OSA symptom subtypes and hypoxic burden independently predict distinct cardiovascular outcomes

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Shareable abstract (@ERSpublications)
This study shows OSA symptom subtypes are independently associated with major adverse cardiovascular events and that hypoxic burden is independently associated with cardiovascular mortality. Both can be readily observed at the time of a sleep study. https://bit.ly/4b20XRG

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Abstract

Study objectives Studies on obstructive sleep apnoea (OSA) have identified clinically relevant symptom-based subtypes and novel OSA-specific nocturnal hypoxic measures. Both traits are individually associated with cardiovascular outcomes, but evidence about their independent or shared effects is unknown. This study investigated the simultaneous contributions of OSA symptom subtypes and hypoxic burden (HB) on incident cardiovascular outcomes.

Methods Sleep Heart Health Study participants with high-quality oxygen saturation, apnoea–hypopnea index (AHI) and symptom data were included. Participants with OSA (AHI $\geqslant$5 events·h^{-1}) were grouped into symptom subtypes. HB was calculated from respiratory event-related hypoxia. Cox proportional hazards models assessed whether symptom subtypes and/or HB were independently associated with cardiovascular mortality and major adverse cardiovascular events (MACE).

Results 4396 participants free of cardiovascular disease were analysed, with median follow-up >11 years. Higher HB was associated with worse cardiovascular mortality (HR (95% CI): 1.63 (1.13–2.35); p=0.009) independently of symptom subtypes. Compared to those without OSA, the excessively sleepy OSA subtype had higher risk of incident MACE (1.62 (1.23–2.15); p<0.001), independently of HB. Among participants with moderate–severe OSA (AHI $\geqslant$15 events·h^{-1}), excessively sleepy participants had higher risk of cardiovascular end-points compared to other subtypes, but HB was not associated with cardiovascular mortality or MACE risk.

Conclusion OSA symptom subtypes and HB are independently associated with MACE and cardiovascular mortality, respectively. Thus, both are important for understanding OSA-related cardiovascular risk. Future studies using clinical samples including OSA therapy information that incorporate symptom subtypes and novel biomarkers, such as HB, could improve predictive models for cardiovascular disease risk.

Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent sleep disorder [1], with a large degree of heterogeneity in its pathophysiology, clinical presentation and physiological expression. Distinct symptom-based subtypes of patients with moderate–severe OSA characterised by excessive sleepiness, disturbed sleep or minimal symptoms have been established and replicated worldwide [2–8]. Recent studies have shown that these symptom subtypes are also found when including individuals with mild

OSA severity [9, 10]. Analyses in the community-based Sleep Heart Health Study (SHHS) showed that OSA-related risk for incident cardiovascular events was driven by the excessively sleepy subtype [7]. Studies in clinical cohorts also demonstrated that the excessively sleepy subtype has increased risk of cardiovascular mortality and incident cardiovascular disease (CVD) after adjusting for relevant covariates [5, 11, 12], although results were not replicated in a clinical cohort in France [10].

Studies in large community-based cohorts have shown that the physiological expression of the disease captured by the sleep apnoea-specific hypoxic burden (HB) is also associated with increased cardiovascular mortality risk [13]. However, in the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea (RICCADSA) trial, HB was not associated with continuous positive airway pressure (CPAP) treatment benefit with respect to a composite of repeat revascularisation, myocardial infarction, stroke and cardiovascular mortality, while other physiological biomarkers (*e.g.*, heart rate responses to respiratory events) were associated [14, 15]. Nevertheless, a *post hoc* analysis of the Impact of Sleep Apnoea syndrome in the evolution of Acute Coronary syndrome, Effect of intervention with CPAP (ISAACC) trial among non-sleepy participants with prior CVD has suggested that higher HB was associated with greater long-term protective effects of CPAP against recurrent cardiovascular events [16]. Such effects among patients with OSA and excessive daytime sleepiness are yet to be determined.

Individually, there is evidence that symptom subtypes and HB are important traits explaining OSA-related cardiovascular risk. However, evidence of the relative importance of these traits is conflicting. Trzepizur *et al.* [10, 17, 18] reported that HB, but not symptom subtypes, predicted new major adverse cardiovascular events (MACE, a composite of all-cause mortality, acute myocardial infarction, stroke and unplanned coronary revascularisation) in patients with newly diagnosed OSA and no CVD at the time of diagnosis. This led to an editorial emphasising the importance of HB over symptom subtypes [19], despite no formal evaluation of whether the association between HB and MACE remained significant after controlling for OSA symptom subtypes, or *vice versa*. Intriguingly, a more recent study in the same French cohort [12] found a dose-response association between adherence to continuous positive airway therapy (CPAP) and lower incidence of MACE, with stronger benefits in males, patients free of CVD at baseline and, marginally, among patients with the excessively sleepy subtype [12]. These conflicting results raise important questions.

To date, studies have not determined their combined or independent contributions to cardiovascular risk using multivariate analyses. As such, whether the association of OSA symptom subtypes with cardiovascular risk (including mortality and incident MACE) is independent of OSA-related hypoxia, and *vice versa*, remains unclear. Here, we provide a systematic assessment of this important question. We first describe differences in HB across OSA symptom subtypes. Next, to understand their independent contributions for the first time, we examine whether symptom subtypes were associated with cardiovascular outcomes controlling for level of HB, and *vice versa*. Given that the extant literature supports both factors as relevant to OSA-related cardiovascular risk, as well as the high heterogeneity of OSA causes and consequences, we hypothesised that both HB and symptom subtypes would independently associate with risk for cardiovascular outcomes.

Methods

Details are available in the supplementary material.

Study participants

Clinical, demographic and cardiovascular outcomes information was available for 5804 SHHS participants [20, 21]. We defined a cohort of SHHS participants with available high-quality oxygen saturation data, complete information about OSA severity and symptom subtypes and who were free of CVD at baseline, resulting in 4396 participants (see figure 1). Home-based polysomnography was used to assess OSA using the ⩾4% oxygen desaturation criteria for hypopneas to classify participants according to disease severity as: No OSA (apnoea–hypopnea index (AHI) <5 events·h^{-1}), Mild OSA (5⩽AHI<15 events·h^{-}) and Moderate–Severe OSA (AHI ⩾15 events·h^{-1}).

OSA symptom subtypes

Participants with OSA of all severities were classified into minimally symptomatic, disturbed sleep, moderately sleepy and excessively sleepy subtypes, as previously reported (see supplementary material for details) [7, 9].

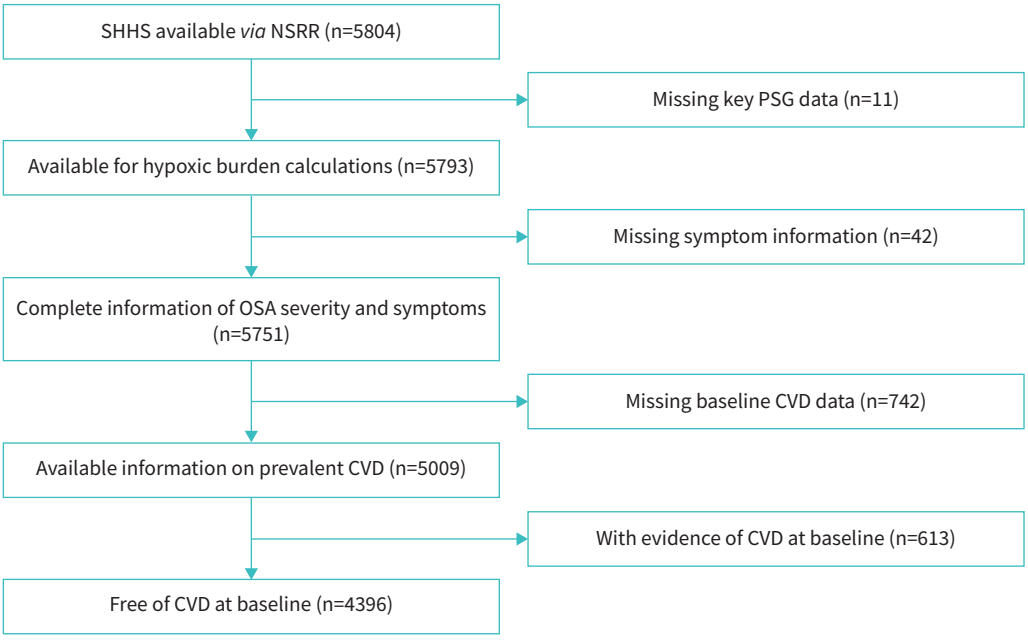

FIGURE 1 Study flowchart describing the steps to achieve the final cohort used in the primary analysis. SHHS: Sleep Heart Health Study; NSRR: National Sleep Research Resource; PSG: polysomnography; CVD: cardiovascular disease; OSA: obstructive sleep apnoea.

Hypoxic burden calculations

Calculation of HB followed the method of AZARBARZIN *et al.* [13], with the implementation verified by comparing results against the authors' published results. Our HB code and verification results are available at https://github.com/pdechazal/Hypoxic-Burden.

Cardiovascular outcomes

We assessed the individual and combined effect of HB and OSA symptom subtypes on cardiovascular mortality and incidence of MACE, defined as one or more event of coronary heart disease (CHD), heart failure (HF), stroke or cardiovascular mortality [7]. Secondary analyses were also performed for each MACE component, all-cause mortality and MACE with all-cause mortality.

Statistical analysis

Descriptive statistics are presented as mean±SD or median and interquartile range (IQR) for continuous data and frequency and percentage for categorical data. Differences in HB distributions among participants categorised as No OSA and the four Symptom Subtypes of OSA (among those with AHI⩾5 events·h^{-1}) were assessed using Kruskal–Wallis tests and pairwise Mann–Whitney U-tests. Cox proportional hazards (PH) regression was used to assess associations with cardiovascular mortality and MACE. HB was log-transformed (ln(HB+0.1)) in survival analyses to satisfy assumptions of normality. Statistical significance in primary and secondary analyses of cardiovascular end-points was based on the Hochberg "step-up" approach [22, 23]. Further details are described in the supplementary methods.

To address our primary question of the independent or combined roles of HB and OSA symptom subtypes, we conducted a series of statistical models. First, to confirm results from previous publications, we examined models including OSA symptom subtypes or HB alone. Second, to understand their independent associations, we evaluated an additional model including both OSA symptom subtypes and HB. These analyses were performed unadjusted (Model A), controlled for sociodemographic factors, comorbidities and cardiovascular risk factors (Model B), and further adjusted for other measures of severity of sleep-disordered breathing (Model C). Covariate definitions are described in the supplementary methods. Finally, to understand whether OSA symptom subtypes and/or HB differentiated cardiovascular risk among participants with more severe OSA, similar analyses were performed restricted to those with moderate–severe OSA (AHI ⩾15 events·h^{-1}).

Results

Sample characteristics

The cohort (n=4396) consisted of 55.8% women, primarily white (86.6%) with mean±SD age of 63.0±11.0 years. A total of 1310 (29.8%) participants had mild OSA (5⩽AHI<15 events·h^{-1}) and 862 (19.6%) participants had moderate–severe OSA (AHI ⩾15 events·h^{-1}). Sample characteristics stratified by the presence of cardiovascular mortality and incident MACE are presented in supplementary tables S1 and S2, respectively. Cardiovascular death occurred in 223 (5.1%) individuals and a MACE in 947 (21.5%) over the follow-up period (median 11.7 years for cardiovascular mortality and 11.4 years for MACE).

Associations between HB and OSA symptom subtypes

We found significant differences in the distribution of HB among OSA symptom subtypes and those with no OSA (p<0.005; figure 2; supplementary table S3). Compared to No OSA (mean±SD HB=17.9±14.9), both the excessively sleepy (60.1±52.0; p<0.001 *versus* No OSA) and moderately sleepy (57.5±49.3; p<0.001 *versus* No OSA) subtypes had significantly higher HB. Among those with moderate–severe OSA (figure 2; supplementary table S4) excessively sleepy participants had significantly higher HB than the minimally symptomatic and disturbed sleep subtypes (both p<0.001), but not than the moderately sleepy subtype (p=0.401).

OSA symptom subtypes and HB independently predict different cardiovascular outcomes

Supplementary tables S1 and S2 compare the distributions of symptom subtypes and HB between those with and without cardiovascular mortality or MACE, respectively, among all participants. Cardiovascular mortality was more likely in participants with OSA and more severe HB. MACE was more likely in participants with the excessively sleepy subtype and more severe HB.

Cox PH models were used to assess the individual and combined effects of symptom subtypes and HB on incidence of cardiovascular outcomes (see table 1 (covariate adjusted) and supplementary table S5 (unadjusted)). Briefly, we observed independent associations of HB and OSA symptom subtypes with distinct cardiovascular end-points. On the one hand, HB was associated with cardiovascular mortality, controlling for symptom subtypes (see table 1). On the other hand, patients with the excessively sleepy subtype were at higher risk of MACE and its components, controlling for HB (see table 1). Thus, rather than HB mediating relationships with symptom subtypes or *vice versa*, both factors are important for

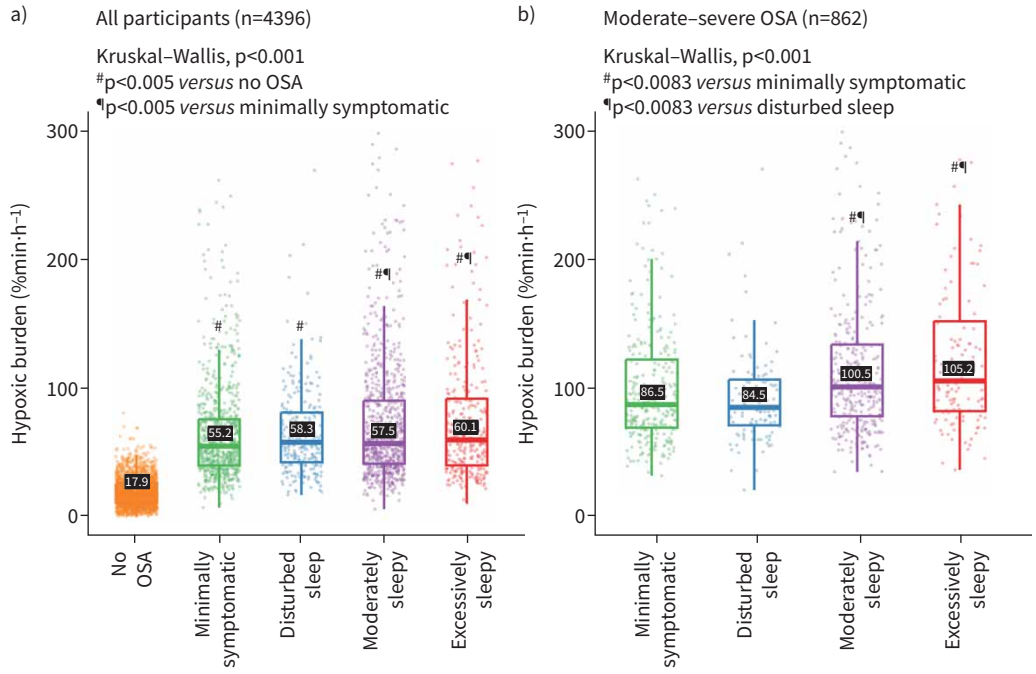

FIGURE 2 Associations between hypoxic burden and obstructive sleep apnoea symptom subtypes among a) all participants and b) participants with moderate–severe obstructive sleep apnoea (OSA).

TABLE 1 Adjusted analyses assessing the effect of OSA symptom subtypes and hypoxic burden on composite incident outcomes in participants of the Sleep Heart Health Study free of any cardiovascular disease at baseline

Model	Variable	CV mortality		MACE	
		HR (95% CI)	p-value[#]	HR (95% CI)	p-value[#]
Model B1: Symptom subtypes + Clinical covariates[¶]	Symptom subtypes	Overall p=0.697		**Overall p<0.001**	
	No OSA	1.00 (reference)	-	1.00 (reference)	-
	Minimally symptomatic	0.86 (0.59–1.27)	0.448	0.85 (0.70–1.03)	0.098
	Disturbed sleep	0.66 (0.35–1.26)	0.206	0.84 (0.62–1.13)	0.251
	Moderately sleepy	0.84 (0.57–1.23)	0.369	0.95 (0.79–1.15)	0.613
	Excessively sleepy	0.95 (0.54–1.66)	0.858	**1.56 (1.22–2.00)**	**<0.001**
Model B2: Hypoxic burden + Clinical covariates[¶]	Hypoxic burden (log scale)	1.04 (0.86–1.24)	0.697	0.98 (0.90–1.07)	0.657
Model B3: Symptom subtypes + Hypoxic burden + Clinical covariates[¶]	Symptom subtypes	Overall p=0.336		**Overall p<0.001**	
	No OSA	1.00 (reference)	-	1.00 (reference)	-
	Minimally symptomatic	0.69 (0.43–1.11)	0.126	0.86 (0.68–1.09)	0.220
	Disturbed sleep	0.52 (0.26–1.06)	0.072	0.86 (0.61–1.19)	0.356
	Moderately sleepy	0.66 (0.41–1.07)	0.095	0.97 (0.77–1.22)	0.815
	Excessively sleepy	0.75 (0.40–1.41)	0.378	**1.59 (1.20–2.11)**	**0.001**
	Hypoxic burden (log scale)	1.22 (0.95–1.56)	0.116	0.98 (0.87–1.11)	0.775
Model C1: Symptom subtypes + Clinical covariates[¶] + Other OSA severity measures[+]	Symptom subtypes	Overall p=0.870		**Overall p<0.001**	
	No OSA	1.00 (reference)	-	1.00 (reference)	-
	Minimally symptomatic	0.95 (0.62–1.47)	0.825	0.91 (0.74–1.13)	0.385
	Disturbed sleep	0.72 (0.37–1.41)	0.341	0.89 (0.65–1.22)	0.471
	Moderately sleepy	0.93 (0.60–1.44)	0.732	1.02 (0.83–1.25)	0.855
	Excessively sleepy	1.07 (0.58–1.95)	0.835	**1.67 (1.28–2.17)**	**<0.001**
Model C2: Hypoxic burden + Clinical covariates[¶] + Other OSA severity measures[+]	Hypoxic burden (log scale)	1.41 (1.02–1.94)	0.037	1.05 (0.91–1.21)	0.529
Model C3: Symptom subtypes + Hypoxic burden + Clinical covariates[¶] + Other OSA severity measures[+]	Symptom subtypes	Overall p=0.415		**Overall p<0.001**	
	No OSA	1.00 (reference)	-	1.00 (reference)	-
	Minimally symptomatic	0.72 (0.45–1.16)	0.181	0.89 (0.7–1.12)	0.308
	Disturbed sleep	0.54 (0.27–1.09)	0.087	0.86 (0.62–1.21)	0.392
	Moderately sleepy	0.70 (0.44–1.14)	0.153	0.99 (0.79–1.25)	0.942
	Excessively sleepy	0.83 (0.44–1.54)	0.549	**1.62 (1.23–2.15)**	**<0.001**
	Hypoxic burden (log scale)	**1.63 (1.13–2.35)**	**0.009**	1.05 (0.89–1.23)	0.584

Values in bold represent associations that remained significant after multiple comparisons correction. Overall p-values derived from likelihood ratio tests comparing fully adjusted models with and without OSA symptom subtypes. Total sample size (with non-missing covariates): Model B n=3714; Model C n=3698. OSA: obstructive sleep apnoea; CV: cardiovascular; HR: hazards ratio; MACE: major adverse cardiovascular events. [#]: p-values derived from covariate-adjusted Cox proportional hazards regression analyses including OSA (AHI ⩾5) symptom subtypes only, hypoxic burden (natural logarithmic scale) only or both as independent variables, along with covariates, and incident cardiovascular outcomes as dependent variables; [¶]: clinical covariates included age, sex, body mass index, race, ethnicity, alcohol use, smoking status, presence of COPD, presence of Type 2 diabetes, presence of hypertension, high-density lipoprotein levels, total cholesterol levels, triglyceride levels, use of lipid-lowering medication, total sleep time and presence of cardiovascular disease at baseline; [+]: other OSA Severity Measures included AHI, percentage of time in polysomnography with oxygen saturation <90%, oxygen saturation nadir.

understanding specific aspects of OSA-related CVD risk. Results including OSA symptom subtypes and HB in the same model are described in more detail within the following sections.

Cardiovascular mortality

In models adjusted for clinical covariates, we did not find associations between cardiovascular mortality and either symptom subtypes or HB (see table 1). However, after further adjustment for other OSA severity measures, greater HB was associated with higher cardiovascular mortality (HR (95% CI) 1.63 (1.13–2.35); p=0.009; table 1) and remained significant after multiple comparisons correction. OSA symptom subtypes were not associated with cardiovascular mortality among participants free of CVD at baseline.

MACE

When controlling for clinical covariates, a significantly increased risk of MACE was observed among the excessively sleepy subtype compared to those without OSA after adjusting for HB (HR (95% CI) 1.59

(1.20–2.11); p=0.001; table 1). Results were slightly stronger controlling for additional OSA severity measures (HR (95% CI) 1.62 (1.23–2.15); p<0.001; table 1). No relationship was found between HB and MACE among participants free of CVD at baseline.

Components of MACE (CHD, HF and stroke)

Unadjusted results are shown in supplementary table S6 and adjusted results are shown in supplementary table S7. In models controlled for clinical covariates, the excessively sleepy subtype was at higher risk for incident HF (HR (95% CI) 1.52 (1.02–2.27); p=0.039) and CHD (HR (95% CI) 1.53 (1.08–2.17); p=0.016), after controlling for HB. Results remained significant after further adjusting for other OSA severity measures (HR (95% CI) 1.59 (1.07–2.36); p=0.023 and 1.54 (1.09–2.19); p=0.015, respectively). We did not find evidence of association between HB and components of MACE (see supplementary table S7).

All-cause mortality

Complementary analyses assessing the association of OSA symptom subtypes and HB with all-cause mortality or with MACE plus all-cause mortality, rather than CVD-specific mortality, are also presented (supplementary table S8). Adjusted models revealed that HB was not associated with either end-point. However, the excessively sleepy subtype of moderate–severe OSA was significantly associated with increased MACE or all-cause mortality compared to no OSA after adjusting for HB (HR (95% CI) 1.41 (1.10–1.80); p=0.006; supplementary table S8) and further controlling for other OSA severity measures (HR (95% CI) 1.44 (1.12–1.83); p=0.004; supplementary table S8).

Among moderate–severe OSA, the excessively sleepy subtype predicts cardiovascular outcomes independent of HB

To understand the independent contributions of HB and symptom subtypes among those with moderate–severe OSA, we repeated models including both symptom subtypes and HB among only individuals with AHI $\geqslant$15 events·h^{-1} (see table 2). Overall, results demonstrate a significantly increased risk of MACE and MACE or all-cause mortality among the excessively sleepy patients compared to other symptom subtypes. No significant associations were observed with HB among those with moderate–severe OSA. Thus, symptom subtypes may have more utility in differentiating cardiovascular risk among patients with established OSA. Additional details are provided below.

Cardiovascular mortality

No associations between HB or symptom subtypes were observed among participants with moderate-severe OSA (table 2).

MACE

We observed a more than two-fold increased risk of incident MACE among the excessively sleepy subtype compared to minimally symptomatic (HR (95% CI) 2.42 (1.60–3.67); p<0.001), disturbed sleep (HR (95% CI) 2.52 (1.47–4.32); p<0.001) and moderately sleepy (HR (95% CI) 2.32 (1.57–3.43); p<0.001) in models adjusted for HB, clinical covariates and other OSA severity measures. HB was not a significant predictor of MACE in this group (table 2).

All-cause mortality

Our results support a significantly increased risk of all-cause mortality among participants with moderate–severe OSA and the excessively sleepy subtype when compared to other subtypes (all HR $\geqslant$1.88; table 2). Similar to other end-points, no significant effects of HB on these outcomes were found among patients with moderate–severe OSA.

Discussion

Both OSA-related hypoxia [13] and excessive sleepiness [7] have been associated with cardiovascular end-points; however, to date there are limited data on their shared or independent effects. This study meaningfully extends this literature by demonstrating that OSA symptom subtypes and HB are independently associated with specific cardiovascular end-points related to OSA. We report that the excessively sleepy subtype is at higher risk of incidence of MACE in participants free of CVD at baseline, independently of HB and other relevant risk factors. While not associated with MACE, HB is associated with cardiovascular mortality in those free of CVD at baseline, independently of symptom subtypes and other relevant risk factors. Among patients with moderate–severe OSA, there was no association between HB and any cardiovascular end-point, while the excessively sleepy subtype remained at increased risk of several cardiovascular end-points compared to other subtypes, independent of HB and other covariates. Thus, our findings suggest that both comprehensive symptomatology evaluations and determination of

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TABLE 2 Adjusted analyses assessing hypoxic burden among OSA symptom subtypes in moderate–severe OSA patients on incident outcomes in participants of the Sleep Heart Health Study free of any cardiovascular disease at baseline

Comparison	CV mortality		MACE		All-cause mortality		MACE or mortality	
	HR (95% CI)	p-value[#]	HR (95% CI)	p-value[#]	HR (95% CI)	p-value[#]	HR (95% CI)	p-value[#]
Model B[¶]								
Hypoxic burden	0.80 (0.41–1.58)	0.518	0.84 (0.61–1.15)	0.272	0.89 (0.64–1.25)	0.507	0.86 (0.65–1.12)	0.259
OSA symptom subtypes	Overall p=0.794		Overall p<0.001		Overall p=0.112		Overall p=0.003	
Excessively Sleepy *versus* Minimally Symptomatic	1.54 (0.61–3.89)	0.357	2.42 (1.60–3.65)	<0.001	1.72 (1.10–2.69)	0.017	1.96 (1.36–2.81)	<0.001
Excessively Sleepy *versus* Disturbed Sleep	1.59 (0.50–5.10)	0.434	2.38 (1.40–4.06)	0.001	1.55 (0.89–2.69)	0.123	1.92 (1.22–3.02)	0.005
Excessively Sleepy *versus* Moderately Sleepy	1.56 (0.64–3.83)	0.327	2.26 (1.53–3.34)	<0.001	1.66 (1.08–2.55)	0.020	1.88 (1.34–2.66)	<0.001
Moderately Sleepy *versus* Minimally Symptomatic	0.99 (0.48–2.03)	0.970	1.07 (0.76–1.50)	0.706	1.04 (0.73–1.47)	0.843	1.04 (0.79–1.37)	0.791
Moderately Sleepy *versus* Disturbed Sleep	1.02 (0.38–2.74)	0.973	1.05 (0.65–1.70)	0.829	0.93 (0.58–1.49)	0.765	1.02 (0.69–1.50)	0.920
Disturbed Sleep *versus* Minimally Symptomatic	0.97 (0.36–2.62)	0.951	1.01 (0.62–1.64)	0.958	1.11 (0.69–1.79)	0.658	1.02 (0.69–1.51)	0.930
Model C[+]								
Hypoxic burden	1.58 (0.42–5.98)	0.497	0.72 (0.40–1.31)	0.287	0.84 (0.47–1.50)	0.559	0.77 (0.47–1.26)	0.304
OSA symptom subtypes	Overall p=0.783		Overall p<0.001		Overall p=0.112		Overall p=0.003	
Excessively Sleepy *versus* Minimally Symptomatic	1.57 (0.61–3.99)	0.347	2.42 (1.60–3.67)	<0.001	1.69 (1.08–2.65)	0.022	1.94 (1.35–2.79)	<0.001
Excessively Sleepy *versus* Disturbed Sleep	1.67 (0.51–5.45)	0.393	2.52 (1.47–4.32)	<0.001	1.58 (0.91–2.76)	0.105	1.96 (1.24–3.08)	0.004
Excessively Sleepy *versus* Moderately Sleepy	1.55 (0.63–3.83)	0.338	2.32 (1.57–3.43)	<0.001	1.70 (1.10–2.61)	0.016	1.90 (1.35–2.69)	<0.001
Moderately Sleepy *versus* Minimally Symptomatic	1.01 (0.48–2.11)	0.984	1.04 (0.74–1.47)	0.805	1.00 (0.70–1.41)	0.981	1.02 (0.77–1.35)	0.892
Moderately Sleepy *versus* Disturbed Sleep	1.08 (0.39–2.95)	0.885	1.09 (0.68–1.75)	0.731	0.93 (0.58–1.50)	0.772	1.03 (0.70–1.51)	0.890
Disturbed Sleep *versus* Minimally Symptomatic	0.94 (0.34–2.60)	0.898	0.96 (0.59–1.56)	0.870	1.07 (0.66–1.72)	0.789	0.99 (0.67–1.47)	0.968

Overall p-values derived from likelihood ratio tests comparing fully adjusted models with and without OSA symptom subtypes. OSA: obstructive sleep apnoea; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular events. [#]: p-values derived from covariate-adjusted Cox proportional hazards regression analyses among participants with moderate–severe OSA, including OSA symptom subtypes and hypoxic burden (natural logarithmic scale) along with covariates, and incident CV outcomes as dependent variables; [¶]: covariates included baseline age, sex, body mass index, race, ethnicity, alcohol use, smoking status, presence of COPD, presence of Type 2 diabetes, presence of hypertension, high-density lipoprotein levels, total cholesterol levels, triglyceride levels, use of lipid-lowering medication, total sleep time and presence of cardiovascular disease at baseline; [+]: covariates included all Model B covariates plus apnoea–hypopnoea index, percentage of time in polysomnography with oxygen saturation <90%, oxygen saturation nadir.

OSA-specific hypoxaemia can independently inform general CVD risk related to OSA, although symptom subtypes may better differentiate CVD risk among those with moderate–severe disease.

A wealth of literature supports the individual roles of OSA symptom subtypes and OSA-related hypoxia with cardiovascular risk. Multiple studies support the increased risk of cardiovascular outcomes among patients with the excessively sleepy subtype [5, 7, 11, 24]. Similarly, studies report sleep apnoea-related nocturnal hypoxaemia as an independent CVD risk factor [10, 13, 25–29]. In these studies, measures focused on desaturations associated with OSA-related respiratory events seem the most relevant, including desaturation severity, the area under the desaturation curve among events with at least 4% desaturation associated with respiratory events, and the HB [13, 25–27, 28, 30].

There are also a few studies that do not find these associations. For example, a recent secondary analysis of the RICCADSA study did not find differences in adverse cardiovascular outcomes among patients with coronary artery disease that expressed excessive daytime sleepiness compared to those that did not [29]. In the same study, HB was not associated with differential benefits of CPAP with respect to a composite of repeat revascularisation, myocardial infarction, stroke and cardiovascular mortality [14, 15]. Most notably, a recent study from the Pays de la Loire cohort in France examined the roles of both HB and symptom subtypes (individually), finding that HB, but not symptom subtypes, predicted the incidence of MACE (including all-cause mortality) in patients with newly diagnosed OSA without CVD [10]. While this led to claims as to the "value of HB – and not symptom subtypes – in the prediction of cardiovascular events and mortality" [19], others have raised alternative explanations for the inconsistent findings [31, 32], such as the higher prevalence of CPAP treatment among excessively sleepy patients [10]. A follow-up study in this same cohort observed associations between CPAP adherence and lower incidence of MACE with all-cause mortality, with evidence of stronger cardiovascular benefits of CPAP among excessively sleepy patients [12, 33]. In contrast, the effect of CPAP did not significantly differ across HB severity groupings (although a significant benefit of CPAP was found in those with very severe HB) [12].

Ultimately, while critical assessments of recent literature highlight heterogeneity across studies that may explain some inconsistencies in results, nearly all studies support a link between both OSA with excessive sleepiness and more severe HB as individual risk factors for cardiovascular-related end-points. Our study fills an important gap in existing literature by providing a comprehensive assessment of the simultaneous role of OSA symptom subtypes and HB on different cardiovascular end-points. We provide data showing that patients in the excessively sleepy subtype have more severe HB. As such, a salient question is whether prior observations between cardiovascular risk and excessive sleepiness were driven by underlying differences in hypoxia burden, or *vice versa*. Our multivariate models show that this is not the case in the community-based SHHS cohort. Instead, each trait predicts distinct aspects of cardiovascular risk independent of the other factor. The excessively sleepy subtype is associated with increased MACE but not cardiovascular mortality alone, while HB is associated with increased cardiovascular mortality but not MACE. Interestingly, myocardial infarction that occurs during the night has been associated with OSA [34], and it is plausible that hypoxia might trigger fatal events. Future studies should focus on potential mechanisms linking more severe hypoxaemia with increased mortality, including evaluating whether cardiovascular mortality in patients with high HB is more frequent than in patients with lower HB; data on time of death were not available in SHHS.

To move towards clinical translation, future studies in clinical cohorts with data on OSA symptom subtypes, HB and other novel physiological markers, as well as cardiovascular end-points, are needed. In addition to confirming or refuting the distinct influences of symptoms and hypoxia observed in the community-based SHHS, these clinical samples would provide an ideal population in which to develop and validate clinical tools combining symptoms, hypoxia and other conventional risk factors to identify patients with OSA at greatest risk for cardiovascular events. The relationship of these factors with respect to outcomes of OSA therapies in these samples would also be beneficial to interrogate. To facilitate these studies, we have made available a simple decision tree algorithm to identify patients belonging to the excessively sleepy subtype [35] and made available the algorithmic details and code we utilised for determining HB [36] at: https://github.com/pdechazal/Hypoxic-Burden.

This study has some important limitations. The study population enrolled in the SHHS is relatively older, and thus not representative of younger individuals with potentially higher OSA-related cardiovascular risk [37]. No information about CPAP utilisation is a limitation, although the impact is mitigated by the relatively low (~2%) report of CPAP treatment among SHHS participants [38]. Further adjustment for other cardiovascular risk factors (*e.g.*, fat distribution, diet, exercise) was not possible as these data are not available in the SHHS. It is plausible to suggest specific SHHS recruitment cohort effects on identified

associations, which we did not evaluate, although this has not been observed in prior SHHS studies on incident cardiovascular end-points [37].

Our study also has several strengths. Inferences were made in a large community-based cohort with long-term follow-up and validated adjudication of cardiovascular events. We also extend our prior work on symptom subtypes of moderate–severe OSA [7] to estimate the effect of symptom subtypes at all OSA severity levels. Reporting on associations with different definitions of cardiovascular outcomes enhances the ability to compare with other published studies. We have provided adjustment for many established cardiovascular risk factors and other conditions that may impact OSA-related hypoxaemia, as well as rigorous control for multiple comparisons, enhancing robustness. Ultimately, the current study also highlights the importance of using harmonised sleep data and tools towards reproducible science, such as the SHHS, as warranted in a recent report by the Sleep Research Network Task Force [39].

In summary, our data support the role of OSA symptom subtypes, particularly the excessively sleepy subtype, and higher HB as independent predictors of distinct cardiovascular end-points in the general population. Thus, both factors are important for understanding OSA-related CVD risk. Within moderate–severe OSA patients, our data indicate that symptom subtypes, but not HB, are useful for differentiating those at higher risk for cardiovascular complications. Future studies using clinical samples including OSA therapy information that incorporate symptom subtypes and novel biomarkers, such as HB, could improve predictive models for CVD risk.

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