

# Characterisation of Symptom and Polysomnographic Profiles Associated with Cardiovascular Risk in a Sleep Clinic Population with Obstructive Sleep Apnoea

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**Aim:** Recent data have identified specific symptom and polysomnographic profiles associated with cardiovascular disease (CVD) in patients with obstructive sleep apnoea (OSA). Our aim was to determine whether these profiles were present at diagnosis of OSA in patients with established CVD and in those with high cardiovascular risk. Participants in the Sydney Sleep Biobank (SSB) database, aged 30–74 years, self-reported presence of CVD (coronary artery disease, cerebrovascular disease, or heart failure). In those without established CVD, the Framingham Risk Score (FRS) estimated 10-year absolute CVD risk, categorised as “low” (<6%), “intermediate” (6–20%), or “high” (>20%). Groups were compared on symptom and polysomnographic variables.

**Results:** 629 patients (68% male; mean age 54.3 years, SD 11.6; mean BMI 32.3 kg/m<sup>2</sup>, SD 8.2) were included. CVD was reported in 12.2%. A further 14.3% had a low risk FRS, 38.8% had an intermediate risk FRS, and 34.7% had a high risk FRS. Groups differed with respect to age, sex and BMI. OSA severity increased with established CVD and increasing FRS. The symptom of waking too early was more prevalent in the higher FRS groups ( $p=0.004$ ). CVD and FRS groups differed on multiple polysomnographic variables; however, none of these differences remained significant after adjusting for age, sex, and BMI.

**Conclusion:** Higher CVD risk was associated with waking too early in patients with OSA. Polysomnographic variations between groups were explained by demographic differences. Further work is required to explore the influence of OSA phenotypic characteristics on susceptibility to CVD.

**Keywords:** obstructive sleep apnoea, cardiovascular disease

## Introduction

Obstructive Sleep Apnoea (OSA) is a highly prevalent sleep disorder estimated to affect nearly one billion people globally.<sup>1</sup> Repetitive collapse of the pharyngeal airway promotes sympathetic activation, oxidative stress, inflammation, and mechanical strain on the heart, which mechanistically links OSA to the development of cardiovascular disease (CVD).<sup>2</sup>

In recent years, there has been increasing recognition of OSA as a heterogeneous disorder.<sup>3,4</sup> Specific phenotypes have been identified,<sup>4-6</sup> some of which have links to CVD. For example, an excessively sleepy symptom subtype has been linked to the development of CVD.<sup>7</sup> Similarly, polysomnographic variables such as hypoxia,<sup>8,9</sup> breathing disturbance

during rapid eye movement (REM) sleep<sup>10</sup> and presence of periodic limb movements<sup>8</sup> may also predict cardiovascular outcomes over and above the apnoea hypopnoea index (AHI).

It is unknown whether these same phenotypes are evident at diagnosis of OSA in both those with established CVD and in individuals without CVD but with elevated CVD risk, as assessed by Framingham Risk Score.<sup>11</sup> Our aims were firstly to characterise symptom and polysomnographic profiles that were associated with established CVD at diagnosis of OSA. Secondly, we aimed to see whether these same patterns were evident in those without CVD but with elevated CVD risk. We hypothesised that those with established CVD, and those with high CVD risk, would be more likely to be excessively sleepy, and display polysomnographic features such as hypoxia and more breathing disturbances in REM sleep.

## Methods

### Participants

The Sydney Sleep Biobank (SSB)<sup>12</sup> prospectively recruits participants at three tertiary hospital sleep laboratories in Sydney, Australia (Royal North Shore Hospital, Royal Prince Alfred Hospital, Westmead Hospital). Participants were eligible for recruitment if they were aged over 18 years, could give informed consent, and were attending for overnight polysomnography at one of the three sites. The SSB protocol complies with the declaration of Helsinki and has been approved by the Northern Sydney Local Health District (NSLHD) Human Research Ethics Committee (HREC) protocol number HREC/17/HAWKE/340, with site specific approval at all sites (Royal North Shore Hospital no. SSA/18/HAWKE/127, Westmead no. SSA/18/WMEAD/163, Royal Prince Alfred no. SSA/18/RPAH/470). SSB data collection occurred on the night preceding and morning after polysomnography and included demographic information, anthropometric data, detailed questionnaire data and biological samples. Participants did not have a pre-existing diagnosis of OSA. Data from participants in the SSB database as of 26 April 2022 who were aged 30–74, completed the required information for this analysis, and whose polysomnogram was diagnostic of OSA (AHI  $\geq$  5) were included.

### Cardiovascular Disease

Participants were classified as having established CVD if they self-reported having ever been diagnosed with: 1) coronary artery disease (eg angina, myocardial infarction, heart attack, coronary artery stent, coronary artery bypass surgery); 2) cerebrovascular disease (eg stroke or transient ischaemic attack [TIA]); or 3) heart failure, in the medical history component of the SSB questionnaire. Otherwise, they were classified as not having CVD.

### Cardiovascular Risk Assessment

In those without established CVD, the Framingham Risk Score (FRS) for 10-year general CVD risk was calculated using the office-based, non-laboratory version (body mass index [BMI], instead of total and HDL Cholesterol) of the prediction model.<sup>11</sup> Participants were restricted to ages 30–74 years, as the model is only validated for these age groups. Variables used to calculate FRS risk included: sex, age, systolic blood pressure (BP), BMI, use of anti-hypertensive medication, cigarette smoking, and history of diabetes; and was performed using a freely available Microsoft Excel spreadsheet calculator (<https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/>). Systolic BP measurement was obtained in the evening prior to polysomnography and on the following morning by a trained research assistant for resting, seated office BP measurement. The higher of the two values was used to calculate the FRS risk. Height and weight were also measured in the evening. The other risk predictor variables were obtained from the SSB medical history questionnaire completed by the participant. A ten-year risk score designated as low (<6%), intermediate (6–20%) or high ( $\geq$ 20%) risk for general CVD was obtained from the equation.<sup>11</sup>

### Sleep Symptoms and Quality

Comprehensive symptom data were collected using standard validated questionnaires, including the Epworth Sleepiness Scale (ESS),<sup>13</sup> Functional Outcomes of Sleep Questionnaire short form (FOSQ-10),<sup>14</sup> Pittsburgh Sleep Quality Index (PSQI),<sup>15</sup> SAGIC Sleep Questionnaire,<sup>16</sup> Insomnia Severity Questionnaire (ISQ),<sup>17</sup> and the Berlin Sleep Questionnaire.<sup>18</sup> Total scores for the ESS, FOSQ-10 and PSQI were calculated. Additionally, twelve symptom variables (Table 1) were chosen from these

**Table 1** Symptom Variables Included for Analysis

Domain	Symptom
Sleepiness	How often do you feel tired or fatigued after your sleep?
	I feel very sleepy during the day
	During your waking time, do you feel tired, fatigued, or not up to par?
	I fall asleep involuntarily during the day
	I often take naps or doze off
Insomnia	During the past month, how often have you had difficulty staying asleep?
	During the past month, how often have you had difficulty falling asleep?
	During the past month, how often have you had trouble waking up too early in the morning and being unable to fall back asleep?
Disturbed sleep	I toss, turn and thrash excessively during the night
	I sweat/perspire excessively during the night
	I wake up suddenly and feel as if I cannot breathe
Upper airway symptoms	Do you snore?

questionnaires to align with previously published work investigating symptom phenotypes in OSA.<sup>19,20</sup> Participant responses were dichotomised into “present” if they occurred at least once per week, or “absent” if they occurred less frequently or did not occur at all. Results for total scores and dichotomised variables were compared between cardiovascular groups.

## Polysomnography

All polysomnography was scored using standard criteria (AASM Manual V2.6,<sup>21</sup> with minor clarifications recommended for standardisation across Australasian sleep services).<sup>22</sup> Polysomnographic variables in the domains of sleep architecture (sleep stages, sleep latency and efficiency), breathing disturbance (respiratory events in NREM and REM, apnoeas versus hypopnoeas), hypoxaemia (oxygen saturation, time spent below 90% oxygen saturation, oxygen desaturation index) and other (cortical arousals and periodic limb movements [PLMs]) were assessed and compared between cardiovascular groups.

## Statistical Analysis

Statistical analysis was performed using Jamovi v2.3.<sup>23</sup> Data are presented as mean (standard deviation) or N (%). Continuous variables were assessed for normality of distribution using the Shapiro–Wilk test and for the most part were found to have a non-parametric distribution. Polysomnographic and symptom variables were compared between those with and without established cardiovascular disease using the Mann–Whitney *U*-test for continuous variables and Chi Squared test of independence for categorical variables. In those without established cardiovascular disease, polysomnographic and symptom variables were compared across FRS groups using the Independent Samples Kruskal–Wallis test for continuous data and Chi Squared tests for categorical data. Polysomnographic variables were additionally assessed using ANCOVA to adjust for age, sex and BMI. As this was an exploratory study, no adjustment for multiple comparisons was made. Statistical significance was accepted at  $p < 0.05$ .

## Results

### Participant Characteristics

Of the 1062 participants recruited to the SSB at the time of analysis, 629 participants were aged between 30–74 years, had an apnoea hypopnoea index (AHI)  $\geq 5$ , and had completed the required questions for assessing cardiovascular risk. The cohort contained more males (67.7%), and the most common ethnicities were Caucasian (64.0%) and South-East

Asian (9.4%). The mean age was 54.3 years (SD 11.6) and the mean BMI was 32.3 kg/m<sup>2</sup> (SD 8.2). Forty four percent of the cohort had ever been smokers. Two hundred and forty-seven participants (39.4%) reported a diagnosis of hypertension; 238 participants (38%) reported dyslipidaemia; 98 participants (15.6%) reported presence of diabetes and 37 participants (5.9%) reported chronic lung disease.

## Prevalence of Established Cardiovascular Disease and Cardiovascular Disease Risk

Seventy seven participants (12.2%) reported established CVD, which was comprised of coronary artery disease (n=48, 7.7%), cerebrovascular disease (n=23, 3.7%), and heart failure (n=25, 4.0%). Those with established CVD were older (mean age 61 years) and had a higher BMI (mean 34.7 kg/m<sup>2</sup>) than those without CVD (53 years and 32.0 kg/m<sup>2</sup>, respectively). There was no sex difference between those with and without established CVD.

In those without established CVD (n=552), 90 participants (14.3%) had a Framingham risk score (FRS) less than 6% (“low Risk”); 244 participants (38.8%) had an FRS between 6% and 20% (“intermediate Risk”); and 218 participants (34.7%) had an FRS over 20% (“high Risk”). Low, intermediate, and high CVD risk groups differed with respect to age (40.3 years vs 51.2 years vs 61.1 years, respectively, p<0.001), sex (51% male vs 61% male vs 82% male, p<0.001), and BMI (29.1 kg/m<sup>2</sup> vs 31.9 kg/m<sup>2</sup> vs 33.2 kg/m<sup>2</sup>, p<0.001). The prevalence of smoking, hypertension and diabetes across groups is presented in Table 2.

## Sleep Symptoms

### Established Cardiovascular Disease

Presence of established CVD was not associated with significant differences in any measured symptom variable including total scores on sleep questionnaires (ESS, FOSQ-10 and PSQI) (Table 3).

## Cardiovascular Risk Groups

Intermediate and high cardiovascular risk groups were associated with waking too early (p=0.004); however, there were no other differences for symptom variables and no significant difference for total ESS, FOSQ-10 or PSQI scores (Table 4).

**Table 2** Prevalence of Smoking, Hypertension and Diabetes Across Groups

	Total Sample	Low Risk FRS	Intermediate Risk FRS	High Risk FRS	Established CVD
Age (years)	54.3 (11.6)	40.3 (8.2)	51.2 (9.8)	61.1 (8.2)	61.2 (10.0)
Male sex	426 (67.7%)	46 (51.1%)	148 (60.7%)	178 (81.7%)	54 (70.1%)
BMI (kg/m <sup>2</sup> )	32.3 (8.2)	29.1 (7.4)	31.9 (8.2)	33.2 (7.9)	34.7 (8.7)
Ever smoked	277/629 (44%)	16/90 (17.8%)	86/244 (35.2%)	130/218 (59.6%)	45/77 (58.4%)
Hypertension	247/609 (40.6%)	6/87 (6.9%)	66/236 (28.0%)	127/209 (60.8%)	48/77 (62.3%)
Diabetes	98/621 (15.8%)	1/89 (1.1%)	14/239 (5.9%)	59/216 (27.3%)	24/77 (31.2%)

Notes: Data are presented as N(%), except for age and BMI, which are presented as mean(SD).

**Table 3** Symptom Variables: Established CVD Vs No CVD

	Established CVD	No CVD	P
How often do you feel tired or fatigued after your sleep?	52 (70.3%)	410 (76.4%)	0.254
I feel very sleepy during the day	43 (58.1%)	327 (61.1%)	0.619
During your waking time, do you feel tired, fatigued, or not up to par?	54 (72.0%)	422 (78.1%)	0.233
I fall asleep involuntarily during the day	23 (31.5%)	142 (26.7%)	0.386

(Continued)

**Table 3** (Continued).

	Established CVD	No CVD	P
I often take naps or doze off	38 (52.1%)	239 (44.7%)	0.235
During the past month, how often have you had difficulty staying asleep?	37 (50.7%)	252 (47.4%)	0.595
During the past month, how often have you had difficulty falling asleep?	31 (41.9%)	191 (35.7%)	0.300
During the past month, how often have you had trouble waking up too early in the morning and being unable to fall back asleep?	36 (48.6%)	243 (45.8%)	0.641
I toss, turn and thrash excessively during the night	31 (43.1%)	251 (46.6%)	0.574
I sweat/perspire excessively during the night	15 (20.8%)	111 (20.8%)	0.999
I wake up suddenly and feel as if I cannot breathe	10 (13.7%)	99 (18.5%)	0.318
Do you snore?	55 (73.3%)	448 (82.7%)	0.082
Epworth Sleepiness Score	7.9 (5.0)	7.5 (4.7)	0.589
Functional Outcomes of Sleep Questionnaire-10 Score	29.7 (8.7)	29.6 (8.8)	0.933
Pittsburgh Sleep Quality Index Score	8.6 (5.2)	8.6 (5.5)	0.878

**Notes:** Data are presented as n(%) of participants who responded positively to the symptom occurring at least once per week. Scores are presented as mean(SD).

**Table 4** Symptom Variables: CVD Risk Groups

	Low Risk	Intermediate Risk	High Risk	P
How often do you feel tired or fatigued after your sleep?	68 (76.4%)	182 (77.8%)	160 (74.8%)	0.755
I feel very sleepy during the day	55 (62.8%)	148 (63.2%)	124 (58.5%)	0.583
During your waking time, do you feel tired, fatigued, or not up to par?	68 (76.4%)	188 (80.0%)	166 (76.9%)	0.656
I fall asleep involuntarily during the day	19 (21.3%)	62 (27.0%)	61 (29.0%)	0.388
I often take naps or doze off	37 (41.6%)	104 (44.3%)	98 (46.4%)	0.729
During the past month, how often have you had difficulty staying asleep?	32 (36.4%)	113 (48.7%)	107 (50.7%)	0.072
During the past month, how often have you had difficulty falling asleep?	34 (38.6%)	85 (36.2%)	72 (34.0%)	0.729
During the past month, how often have you had trouble waking up too early in the morning and being unable to fall back asleep?	26 (29.5%)	113 (48.9%)	104 (49.1%)	0.004**
I toss, turn and thrash excessively during the night	32 (36.0%)	115 (49.0%)	104 (48.4%)	0.089
I sweat/perspire excessively during the night	22 (25.3%)	41 (17.6%)	48 (22.5%)	0.234
I wake up suddenly and feel as if I cannot breathe	18 (20.2%)	43 (18.2%)	38 (18.0%)	0.895
Do you snore?	76 (85.4%)	194 (81.9%)	178 (82.4%)	0.748
Epworth Sleepiness Score	8.3 (5.7)	7.3 (4.4)	7.3 (4.7)	0.548
Functional Outcomes of Sleep Questionnaire-10 Score	29.7 (7.9)	29.3 (8.9)	29.9 (9.0)	0.542
Pittsburgh Sleep Quality Index Score	8.0 (5.2)	8.6 (5.7)	8.8 (5.5)	0.514

**Notes:** Data are presented as n(%) of participants who responded positively to the symptom occurring at least once per week. Scores are presented as mean(SD)  
\*\*Significant,  $p < 0.05$ .

## Polysomnographic Characteristics Established Cardiovascular Disease

Compared to participants without CVD, participants with established CVD had a lower sleep efficiency ( $p<0.05$ ); lower proportion of REM sleep ( $p=0.01$ ); higher AHI ( $p<0.05$ ); higher NREM AHI ( $p<0.05$ ); lower REM:NREM AHI ratio ( $p<0.05$ ); higher 3% oxygen desaturation index (ODI3%) ( $p<0.05$ ); and a higher arousal index ( $p=0.02$ ). However, none of these differences remained significant after adjusting for age, sex and BMI. All other polysomnographic differences between groups did not remain significant after adjusting for age and sex (see [Table 5](#)).

## Cardiovascular Risk Groups

There was a clear positive relationship between FRS and OSA severity (median AHI of 13.6/hr (IQR 18.9) in the low risk category; 18.9/hr (IQR 26.4) in the intermediate risk category; 27.6/hr (IQR 26.9) in the high risk category;  $p<0.001$ ); however, this did not remain significant after adjusting for age, sex, and BMI. Higher CVD risk was also significantly associated with longer sleep latency ( $p=0.05$ ); lower sleep efficiency ( $p<0.001$ ); lower total sleep time ( $p=0.004$ ); higher proportion of total sleep time spent in stage 1 sleep ( $p=0.006$ ); higher NREM AHI ( $p<0.001$ ); higher arousal index ( $p<0.001$ ); higher PLM index ( $p<0.001$ ); and a greater degree of awake and asleep hypoxia, as assessed by the time spent with oxygen saturation ( $\text{SpO}_2$ ) below 90% ( $p<0.001$ ); ODI3% ( $p<0.001$ ); average awake  $\text{SpO}_2$  ( $p<0.001$ ); and nadir  $\text{SpO}_2$  ( $p<0.001$ ). However, none of these differences remained significant in the adjusted analyses (see [Table 6](#)).

**Table 5** Polysomnographic Variables: Established CVD Vs No CVD

	Established CVD (n=77)	No CVD (n=548)	P (Unadjusted)	P (Adjusted for Age, Sex, BMI)
Sleep latency (mins)	18.0 (36.5)	19.5 (26.5)	0.640	
REM latency (mins)	125.0 (122.5)	110.5 (91.0)	0.258	
Sleep efficiency (%)	72.3 (27.3)	76.3 (18.3)	0.013**	0.196
Total sleep time (mins)	336.0 (137.0)	355.0 (96.8)	0.062	0.426
REM Sleep (%)	14.0 (10.4)	16.6 (8.8)	0.017**	0.103
Stage 1 (%)	11.6 (11.5)	8.4 (10.0)	0.119	
Stage 2 (%)	57.6 (14.3)	57.1 (15.6)	0.945	
Stage 3 (%)	15.0 (19.2)	14.4 (14.6)	0.987	
AHI (events/hr)	29.4 (33.5)	20.7 (31.3)	0.041**	0.723
REM AHI (events/hr)	33.8 (34.9)	32.2 (41.3)	0.890	
NREM AHI (events/hr)	27.4 (36.0)	18.5 (33.6)	0.018**	0.930
REM:NREM AHI ratio	1.1 (1.2)	1.3 (2.2)	0.027**	0.254
Central apnoea index (events/hr)	0.0 (0.3)	0.1 (0.6)	0.202	
$\text{SpO}_2 < 90\%$ (mins)	2.3 (10.9)	1.4 (7.6)	0.102	
ODI (events/hr)	23.5 (31.3)	14.4 (26.4)	0.025**	0.836
Awake average $\text{SpO}_2$ (%)	95.0 (2.0)	95.0 (2.0)	0.141	
Lowest $\text{SpO}_2$ (%)	84.0 (11.0)	84.0 (10.0)	0.378	
Arousal index (events/hr)	33.8 (30.9)	27.2 (22.9)	0.050**	0.358
PLM index (events/hr)	0.3 (21.4)	0.0 (9.3)	0.062	

**Notes:** Data are presented as median (IQR). \*\*Significant,  $p<0.05$ .



**Table 6** Polysomnographic Variables: CVD Risk Groups

	Low Risk (n=90)	Intermediate Risk (n=244)	High Risk (n=218)	P (Unadjusted)	P (Adjusted for Age, Sex, BMI)
Sleep latency (mins)	15.3 (24.3)	18.0 (25.1)	21.5 (28.6)	0.050**	0.53
REM latency (mins)	109.0 (82.9)	111.5 (93.1)	110.5 (88.5)	0.888	
Sleep efficiency (%)	80.1 (19.3)	76.7 (16.9)	74.3 (17.8)	<0.001**	0.18
Total sleep time (mins)	370.0 (90.2)	355.8 (92.3)	345.0 (103.0)	0.004**	0.19
REM Sleep (%)	16.7 (8.5)	16.9 (8.9)	15.9 (8.4)	0.653	
Stage 1 (%)	7.9 (5.9)	7.7 (9.1)	9.7 (12.2)	0.006**	0.24
Stage 2 (%)	57.8 (13.1)	57.1 (14.4)	55.9 (17.9)	0.914	
Stage 3 (%)	17.2 (12.8)	14.8 (13.9)	11.9 (17.6)	0.003**	0.72
AHI (events/hr)	13.6 (18.8)	18.9 (26.4)	27.6 (40.2)	<0.001**	0.70
REM AHI (events/hr)	27.6 (32.6)	30.1 (39.4)	38.6 (41.9)	0.084	
NREM AHI (events/hr)	10.4 (19.6)	17.1 (27.5)	26.4 (41.3)	<0.001**	0.73
REM:NREM AHI ratio	1.9 (3.9)	1.4 (2.5)	1.2 (1.2)	0.002**	0.20
Central apnoea index (events/hr)	0.2 (0.5)	0.2 (0.5)	0.0 (0.6)	0.748	
SpO <sub>2</sub> < 90% (mins)	0.4 (2.3)	1.2 (6.0)	3.2 (12.9)	<0.001**	0.53
ODI (events/hr)	9.1 (15.2)	14.1 (21.0)	20.0 (31.7)	<0.001**	0.35
Awake average SpO <sub>2</sub> (%)	96.0 (2.0)	96.0 (2.0)	95.0 (2.0)	<0.001**	0.12
Lowest SpO <sub>2</sub> (%)	86.0 (8.0)	84.5 (10.0)	83.0 (12.5)	<0.001**	0.71
Arousal index (events/hr)	22.8 (20.1)	25.6 (21.0)	30.2 (26.5)	<0.001**	0.69
PLM index (events/hr)	0.0 (1.0)	0.0 (4.3)	0.8 (16.5)	<0.001**	0.83

**Note:** Data are presented as median (IQR). \*\*Significant, p<0.05.

## Discussion

We assessed prevalence of CVD and CVD risk at time of diagnosis of OSA in a sleep clinic population. Overall, 12.2% of those with OSA reported diagnosed CVD and a further 34.7% of the population met the FRS criteria for a high 10-year CVD risk. We sought to assess whether presence of CVD and 10-year CVD risk was associated with a particular clinical presentation in symptom profile or OSA disease characteristics on polysomnography. We found that higher FRS was associated with waking too early, which occurred at least once per week in 29.5% of the low CVD risk group, compared to 48.9% of the intermediate risk group and 49.1% of the high risk group. Polysomnography data demonstrated significant associations between increasing risk of CVD and increased OSA severity, as well as a number of polysomnographic variables including oxygen desaturation indices and sleep architecture characteristics. However, none of these associations remained statistically significant after adjusting for age, sex and BMI.

There was no evidence of a particular symptom profile that was associated with CVD or FRS groups. The exception was an increased proportion of participants waking too early in the higher FRS groups. This difference may have been due to differences in age and sex between these groups. However, insomnia symptoms have been linked to cardiovascular mortality in large prospective studies.<sup>24,25</sup> In a recent study, comorbid insomnia and obstructive sleep apnoea, or COMISA, was associated with an increased likelihood of having cardiovascular disease at baseline.<sup>26</sup> Interestingly, we also found an association between high CVD risk and shorter sleep efficiency and lower sleep time; however, this was not statistically significant when adjusted for age, sex and BMI.

We did not find that subjective daytime sleepiness, as measured by the ESS, differed between any of the groups. Excessive daytime sleepiness (EDS) has been associated with increased CVD morbidity and mortality.<sup>27,28</sup> In recent years, latent class analyses of self-reported symptoms in large cohorts of patients with moderate-to-severe OSA have consistently identified three to five symptom subtypes,<sup>19,20,29–31</sup> which have all included core subtypes labelled “excessively sleepy”, “disturbed sleep” and “minimally symptomatic”. The replication of these subtypes across different cohorts suggest a biological basis. The “excessively sleepy” subtype in moderate-to-severe OSA (AHI>15) has been linked to increased prevalence and incidence of cardiovascular disease, including cardiovascular mortality.<sup>7,31</sup> However, a recent study by Trzepizur et al<sup>32</sup> did not replicate this finding in a large sleep clinic-based population; they found no association between symptom subtype and major adverse cardiac events in OSA of all severity (AHI≥5). Whilst our study was cross sectional and did not assess these recognised symptom subtypes, we also found no association between prevalent cardiovascular disease or CVD risk and sleepiness as measured by the ESS. However, there are recent data that the ESS alone may not fully capture the symptom of sleepiness.<sup>33</sup>

FRS has previously been assessed in a number of sleep populations using the laboratory test-based score (including total and HDL cholesterol values). In a sleep clinic cohort with newly diagnosed OSA in Greece, AHI modestly correlated with FRS<sup>34</sup> which remained significant after controlling for age and BMI. That population was restricted to an age less than 65 years and excluded patients with comorbidities placing them at high CVD risk. A Chinese study<sup>35</sup> calculating FRS in those with OSA found a correlation between AHI and ODI and time below SpO<sub>2</sub> 90% which was significant on a stepwise multivariate regression analysis. In a Brazilian study,<sup>36</sup> FRS was calculated on a randomly sampled general (non-sleep clinic based) population who then underwent polysomnography. There was an increased prevalence of OSA across FRS groups; and as with our study there was a significant correlation between most sleep variables and high FRS; however, only a sleep efficiency of less than 85% was associated with a high FRS in the adjusted analyses. Using the office-based FRS (BMI predictor instead of laboratory cholesterol values), we also identified a clear positive relationship between FRS and AHI; however, this relationship was not significant after adjusting for age, sex and BMI. The nature of the relationship between cardiovascular risk and OSA severity is a subject of ongoing debate and may be heavily influenced by confounding common risk factors, such as obesity.<sup>37</sup>

We also showed non-significant correlations between CVD risk and polysomnographic measures of oxygen saturation, including ODI, time spent below SpO<sub>2</sub> 90% (T90), lowest SpO<sub>2</sub>, and awake average SpO<sub>2</sub>; such that those with higher CVD risk had a higher degree of hypoxia. Interestingly, this same association was not observed between these indices and presence of established CVD, with the exception of ODI. Nocturnal intermittent hypoxia has been specifically associated with CVD in population studies.<sup>8,38,39</sup> Hypoxic burden, determined by measuring the respiratory event-related area under the desaturation curve from a pre-event baseline,<sup>40</sup> has been strongly associated with CVD mortality, cardiovascular events and incident heart failure across populations.<sup>9,32,41,42</sup> Whilst our study also reported more severe hypoxia with increased FRS, the association was not significant after adjusting for age, sex and BMI. This may be a consequence of common risk factors for both OSA and CVD, including age, male sex and obesity, which are included in the FRS calculation, making it difficult to determine the independent contribution to CVD from OSA.

We showed that established CVD and high CVD risk were associated with more arousals. PLMs also increased with FRS group (but not with established CVD). This same pattern was also seen in the Brazilian sleep cohort study.<sup>36</sup> Significant PLMs have been identified as a polysomnographic subtype of OSA that has been linked with higher incident CVD and CVD-specific mortality risk.<sup>4,43</sup> Arousals have also been shown to be independently associated with prevalent hypertension in patients with OSA.<sup>44</sup> Although this finding was only suggestive in our population, it is in line with these previous findings of an association with CVD risk.

## Limitations

This cross-sectional study of a sleep clinic population has limitations. Recruitment to the SSB is via an opt-in process, and therefore the sample may be subject to volunteer bias and may not represent the sleep clinic in its entirety. The CVD data used in this study were collected by self-report and therefore could be subject to recall bias. Our sample size may have been too small to detect significant associations between OSA and CVD given the confounding effects of age, sex and BMI. Other variables such as medication use may also mediate associations but were unmeasured in this study. Additionally, this was an observational study. By adjusting analyses for factors already included in the calculation of FRS



(namely, age, sex, and BMI), we may have underestimated the significance of the correlations between the polysomnographic variables and cardiovascular risk. Finally, this study had an AHI threshold  $\geq 5$ , which may have underestimated correlations between cardiovascular risk and both symptoms and polysomnographic variables compared to a higher threshold of  $\geq 15$ .

## Conclusions

Higher CVD risk, but not established CVD, was associated with more frequent insomnia symptoms in a multi-site sleep clinic population newly diagnosed with OSA. There were multiple variations in sleep architecture, OSA severity, oxygen desaturation, PLMs and arousals between CVD and CVD risk groups; however, these associations appeared to be due to differences in age, sex and BMI. Further research is needed to elucidate OSA phenotypic subtypes that are associated with CVD risk for the purposes of delineating personalised management strategies. The cardiovascular impact of OSA treatment, for example CPAP, in relation to such subtypes also merits exploration.

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