1.42–1.46)	5		
6 h sleep	82,808	1.44 (1.43–1.45)	8			1.42 (1.41–1.43)	6			1.38 (1.37–1.38)	0		
7–8 h sleep	299,913	1.33 (1.32–1.33)	Ref.			1.34 (1.34–1.35)	Ref.			1.37 (1.37–1.38)	Ref.		
9 h sleep	25,900	1.56 (1.54–1.58)	17			1.54 (1.52–1.56)	15			1.49 (1.48–1.51)	9		
>9 h sleep	7760	2.04 (2.00–2.09)	54	555	<0.001	1.88 (1.83–1.92)	40	334	<0.001	1.67 (1.64–1.71)	22	120	<0.001
Vitamin D, nmol/L													
<5 h sleep	4236	39.52 (39.02–40.02)	–13			40.99 (40.48–41.50)	–10			41.83 (41.32–42.35)	–8		
5 h sleep	17,435	42.44 (42.18–42.71)	–7			43.11 (42.85–43.37)	–5			43.64 (43.37–43.90)	–4		
6 h sleep	79,410	43.77 (43.65–43.90)	–4			43.94 (43.82–44.07)	–3			44.16 (44.03–44.28)	–2		
7–8 h sleep	287,800	45.59 (45.52–45.66)	Ref.			45.41 (45.34–45.48)	Ref.			45.26 (45.19–45.33)	Ref.		
9 h sleep	24,631	45.34 (45.10–45.58)	–1			45.56 (45.32–45.80)	0			45.79 (45.55–46.02)	1		
>9 h sleep	7329	41.19 (40.79–41.59)	–10	338	<0.001	42.76 (42.36–43.17)	–6	186	<0.001	43.62 (43.21–44.03)	–4	108	<0.001
Alkaline phosphatase, U/L													
<5 h sleep	4506	87.08 (86.39–87.78)	10			85.06 (84.39–85.73)	7			84.21 (83.55–84.87)	5		
5 h sleep	18,357	83.47 (83.14–83.80)	5			82.62 (82.29–82.94)	4			82.07 (81.75–82.39)	3		
6 h sleep	82,971	81.13 (80.98–81.28)	2			80.92 (80.78–81.07)	2			80.70 (80.55–80.85)	1		
7–8 h sleep	300,537	79.49 (79.42–79.57)	Ref.			79.68 (79.60–79.76)	Ref.			79.83 (79.75–79.90)	Ref.		
9 h sleep	25,961	81.24 (80.97–81.51)	2			81.06 (80.79–81.32)	2			80.82 (80.56–81.08)	1		
>9 h sleep	7794	85.47 (84.95–85.99)	8	350	<0.001	84.01 (83.51–84.52)	5	191	<0.001	83.16 (82.67–83.65)	4	115	<0.001
Gamma glutamyltransferase, U/L													
<5 h sleep	4501	34.22 (33.64–34.82)	21			33.97 (33.40–34.55)	20			32.57 (32.04–33.11)	14		
5 h sleep	18,337	31.69 (31.42–31.97)	12			31.51 (31.25–31.78)	11			30.67 (30.43–30.92)	7		
6 h sleep	82,933	29.68 (29.56–29.80)	5			29.62 (29.51–29.74)	4			29.30 (29.18–29.41)	2		
7–8 h sleep	300,382	28.34 (28.28–28.40)	Ref.			28.40 (28.34–28.46)	Ref.			28.61 (28.55–28.67)	Ref.		
9 h sleep	25,947	30.38 (30.17–30.60)	7			30.20 (29.99–30.42)	6			29.86 (29.66–30.06)	4		
>9 h sleep	7782	34.15 (33.71–34.60)	20	422	<0.001	33.46 (33.03–33.89)	18	357	<0.001	32.11 (31.71–32.51)	12	178	<0.001

Minimally-adjusted model was adjusted for sex and age at recruitment (and month of blood collection for the analysis of vitamin D); multivariable-adjusted model was additionally adjusted for physical activity, alcohol intake, smoking status, and time of blood collection.

4. Discussion

4.1. Findings

We found that serum CRP and GGT concentrations varied noticeably by sleep duration, with higher concentrations of both biomarkers in those with shorter and longer sleep duration. However, sleep duration was correlated with body mass index and with other health behavioural factors, and when we accounted for these characteristics, the differences in biomarker concentrations were markedly attenuated. Hence, residual confounding may explain the remaining associations. For other biomarkers, the percentage differences in geometric means of biomarkers across sleep duration groups were small.

CRP is an acute phase protein primarily synthesised by hepatocytes [16], and the circulating levels of CRP is a marker of inflammation and a potential biomarker of some chronic diseases (eg cardiovascular diseases [17–19]). There is inconclusive observational evidence mainly from cross-sectional studies for the association between sleep duration and CRP concentrations [15,20–23]. In this large study of over 400,000 participants, the relative differences in CRP concentrations across sleep duration became clearly smaller when we took account of other participants' characteristics and when we excluded participants who reported use of selected medications and those with poor or fair self-rated health. While the remaining association of long sleep duration with serum CRP may partly be explained by residual confounding, long sleep duration may be related to sleepiness, which could be a physiological/behavioural marker of underlying inflammation or related conditions [24].

Circulating GGT is primarily produced from the liver and its elevation may reflect liver diseases or excessive alcohol consumption [25,26]. Few meta-analyses of prospective studies reported that higher serum GGT concentrations were associated with elevated risks of hypertension [27], diabetes [28], and vascular diseases [29]. GGT may have a role in maintaining concentrations of glutathione (the main thiol antioxidant) in the cytoplasm [30]. Elevated serum GGT may reflect increased oxidative and/or cellular stress [26,27], and serum GGT was associated with markers of systemic inflammation (eg CRP) [31]. To our knowledge, the association between short/long sleep duration and circulating GGT has not been described previously in any large population-based studies. In a German study of 328 patients with insomnia, patients with short polysomnographic sleep duration (<6 h) had a higher GGT concentration in the fasting blood sample collected in the morning, compared to insomnia patients with normal sleep duration [32]. Further, we did not see consistent moderate variation in other liver biomarkers by sleep duration. Taken together, the association of sleep duration with circulating GGT may be due to residual confounding by body mass index or chance, or be related to other distinctive pathways.

Participants reporting shorter sleep tended to have a lower vitamin D concentration than those with 7–8 h of sleep, but it appeared that only men with longer sleep also had a lower vitamin D concentration. However, at least some of the differences in biomarkers we observed are likely to be due to residual confounding, as suggested by the substantial attenuation in the associations after covariate adjustment. While the presence of vitamin D receptors in brain regions involving in sleep regulation may suggest a role of vitamin D in sleep [33], the limited available cross-sectional data reported inconsistent findings of the association between sleep duration and vitamin D concentrations [34,35].

4.2. Strengths and limitations

To our best knowledge, the current study is the largest study of blood biomarkers in relation to sleep duration in a population-based sample. The standardised analysis simultaneously applied across multiple biomarkers, which are known to be related to various major diseases, offered an opportunity to gain insights into possible mechanisms linking sleep duration with disease risks.

As with many other population-based studies, an important limitation of the current study is that we used self-reported questionnaire data to characterise sleep duration, which may be prone to measurement error. However, a previous comparison between self-reported questionnaires and sleep diary data suggested a good correlation between two measurements of sleep duration [36]. Furthermore, total sleep duration has been shown in the Million Women Study to be reproducible over ~2 years in women in middle or old age [37], supporting that short-term total sleep duration can be reliably reported by participants. While accelerometer data were only collected in one-fifth of the UK Biobank cohort, future studies should explore the associations in this subset of participants with the use of accelerometer-derived sleep parameters, which itself is also a rapidly evolving research area. Moreover, we cannot determine from the UK Biobank data whether short and long sleep duration can cause a change in the concentrations of these biomarkers. Although the response rate of UK Biobank was about 5%, this should not affect the internal validity of the sleep duration–biomarker associations, as the study population is large with heterogeneous characteristics in terms of sleep duration and blood biomarker levels [5]. Lastly, the study was conducted in a white British population and the findings are not generalisable to other populations.

5. Conclusions

In this large British cohort, there is limited evidence that blood biomarkers vary materially by sleep duration once differences in several personal characteristics are accounted for.

Author credit statement

T.Y. Wong: Conceptualisation, Methodology, Formal analysis, Writing – Original Draft, Visualisation.

R.C. Travis: Conceptualisation, Supervision, Methodology, Writing – Review & Editing, Funding acquisition, Resources.

T.Y.N. Tong: Conceptualisation, Supervision, Methodology, Writing – Review & Editing.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2021.10.018>.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2021.10.018>.

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