REM-associated sleep apnoea: prevalence and clinical significance in the HypnoLaus cohort

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ABSTRACT This study determined the prevalence of rapid eye movement (REM) related sleep-disordered breathing (REM-SDB) in the general population and investigated the associations of REM-SDB with hypertension, metabolic syndrome, diabetes and depression.

Home polysomnography (PSG) recordings (n=2074) from the population-based HypnoLaus Sleep Cohort (48.3% men, 57±11 years old) were analysed. The apnoea–hypopnoea index was measured during REM and non-REM sleep (as REM-AHI and NREM-AHI, respectively). Regression models were used to explore the associations between REM-SDB and hypertension, diabetes, metabolic syndrome and depression in the entire cohort and in subgroups with NREM-AHI <10 events·h^{-1} and total AHI <10 events·h^{-1}.

The prevalence of REM-AHI ⩾20 events·h^{-1} was 40.8% in the entire cohort. An association between increasing REM-AHI and metabolic syndrome was found in the entire cohort and in both the NREM-AHI and AHI subgroups (p-trend=0.014, <0.0001 and 0.015, respectively). An association was also found between REM-AHI ⩾20 events·h^{-1} and diabetes in both the NREM-AHI <10 events·h^{-1} (odds ratio (OR) 3.12 (95% CI 1.35–7.20)) and AHI <10 events·h^{-1} (OR 2.92 (95% CI 1.12–7.63)) subgroups. Systolic and diastolic blood pressure were positively associated with REM-AHI ⩾20 events·h^{-1}.

REM-SDB is highly prevalent in our middle-to-older age sample and is independently associated with metabolic syndrome and diabetes. These findings suggest that an increase in REM-AHI could be clinically relevant.

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Introduction

Sleep-disordered breathing (SDB) is highly prevalent in the general population [1], causing intermittent hypoxaemia, microarousals, sleep fragmentation, and acute changes in blood pressure (BP) and heart rate. SDB during rapid eye movement (REM) sleep (REM-SDB) is estimated to occur in 10–36% of patients with SDB [2], but its prevalence in the general population is not yet known.

REM-SDB is more common in patients with mild and moderate SDB [3] and has a higher prevalence in younger women than in men [4]. Data about sleepiness and REM-SDB are conflicting, but studies found no association between REM-SDB and daytime sleepiness or reduced quality of life [5–8].

Nocturnal respiratory events are usually more frequent and of longer duration in REM sleep compared with non-REM (NREM) sleep, probably due to greater pharyngeal muscle relaxation [9–11] and a reduction in the hypoxic and hypercapnic ventilatory response throughout REM sleep [12, 13].

Along with intermittent hypoxia, elevated sympathetic activity is thought to be the most important mechanism underlying the increased cardiovascular risk associated with SDB [14]. Compared with NREM sleep, REM sleep is associated with higher sympathetic activity and cardiovascular instability [15–17]. Recent studies have shown an association between REM-SDB and non-dipping nocturnal BP and hypertension [18–20]. Furthermore, REM-SDB has been reported to have an adverse effect on long-term glycaemic control and insulin resistance [21, 22]. However, the specific impact of REM-SDB on cardiovascular risk factors and psychiatric comorbidities is not yet known.

This study evaluated the prevalence of REM-SDB in the general population and investigated the associations between REM-SDB and cardiovascular, metabolic and psychiatric comorbidities.

Methods

Population sample

The HypnoLaus Sleep Cohort study has been described previously [1]. It included a random subset of the population-based CoLaus/PsyCoLaus cohort [23, 24] who underwent full polysomnography (PSG) at home and answered questionnaires about their sleep complaints, including the Epworth Sleepiness Scale (ESS) [25]. The ethics committee of the University of Lausanne approved the CoLaus/PsyCoLaus cohort study and the HypnoLaus Sleep Cohort study. Written informed consent was obtained from all participants.

Sleep data analysis

PSG was performed by certified technicians who equipped participants with a polysomnographic recorder (Titanium, Embla Flaga, Reykjavik, Iceland) in accordance with the 2007 American Academy of Sleep Medicine (AASM) recommended setup specifications [26] at the Center for Investigation and Research in Sleep (CIRS) at the University Hospital of Lausanne. All PSGs took place in the patients' home environment. Sleep stages were scored in 30-s epoch according to the 2007 AASM criteria. Apnoeas, hypopnoeas and respiratory effort related arousals were scored according to the 2012 AASM criteria [27].

The average number of apnoeas–hypopnoeas per hour of sleep (the apnoea–hypopnoea index (AHI)) was calculated for the whole night and for REM and NREM sleep separately. The percentage of total sleep time (TST) with oxygen saturation below 90% (T90) and the number of 3% or greater oxygen desaturations per hour (the oxygen desaturation index (ODI)) were assessed.

Quality control for concordance between the two PSG scorers was implemented periodically to ensure that both achieved at least 90% agreement for sleep stages and respiratory events, and 85% agreement for arousals. An expert sleep clinician reviewed every recording and a second sleep expert performed quality checks. We asked individuals who were currently receiving treatment for SDB (n=38) to discontinue their treatment 1 week before the sleep recording.

Outcome variables

Body weight and height were measured with participants standing without shoes in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g using a Seca scale (Seca, Hamburg, Germany), which was calibrated regularly. Height was measured to the nearest 5 mm using a Seca height gauge. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Waist was measured with a non-stretchable tape over the unclothed abdomen at the narrowest point between the lowest rib and the iliac crest, while hip was measured at the largest part of the hips. Two measures were made for waist and hip and the mean (expressed in centimetres) was used to assess the waist-to-hip ratio (WHR). Neck circumference was measured at the middle of the neck between the mid-cervical spine and the superior line of the cricothyroid membrane.

BP was measured three times on the left arm in the morning and the average of the last two readings was considered. Arterial hypertension was defined as systolic BP ⩾140 mmHg, diastolic BP ⩾90 mmHg, or current use of antihypertensive drugs. Diabetes was defined as fasting blood glucose ⩾7 mmol·L^{-1} or current antidiabetic drug treatment. Metabolic syndrome was defined according to the Adult Treatment Panel III (ATP-III) report [28]. Smoking status, alcohol consumption and the number of alcoholic drinks taken before the PSG recording and weekly were self-reported. The semi-structured Diagnostic Interview for Genetic Studies (DIGS) was used to diagnose current major depressive disorder, which was defined according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [29]. Interviewers were required to be masters-level psychologists and were trained over a two-month period. During data collection, each interview was reviewed by an experienced senior clinical psychologist. The DIGS interview systematically assesses the last and the most severe depressive episodes.

Statistical analysis

All statistical analyses were performed with IBM SPSS version 21.0 (IBM Corp, Armonk, NY, USA). Bivariate analyses were performed using the Chi-squared test for categorical variables and the Kruskal–Wallis test for continuous variables. Pairwise comparisons were performed using the Mann–Whitney test with Bonferroni's correction for p-value. Logistic regression models were used to estimate the association between REM-SDB and the presence of hypertension, diabetes, metabolic syndrome and depression.

The AHI during REM sleep (REM-AHI) was classified into four severity categories (REM-AHI <5 events·h^{-1} (reference group), 5–9.9 events·h^{-1}, 10–19.9 events·h^{-1} and ⩾20 events·h^{-1}) for the primary analysis (according to previous results of the HypnoLaus cohort) and used as a continuous variable for sensitivity analysis. A linear regression model was also used to assess the association between REM-AHI (as a continuous and a dummy variable) and diastolic and systolic BP.

Analyses were performed on the entire cohort and in two subgroups: one restricted to subjects with a total AHI <10 events·h^{-1} (absent or mild SDB) and another in those with AHI in NREM sleep (NREM-AHI) <10 events·h^{-1} (exclusive REM-SDB). For hypertension, diabetes and metabolic syndrome, the models were adjusted for age, sex, BMI, WHR, TST, logarithm of NREM-AHI (log-NREM-AHI), smoking and alcohol consumption. An additional adjustment for antihypertensive treatment was added when systolic BP and diastolic BP were used as outcome variables in the linear regression models. For depression, the model was adjusted for age, sex, and consumption of benzodiazepines and antidepressants. Results were expressed as odds ratios (ORs) with 95% CIs. Statistical significance was considered as $p<0.05$ for a two-sided test and as $p<0.008$ for multiple comparisons in univariate analysis.

Results

Study population

Of the 2168 subjects (48.3% men; 59±11 years old (range 40–85); BMI 25.6±4.1 kg·m^{-2}) who underwent complete PSG at home, 60 (3%) had technical problems, 54 underwent a second recording and six subjects refused resulting in 2162 valid PSG recordings. Of these, 41 subjects with less than 4 h of TST were excluded to avoid the risk of unbalanced representation of different sleep stages. In addition, a further 47 patients with less than 30 min of REM sleep were excluded to allow a proper assessment of REM sleep [18, 19]. Therefore, 2074 PSG recordings were included in the analysis. Clinical and polysomnographic characteristics of the total sample are shown in table 1.

REM-SDB in the entire cohort

The overall prevalence of moderate-to-severe REM-SDB (REM-AHI ⩾20 events·h^{-1}) was 40.8% in the HypnoLaus middle-to-older age general population sample. As REM-AHI increased there was a corresponding increase in mean age, BMI, WHR and neck circumference, as well as in the prevalence of hypertension, diabetes and metabolic syndrome (table 1). Patients in the higher REM-AHI severity categories had lower TST and lower proportions of slow wave sleep (SWS) and REM sleep. They also had higher ODIs and arousal indices and spent more time with oxygen saturation at less than 90% (higher T90); however, there was no difference between the ESS scores for the REM-SDB severity categories. The results for the association of REM-SDB with metabolic syndrome, diabetes, hypertension and depression are shown in figure 1.

The REM-AHI categories of 5–9.9 events·h^{-1} (OR 1.78 (1.13–2.81), p=0.013), 10–19.9 events·h^{-1} (OR 1.69 (1.12–2.57), p=0.013) and ⩾20 events·h^{-1} (OR 1.94 (1.29–2.92), p=0.001) were independently associated with metabolic syndrome but not diabetes or depression. Although we found no association between hypertension and REM-SDB, there was a significant association of REM-AHI ⩾20 events·h^{-1} with both systolic and diastolic BP (table 2).

TABLE 1 Subject characteristics in the entire cohort based on rapid eye movement (REM) apnoea–hypopnoea index (AHI) severity (REM-AHI severity)

	REM-AHI severity categories in the entire cohort					
	All	**<5 events·h^{-1}**	**5–9.9 events·h^{-1}**	**10–19.9 events·h^{-1}**	**⩾20 events·h^{-1}**	**p-value**
Subjects	2074 (100)	456 (22.0)	331 (16.0)	441 (21.3)	846 (40.8)	
Female	1079 (52.0)	318 (69.7)$^{\#}$	189 (57.1)$^{\#}$	220 (49.9)	352 (41.6)	**<0.0001**
Age years	56.3 (48.5–66.2)	51.3 (45.6–59.6)	54.1 (47.0–63.1)$^{\#}$	55.9 (48.9–65.7)$^{\#}$	60.6 (52.5–68.4)$^{\#,¶,+}$	**<0.0001**
BMI kg·m^{-2}	25.7 (23.2–28.5)	23.7 (21.5–26.3)	24.2 (22.1–26.5)	25.6 (23.3–27.9)$^{\#,+}$	27.4 (25.0–30.4)$^{\#,¶,+}$	**<0.0001**
WHR	0.92 (0.87–0.97)	0.89 (0.84–0.94)	0.90 (0.85–0.95)	0.91 (0.87–0.97)$^{\#,+}$	0.94 (0.90–0.98)$^{\#,¶,+}$	**<0.0001**
Neck circumference cm	37.0 (33.5–39.8)	34.0 (32.0–37.5)	35.0 (33.0–38.5)	37.0 (34.0–39.0)$^{\#,+}$	38.0 (35.0–41.0)$^{\#,¶,+}$	**<0.0001**
Hypertension	846 (40.8)	111 (24.3)	115 (34.7)	165 (37.4)	455 (53.9)$^{\#}$	**<0.0001**
Type 2 diabetes	200 (9.7)	15 (3.3)	18 (5.4)	30 (6.8)	137 (16.2)$^{\#}$	**<0.0001**
Metabolic syndrome	623 (30.0)	56 (12.3)	64 (19.3)	120 (27.2)	383 (45.3)	**<0.0001**
Depression	107 (6.2)	23 (6.3)	13 (4.6)	25 (6.6)	46 (6.6)	0.668
Antihypertensive medication	532 (25.7)	66 (14.5)	66 (19.9)	95 (21.5)	305 (36.1)$^{\#}$	**<0.0001**
Antidepressant medication	115 (5.7)	31 (7.1)	11 (3.4)	20 (4.6)	53 (6.4)	0.096
Benzodiazepines	171 (8.4)	33 (7.4)	28 (8.5)	35 (8.1)	75 (8.9)	0.815
Current smoking	379 (18.5)	92 (20.3)	60 (18.3)	78 (17.8)	149 (17.9)	0.063
Alcohol consumption before PSG§	0.45±0.89	0.42±0.82	0.43±0.82	0.40±0.88	0.49±0.93	0.276
Alcohol consumption weekly§	6.5±7.9	5.5±7.2	5.8±6.9	6.7±8.2	7.1±8.4$^{\#}$	**0.007**
TST min	406.5 (364.0–449.6)	409.2 (370.6–453.5)	411.5 (370.5–454.0)	415.0 (367.3–457.3)	397.5 (353.9–441.5)$^{\#,¶,+}$	**<0.0001**
TST in supine min	120.4 (53.4–196.1)	105.4 (49.0–174.3)	125.6 (62.5–194.6)$^{\#}$	127.5 (58.4–187.0)	122.6 (49.6–209.3)	**0.040**
REM time in supine min	20.0 (2.0–44.2)	17.1 (0–42.2)	20.0 (3.1–47.0)	20.5 (2.1–40.5)	21.4 (2.9–46.4)	0.094
REM time % of TST	22.5 (18.6–26.1)	23.6 (19.9–27.0)	23.0 (19.9–26.3)	22.9 (19.3–26.2)	21.1 (17.2–25.4)$^{\#,¶,+}$	**<0.0001**
SWS time % of TST	19.4 (14.2–25.0)	20.8 (16.3–25.8)	20.0 (15.3–25.6)	19.8 (14.3–25.7)	18.0 (12.5–23.9)$^{\#,¶,+}$	**<0.0001**
Arousal index events·h^{-1}	18.7 (13.8–25.9)	14.2 (10.4–19.7)$^{\#}$	17.1 (13.6–22.0)$^{\#}$	18.1 (14.1–23.8)$^{\#}$	23.2 (16.6–31.1)$^{\#,¶,+}$	**<0.0001**
Total AHI events·h^{-1}	9.8 (4.2–20.1)	2.0 (1.0–4.8)	4.3 (2.9–8.1)$^{\#}$	9.0 (6.0–13.5)$^{\#,+}$	21.4 (13.9–34.5)$^{\#,¶,+}$	**<0.0001**
NREM-AHI events·h^{-1}	7.4 (2.3–17.2)	1.7 (0.6–5.0)	3.4 (1.4–7.8)$^{\#}$	6.6 (3.0–12.0)$^{\#,+}$	16.6 (8.3–30.1)$^{\#,¶,+}$	**<0.0001**
REM-AHI events·h^{-1}	15.3 (5.7–30.3)	2.2 (0.9–3.4)	7.1 (6.0–8.6)$^{\#}$	14.5 (12.4–16.8)$^{\#,+}$	34.4 (25.7–46.8)$^{\#,¶,+}$	**<0.0001**
REM-AHI non-supine events·h^{-1}	8.8 (2.6–23.0)	1.3 (0–2.7)	5.1 (2.2–7.3)$^{\#}$	10.4 (6.2–14.3)$^{\#,+}$	26.7 (18.2–40.9)$^{\#,¶,+}$	**<0.0001**
REM-AHI supine events·h^{-1}	27.9 (8.4–52.7)	2.7 (0–6.2)	10.8 (7.0–23.4)$^{\#}$	25.1 (16.4–42.5)$^{\#,+}$	52.2 (37.5–68.6)$^{\#,¶,+}$	**<0.0001**
ODI 3% events·h^{-1}	9.9 (4.3–19.0)	2.4 (1.0–5.5)	4.7 (3.0–9.0)$^{\#}$	8.7 (5.6–14.3)$^{\#,+}$	19.8 (12.9–30.9)$^{\#,¶,+}$	**<0.0001**
T90 % of TST	4.1±12.3	7.2±1.1	9.3±1.4$^{\#}$	13.0±3.5$^{\#,+}$	14.3±7.0$^{\#,¶,+}$	**<0.0001**
ESS score	6.0 (3.0–9.0)	6.0 (3.0–8.0)	5.0 (3.0–9.0)	6.0 (3.8–8.0)	6.0 (3.0–9.0)	0.690

Data are presented as n (%), median (interquartile range) or mean±SD, unless otherwise stated. Data was analysed by Pearson's Chi-squared test or the Kruskal–Wallis test followed by Mann–Whitney pairwise comparisons. The number of participants with missing data was as follows: alcohol consumption before PSG (n=31), antidepressant medication (n=49), benzodiazepines (n=27), BMI (n=12), smoking (n=22), depression (n=353), diabetes (n=2), hypertension (n=2), neck circumference (n=57), REM-AHI non-supine (n=89), REM-AHI supine (n=394), REM time in supine (n=1), T90 (n=28), WHR (n=2). Values in bold indicate significant results (p<0.05). BMI: body mass index; WHR: waist-to-hip ratio; PSG: polysomnography; TST: total sleep time; NREM: non-rapid eye movement; SWS: slow wave sleep; ODI: oxygen desaturation index (number of 3% or greater oxygen desaturations per hour); T90: percentage of TST with oxygen saturation below 90%; ESS: Epworth Sleepiness Scale. $^{\#}$: p<0.008 compared to <5 events·h^{-1}; ¶: p<0.008 compared to 10–19.9 events·h^{-1}; $^{+}$: p<0.008 compared to 5–9.9 events·h^{-1}; §: alcohol consumption=mean consumption of standard drinks containing 10 g of alcohol.

Exclusive REM-SDB

A subgroup of 1241 subjects (59.8%) with NREM-AHI <10 events·h^{-1}was analysed to better define the specific influence of REM-SDB (table 3). In this subgroup, the prevalence of moderate-to-severe REM-SDB (REM-AHI ⩾20 events·h^{-1}) was 21.2% (n=263). As in the overall analysis, patients in the highest REM-AHI severity categories were older and had higher BMI, WHR and neck circumference, as well as a higher prevalence of hypertension, diabetes and metabolic syndrome.

Values for TST and REM sleep time were reduced only in the REM-AHI ⩾20 events·h^{-1}group, while arousal index, ODI and T90 were increased in all REM-SDB subgroups. No significant differences in SWS time and ESS score were found amongst the REM-SDB severity categories.

The same multivariate models were applied to this subgroup (figure 2) and increasing REM-AHI severity was found to be significantly associated with metabolic syndrome and diabetes, while hypertension and

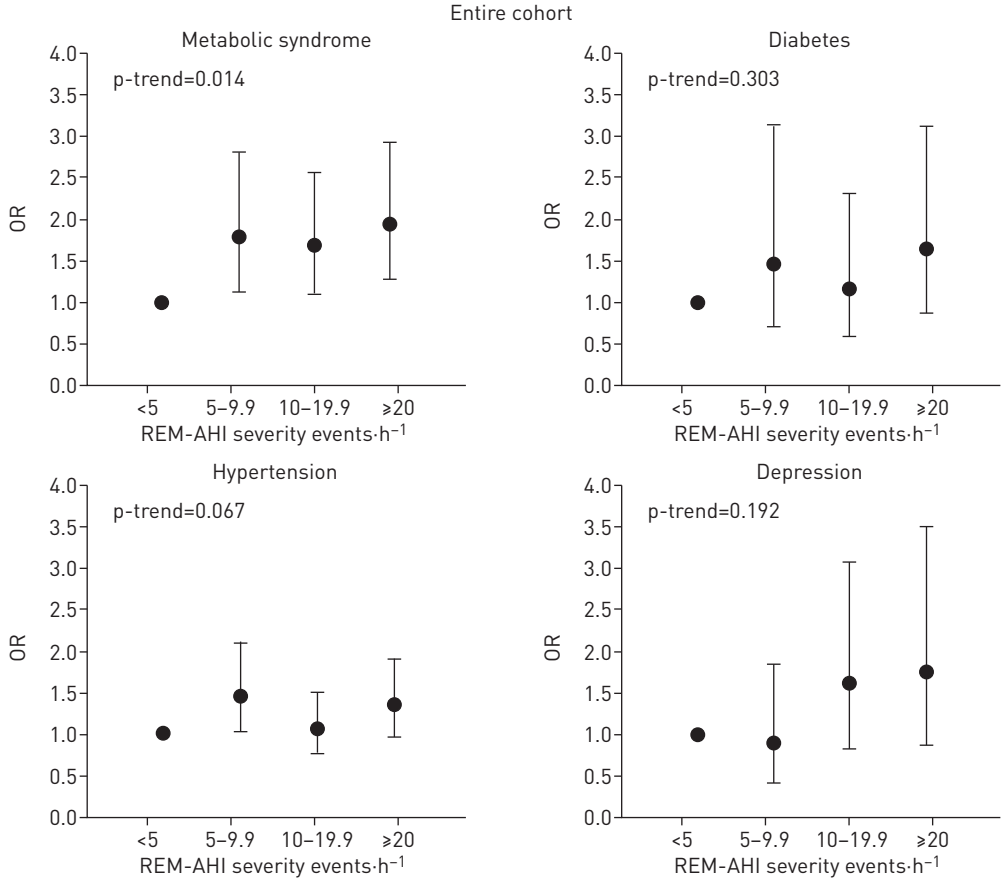

FIGURE 1 Odds ratios (ORs) and 95% CIs for rapid eye movement (REM) apnoea–hypopnoea index (AHI) severity categories (REM-AHI severity) in the entire cohort (n=2074 polysomnographies (PSGs)). Circles represent the ORs and bars represent the 95% CIs. Logistic regression models were fitted to examine the associations for the entire cohort with metabolic syndrome, diabetes, hypertension and depression. Increasing REM-AHI severity was significantly associated with metabolic syndrome. Hypertension, diabetes and depression were not significantly associated with REM related sleep-disordered breathing. Cardiovascular and metabolic comorbidities were adjusted for age, sex, body mass index, waist-to-hip ratio, total sleep time, smoking, alcohol consumption (weekly) and the logarithm of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, consumption of benzodiazepines, antidepressants and log-NREM-AHI. The number of participants with missing data in the models was as follows: metabolic syndrome (n=35), diabetes (n=37), hypertension (n=37), depression (n=389).

depression showed no association with REM-SDB. Although the p-value for trend was not significant for depression, the subgroup with the highest severity of REM-SDB (*i.e.* REM-AHI >20 events·h^{-1}) had a trend towards higher odds of depression (OR 2.14 (0.99–4.64), p=0.054) when compared to the group with no REM-SDB (*i.e.* REM-AHI <5 events·h^{-1}).

Absent or mild SDB

A second subgroup of 1047 subjects (50.5%) with total AHI <10 events·h^{-1} was analysed to evaluate the prevalence and significance of REM-SDB in subjects with absent or mild SDB (table 4). In this subgroup the prevalence of moderate-to-severe REM-SDB (REM-AHI ⩾20 events·h^{-1}) was 9.1% (n=95). As observed in the exclusive REM-SDB subgroup and the overall population, increasing REM-AHI severity was associated in univariate analysis with higher mean age, BMI, WHR and neck circumference, as well as a higher prevalence of metabolic syndrome, diabetes and hypertension.

Only the REM-AHI ⩾20 events·h^{-1} group presented lower TST and REM sleep time compared to the other groups, while all REM-SDB subgroups presented increased arousal index compared to the REM-AHI <5 events·h^{-1} group. Subjects with higher REM-AHI showed increased ODI and T90; however, no significant differences in SWS time and ESS score were found across the REM-AHI categories.

The results of the logistic regression models applied to this subgroup are shown in figure 3. There was a significant association of moderate-to-severe REM-SDB with both metabolic syndrome and diabetes, but not with hypertension or depression.

TABLE 2 Associations between rapid eye movement apnoea–hypopnoea index (REM-AHI) and blood pressure (BP)

	Entire cohort		NREM-AHI <10 events·h^{-1} subgroup		AHI <10 events·h^{-1} subgroup	
	β	p-value	β	p-value	β	p-value
Systolic BP						
REM-AHI (continuous)	0.03	0.167	0.01	0.842	−0.03	0.671
5–9.9 events·h^{-1}	2.02	0.070	1.28	0.275	1.43	0.213
10–19.9 events·h^{-1}	2.11	0.051	1.80	0.135	1.61	0.181
⩾20 events·h^{-1}	2.40	**0.030**	0.50	0.701	−1.18	0.486
Diastolic BP						
REM-AHI (continuous)	0.02	0.208	0.01	0.821	−0.02	0.636
5–9.9 events·h^{-1}	1.27	0.089	1.01	0.193	1.02	0.179
10–19.9 events·h^{-1}	1.20	0.097	1.12	0.159	0.90	0.255
⩾20 events·h^{-1}	1.72	**0.020**	0.23	0.787	−1.19	0.289

Data was analysed by linear regression using REM-AHI as a continuous or dummy variable with adjustment for age, sex, body mass index, waist-to-hip ratio, total sleep time, smoking, alcohol consumption (weekly), antihypertensive drug use and logarithm of NREM-AHI. The number of participants with missing data in the models (for the entire cohort, NREM-AHI <10 events·h^{-1} subgroup and the AHI <10 events·h^{-1} subgroup) was as follows: systolic BP and diastolic BP (n=16, n=6, n=5). Values in bold indicate significant results (p<0.05). β: linear regression coefficient beta; NREM: non-rapid eye movement.

We performed the same analysis using REM-AHI as a continuous variable instead of REM-AHI categories and with the same covariables as previously described. Using these models, we found significant associations between REM-AHI and metabolic syndrome in the entire cohort and the two subgroups, and with diabetes in both the NREM-AHI <10 events·h^{-1} and AHI <10 events·h^{-1} subgroups (see supplementary table S1). However, no association was significant for hypertension or depression.

Discussion

To our knowledge, this is the first study demonstrating an independent association of REM-SDB with metabolic syndrome and diabetes in the general population. We also showed in this analysis that the prevalence of moderate-to-severe REM-SDB (REM-AHI ⩾20 events·h^{-1}) in this middle-to-older age general population sample was 40.6% and that nearly 10% of patients with a global AHI of <10 events·h^{-1} have moderate-to-severe REM-SDB. These findings may have important implications for routine clinical practice in sleep medicine because they suggest that REM-AHI may need to be considered independently from global AHI when interpreting PSG results in patients at risk for metabolic dysfunction.

REM-SDB and metabolic syndrome

Several studies have shown a relationship between SDB and metabolic syndrome [1, 30, 31], but none of them assessed the relationship with REM-SDB. In the present study, there was a clear and independent association between increasing REM-AHI severity and the presence of metabolic syndrome. This association was found in the whole sample as well as in subjects with absent or mild SDB (AHI <10 events·h^{-1}) and in those with exclusive REM-SDB (NREM-AHI <10 events·h^{-1}). This suggests that apnoeas and hypopnoeas occurring during REM sleep may have a specific association with metabolic syndrome.

REM-SDB and diabetes

Previous studies showed an association between REM-AHI severity and increasing levels of glycosylated haemoglobin (HbA1c) in patients with Type 2 diabetes and with insulin resistance [21, 22]. In the present study we found a significant and independent association between diabetes and REM-SDB in both subgroups with NREM-AHI <10 events·h^{-1} and AHI <10 events·h^{-1}. Recently, Mokhlesi *et al.* [32] described an improvement in glycaemic control in patients with Type 2 diabetes and SDB after 1 week of 8-h nightly continuous positive airway pressure (CPAP) treatment. However, another study, in which CPAP was used for a mean of 4.3 h per night, showed no significant improvement in glycaemic control in patients with Type 2 diabetes and SDB [33]. The better results obtained by Mokhlesi *et al.* [32] could be related to the longer duration of CPAP usage resulting in better control of REM-SDB, as REM sleep mainly occurs toward the end of the night. We can thus speculate that the negative results reported by previous studies with shorter CPAP usage (usually limited to the first hours of the night) may be due to

TABLE 3 Patient characteristics in the non-rapid eye movement (NREM) apnoea–hypopnoea index (AHI) subgroup (NREM-AHI <10 events·h^{-1}) based on rapid eye movement (REM)-AHI severity (REM-AHI severity)

	REM-AHI severity categories in the NREM-AHI <10 events·h^{-1} subgroup					
	All	**<5 events·h^{-1}**	**5–9.9 events·h^{-1}**	**10–19.9 events·h^{-1}**	**⩾20 events·h^{-1}**	**p-value**
Subjects	1241 (100)	412 (33.2)	275 (22.2)	291 (23.4)	263 (21.2)	
Female	790 (63.7)	303 (73.5)$^{\#}$	167 (60.7)	171 (58.8)	149 (56.7)	**<0.0001**
Age years	53.5 (46.7–63.2)	50.5 (45.3–58.4)	53.8 (46.5–62.7)$^{\#}$	54.4 (48.0–64.7)$^{\#}$	57.7 (49.2–66.7)$^{\#,+}$	**<0.0001**
BMI kg·m^{-2}	24.7 (22.3–27.3)	23.4 (21.3–26.1)	23.9 (21.9–26.2)	25.4 (22.9–27.5)$^{\#,+}$	26.4 (24.3–29.5)$^{\#,¶,+}$	**<0.0001**
WHR	0.90 (0.85–0.95)	0.89 (0.84–0.93)	0.89 (0.84–0.94)	0.90 (0.86–0.95)$^{\#}$	0.92 (0.87–0.96)$^{\#,+}$	**<0.0001**
Neck circumference cm	35.0 (33.0–38.0)	34.0 (32.0–37.0)	35.0 (33.0–38.0)$^{\#}$	36.0 (33.0–38.0)$^{\#}$	36.5 (34.5–39.0)$^{\#,¶,+}$	**<0.0001**
Hypertension	398 (32.1)	92 (22.3)	90 (32.7)	98 (33.7)	118 (45.0)$^{\#}$	**<0.0001**
Type 2 diabetes	67 (5.4)	9 (2.2)	10 (3.6)	16 (5.5)	32 (12.2)$^{\#}$	**<0.0001**
Metabolic syndrome	257 (20.7)	44 (10.7)	47 (17.1)	64 (22.0)	102 (38.8)$^{\#}$	**<0.0001**
Depression	72 (7.0)	22 (6.6)	13 (5.4)	18 (7.3)	19 (8.8)	0.547
Antihypertensive medication	232 (18.7)	49 (11.9)	51 (18.5)	54 (18.6)	78 (29.7)	**<0.0001**
Antidepressant medication	57 (4.7)	27 (6.8)	10 (3.7)	12 (4.2)	8 (3.1)	0.100
Benzodiazepines	92 (7.5)	25 (6.2)	25 (9.2)	17 (5.9)	25 (9.6)	0.192
Current smoking	246 (20.0)	83 (20.3)	53 (19.5)	57 (19.7)	53 (20.3)	0.832
Alcohol consumption before PSG§	0.41±0.84	0.40±0.79	0.45±0.90	0.34±0.76	0.47±0.93	0.422
Alcohol consumption weekly§	5.7±7.3	5.3±7.1	5.8±7.1	6.1±7.2	5.9±7.8	0.380
TST min	409.5 (367.0–453.5)	411.3 (372.0–455.1)	411.9 (366.5–456.5)	419.0 (374.5–458.3)	394.5 (351.5–438.5)$^{\#,¶,+}$	**0.001**
TST in supine min	122.3 (55.6–192.0)	110.0 (53.0–183.6)	133.0 (62.5–198.5)	128.9 (56.9–185.5)	128.8 (47.1–212.4)	0.148
REM time in supine min	94.5 (76.3–114.0)	21.2 (0.5–46.5)	23.6 (6.0–51.5)	25.0 (7.0–46.5)	28.5 (7.5–52.0)$^{\#}$	**0.028**
REM time % of TST	23.4 (19.7–26.8)	23.8 (20.3–27.2)	23.5 (20.2–26.3)	23.3 (19.4–26.8)	22.3 (17.8–26.2)$^{\#}$	**0.018**
SWS time % of TST	20.8 (16.1–26.0)	21.0 (16.7–26.0)	20.3 (15.6–25.9)	20.9 (15.7–25.9)	20.9 (16.0–26.1)	0.686
Arousal index	15.3 (11.8–20.5)	13.8 (10.1–18.5)	16.5 (12.8–21.4)$^{\#}$	15.7 (12.9–20.5)$^{\#}$	16.5 (12.5–22.6)$^{\#}$	**<0.0001**
Total AHI events·h^{-1}	5.3 (2.4–8.7)	1.8 (0.9–3.4)	3.7 (2.8–6.0)$^{\#}$	6.6 (5.2–9.0)$^{\#,+}$	11.1 (8.9–13.5)$^{\#,¶,+}$	**<0.0001**
NREM-AHI events·h^{-1}	3.1 (1.3–6.1)	1.4 (0.5–3.5)	2.6 (1.2–5.2)$^{\#}$	4.2 (2.0–6.5)$^{\#,+}$	5.6 (3.5–7.7)$^{\#,¶,+}$	**<0.0001**
REM-AHI events·h^{-1}	8.6 (3.4–17.8)	2.1 (0.9–3.4)	7.1 (6.0–8.5)$^{\#}$	14.2 (12.2–16.5)$^{\#,+}$	28.2 (13.5–30.2)$^{\#,¶,+}$	**<0.0001**
REM-AHI non-supine events·h^{-1}	4.7 (1.3–12.5)	1.2 (0–2.6)	5.0 (2.2–7.2)$^{\#}$	10.0 (5.6–14.0)$^{\#,+}$	22.2 (23.5–35.3)$^{\#,¶,+}$	**<0.0001**
REM-AHI supine events·h^{-1}	15.0 (4.3–33.3)	2.7 (0–5.9)	10.6 (6.9–20.5)$^{\#}$	23.0 (15.9–37.4)$^{\#,+}$	41.2 (31.3–53.6)$^{\#,¶,+}$	**<0.0001**
ODI events·h^{-1}	5.3 (2.6–9.0)	2.0 (1.0–4.2)	4.2 (2.7–6.2)$^{\#}$	6.6 (4.7–8.9)$^{\#,+}$	11.0 (8.8–14.2)$^{\#,¶,+}$	**<0.0001**
T90 % of TST	2.5±11.1	1.1±7.6	1.5±10.1	2.9±13.7$^{\#,+}$	5.2±13.0$^{\#,¶,+}$	**<0.0001**
ESS score	6.0 (3.0–9.0)	6.0 (3.0–8.0)	5.0 (3.0–9.0)	6.0 (3.3–8.0)	6.0 (4.0–9.0)	0.344

Data are presented as n (%), median (interquartile range) or mean±SD, unless otherwise stated. Data was analysed by Pearson's Chi-squared test or by the Kruskal–Wallis test, followed by Mann–Whitney pairwise comparisons. The number of participants with missing data was as follows: alcohol consumption before PSG (n=20), antidepressant medication (n=28), benzodiazepines (n=16), BMI (n=3), smoking (n=9), depression (n=206), hypertension (n=1), neck circumference (n=35), REM-AHI non-supine (n=44), REM-AHI supine (n=213), T90 (n=14), WHR (n=1). Values in bold indicate significant results (p<0.05). BMI: body mass index; WHR: waist-to-hip ratio; PSG: polysomnography; TST: total sleep time; SWS: slow wave sleep; ODI: oxygen desaturation index (number of 3% or greater oxygen desaturations per hour); T90: percentage of TST with oxygen saturation below 90%; ESS: Epworth Sleepiness Scale. $^{\#}$: p<0.008 compared to <5 events·h^{-1}; ¶: p<0.008 compared to 10–19.9 events·h^{-1}; $^{+}$: p<0.008 compared to 5–9.9 events·h^{-1}; §: alcohol consumption=mean consumption of standard drinks containing 10 g of alcohol.

insufficient treatment of REM-SDB in the second part of the night. The importance of longer nightly CPAP use was also recently suggested by the results of the SAVE study, where a significant decrease in cerebrovascular events in patients with moderate-to-severe sleep apnoea and coronary or cerebrovascular disease was present only in those who used CPAP for more than 4 h per night [33, 34]. It is, however, unclear why this association was found mainly in the group with NREM-AHI <10 events·h^{-1} in our study.

Different hypotheses can be proposed regarding the underlying mechanisms of the associations between REM-SDB and metabolic syndrome or diabetes. First, it is well established that respiratory events occurring during REM sleep have a longer duration and generate greater oxygen desaturations compared to NREM events [9–11]. This may trigger increased oxidative stress compared with other respiratory events, which could promote metabolic syndrome and diabetes. Acute intermittent hypoxia was also

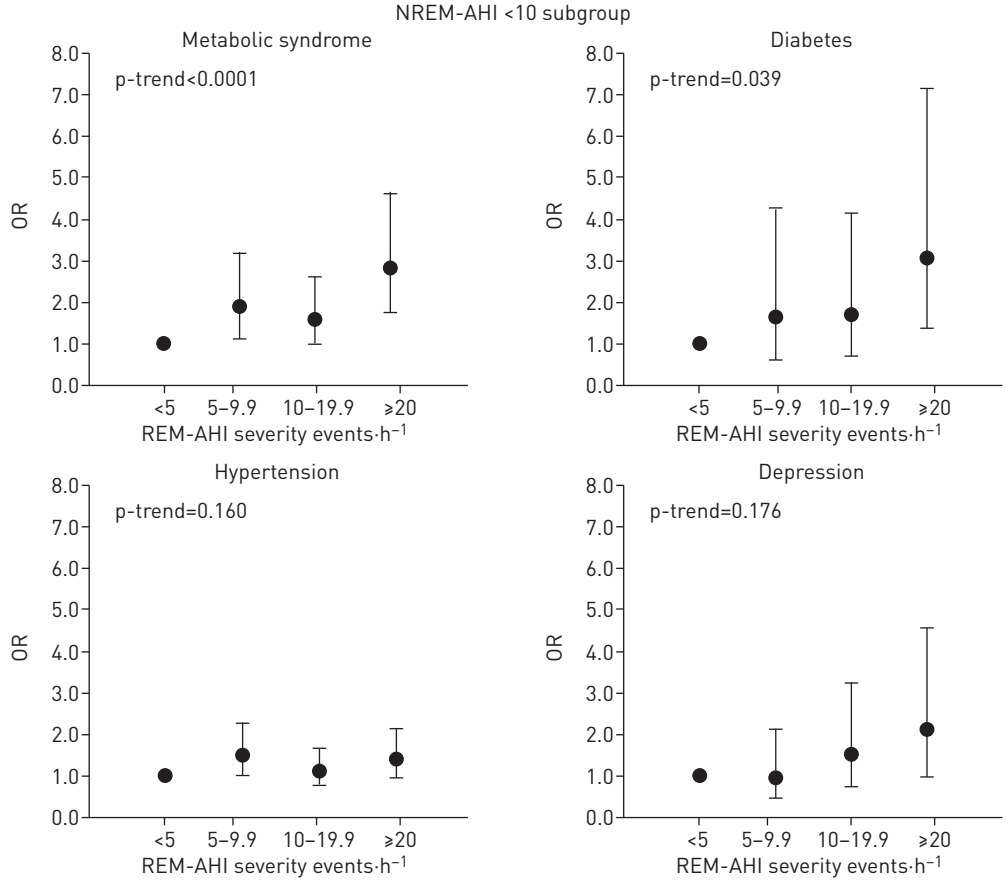

FIGURE 2 Odds ratios (ORs) and 95% CIs for rapid eye movement (REM) apnoea–hypopnoea index (AHI) severity categories (REM-AHI severity) in the subgroup with non-REM-AHI (NREM-AHI) <10 events·h^{-1} (n=1241 polysomnographies (PSGs)). Circles represent the ORs and bars represent the 95% CIs. Logistic regression models were fitted to examine the associations for the entire cohort with metabolic syndrome, diabetes, hypertension and depression. Increasing REM-AHI severity was significantly associated with metabolic syndrome and diabetes. Hypertension and depression showed no association with REM related sleep-disordered breathing. Cardiovascular and metabolic comorbidities were adjusted for age, sex, body mass index, waist-to-hip ratio, total sleep time, smoking, alcohol consumption (weekly) and the logarithm of NREM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, consumption of benzodiazepines, antidepressants and log-NREM-AHI. The number of participants with missing data in the models was as follows: metabolic syndrome (n=13), diabetes (n=13), hypertension (n=14), depression (n=226).

shown to acutely increase insulin resistance in healthy volunteers [35]. In addition, compared to NREM sleep, sympathetic activity is greater during REM sleep and most endocrine organs implicated in glucose metabolism are sensitive to changes in sympathovagal balance [36–38]. Furthermore, SDB in REM reversed the physiological nocturnal decline of interstitial glucose concentration (IGC), while NREM-SDB had no effect on IGC [39]. Lastly, nocturnal hyperglycaemia associated with SDB in patients with diabetes was shown to be specifically accentuated during REM sleep [40].

REM-SDB and hypertension

We previously reported a significant association between SDB severity and hypertension in the population-based HypnoLaus sleep cohort [1]. Considering that two studies have shown a specific association between REM-SDB and increased incident hypertension [18, 19], we tested this association in our sample using a cross-sectional analysis. Surprisingly, there was no significant association between REM-SDB and hypertension in the whole sample, in the subgroups with REM-AHI <10 events·h^{-1} or global AHI <10 events·h^{-1}, nor in a subgroup without antihypertensive medication (supplementary table S2). The reason for the differences between our study and previous studies is unclear. In the Wisconsin cohort, the scoring of hypopnoeas required a 4% oxygen desaturation, which may have selected more severe respiratory events [41]. However, the MAILES study, which also found a significant association between REM-SDB and hypertension, used the currently recommended 3% criteria for scoring hypopnoeas [19]. Another difference is that the MAILES study included only males, whereas we included

TABLE 4 Patient characteristics in the apnoea–hypopnoea index (AHI) <10 events·h^{-1} subgroup based on rapid eye movement (REM)-AHI severity (REM-AHI severity)

	REM-AHI severity categories in the AHI <10 events·h^{-1} subgroup					
	All	**<5 events·h^{-1}**	**5–9.9 events·h^{-1}**	**10–19.9 events·h^{-1}**	**⩾20 events·h^{-1}**	**p-value**
Subjects	1047 (100)	419 (40)	275 (26.3)	258 (24.6)	95 (9.1)	
Female	683 (65.2)	305 (72.8)$^{\#}$	169 (61.5)	153 (59.3)	56 (58.9)	**<0.0001**
Age years	52.8 (46.2–62.4)	50.5 (45.4–58.5)	53.8 (46.5–63.0)$^{\#}$	54.4 (48.0–64.3)$^{\#}$	55.0 (47.2–66.1)$^{\#}$	**<0.0001**
BMI kg·m^{-2}	24.3 (21.9–26.8)	23.4 (21.3–26.1)	24.0 (21.9–26.3)	25.3 (22.7–27.3)$^{\#,+}$	26.3 (23.6–30.4)$^{\#,¶,+}$	**<0.0001**
WHR	0.90 (0.85–0.94)	0.89 (0.84–0.94)	0.89 (0.84–0.94)	0.90 (0.86–0.95)$^{\#}$	0.92 (0.87–0.97)$^{\#,+}$	**<0.0001**
Neck circumference cm	35.0 (33.0–38.0)	34.0 (32.0–37.0)$^{\#}$	35.0 (33.0–38.0)$^{\#}$	35.5 (33.0–38.0)$^{\#}$	36.0 (34.4–39.0)$^{\#,+}$	**<0.0001**
Hypertension	312 (29.8)	96 (22.9)	89 (32.4)	87 (33.7)	40 (42.1)$^{\#}$	**<0.0001**
Type 2 diabetes	45 (4.3)	10 (2.4)	10 (3.6)	14 (5.4)	11 (11.6)$^{\#}$	**0.001**
Metabolic syndrome	187 (17.9)	48 (11.5)	47 (17.1)	55 (21.3)	187 (17.9)$^{\#}$	**<0.0001**
Depression	56 (6.4)	22 (6.5)	13 (5.4)	16 (7.2)	5 (6.3)	0.887
Antihypertensive medication	177 (16.9)	51 (12.2)	50 (18.2)	49 (19.0)	27 (28.4)$^{\#}$	**0.001**
Antidepressant medication	50 (4.9)	28 (6.9)	10 (3.7)	11 (4.3)	1 (1.1)	0.058
Benzodiazepines	79 (7.7)	25 (6.1)	25 (9.2)	16 (6.3)	13 (13.8)$^{\#}$	**0.045**
Current smoking	217 (20.9)	86 (20.7)	53 (19.5)$^{\#}$	56 (21.8)$^{\#}$	22 (23.2)$^{\#,+}$	0.858
Alcohol consumption before PSG§	0.40±0.81	0.39±0.78	0.45±0.90	0.35±0.79	0.41±0.78	0.511
Alcohol consumption weekly§	5.7±7.2	5.4±7.3	5.8±7.1	6.0±7.3	5.6±6.7	0.497
TST min	411.0 (368.5–454.0)	410.5 (372.0–455.5)	411.5 (366.5–458.0)	418.8 (371.9–353.0)	391.5 (353.0–420.4)$^{\#,¶,+}$	**0.002**
TST in supine min	121.2 (55.4–190.0)	109.9 (49.3–177.5)	133.0 (62.5–200.0)	127.9 (54.3–187.0)	131.2 (47.0–189.1)	0.111
REM time in supine min	23.2 (3.1–48.0)	20.6 (0.2–46.0)	23.6 (6.0–51.1)	25.0 (7.3–46.4)	27.8 (6.0–57.5)	0.062
REM time % of TST	23.3 (19.7–26.6)	23.8 (20.3–27.2)	23.5 (20.2–26.3)	23.2 (19.4–26.6)	20.4 (17.0–23.6)$^{\#,¶,+}$	**<0.0001**
SWS time % of TST	20.8 (16.3–25.9)	20.9 (16.6–25.9)	20.1 (15.6–25.9)	20.6 (15.6–25.9)	22.3 (18.0–26.1)	0.237
Arousal index	15.2 (11.5–20.0)	13.8 (10.2–18.6)	16.5 (12.8–21.4)$^{\#}$	15.5 (12.8–20.1)$^{\#}$	15.7 (12.0–21.6)$^{\#}$	**<0.0001**
Total AHI events·h^{-1}	4.2 (2.1–6.9)	1.8 (0.9–3.5)	3.7 (2.8–6.0)$^{\#}$	6.3 (5.1–8.3)$^{\#,+}$	8.1 (6.9–9.2)$^{\#,¶,+}$	**<0.0001**
NREM-AHI events·h^{-1}	2.4 (1.1–4.9)	1.5 (0.5–3.6)	2.6 (1.2–5.2)$^{\#}$	3.7 (1.9–5.7)$^{\#,+}$	3.2 (2.0–4.2)$^{\#}$	**<0.0001**
REM-AHI events·h^{-1}	6.5 (2.7–12.7)	2.1 (0.9–3.4)	7.0 (6.0–8.5)$^{\#}$	13.9 (12.0–16.4)$^{\#,+}$	24.7 (21.7–28.3)$^{\#,¶,+}$	**<0.0001**
REM-AHI non-supine events·h^{-1}	3.5 (1.0–8.6)	1.2 (0–2.6)	5.0 (2.2–7.2)$^{\#}$	10.0 (5.5–13.6)$^{\#,+}$	20.5 (7.0–26.4)$^{\#,¶,+}$	**<0.0001**
REM-AHI supine events·h^{-1}	10.6 (3.0–24.1)	2.7 (0–5.9)	10.6 (7.0–20.5)$^{\#}$	22.3 (15.2–35.1)$^{\#,+}$	31.8 (25.8–46.0)$^{\#,¶,+}$	**<0.0001**
ODI events·h^{-1}	4.4 (2.2–7.0)	2.0 (1.0–4.4)	4.2 (2.7–6.2)	6.2 (4.5–8.2)$^{\#,+}$	8.4 (6.9–10.2)$^{\#,¶,+}$	**<0.0001**
T90 % of TST	2.1±11.1	1.1±7.5	1.5±10.1	2.9±14.3$^{\#,+}$	5.6±15.7$^{\#,¶,+}$	**<0.0001**
ESS score	6.0 (3.0–9.0)	6.0 (3.0–8.0)	5.0 (3.0–9.0)	5.0 (3.5–8.5)	6.0 (3.0–9.0)	0.906

Data are presented as n (%), median (interquartile range) or mean±SD, unless otherwise stated. Data was analysed by Pearson's Chi-squared test or by the Kruskal–Wallis test, followed by Mann–Whitney pairwise comparisons. The number of participants with missing data was as follows: alcohol consumption before PSG (n=19), antidepressant medication (n=27), benzodiazepines (n=15), BMI (n=3), smoking (n=7), depression (n=169), neck circumference (n=33), NREM-AHI supine (n=58), REM-AHI supine (n=194), T90 (n=12), WHR (n=1). Values in bold indicate significant results (p<0.05). BMI: body mass index; WHR: waist-to-hip ratio; PSG: polysomnography; TST: total sleep time; SWS: slow wave sleep; NREM: non-rapid eye movement; ODI: oxygen desaturation index (number of 3% or greater oxygen desaturations per hour); T90: percentage of TST with oxygen saturation below 90%; ESS: Epworth Sleepiness Scale. $^{\#}$: p<0.008 compared to <5 events·h^{-1}; ¶: p<0.008 compared to 10–19.9 events·h^{-1}; $^{+}$: p<0.008 compared to 5–9.9 events·h^{-1}; §: alcohol consumption=mean consumption of standard drinks containing 10 g of alcohol.

both genders in our analysis. However, this is unlikely to explain the lack of association we found because our models were also negative when we restricted the analysis to men (data not shown). The analysis on the Wisconsin cohort by Mokhlesi and colleagues used 24-h BP monitoring while we used three measurements in the morning. Although this is a potential source of difference between the two studies, the MAILES study used the same technique as in the present study and found a significant association between REM-SDB and hypertension. When using BP as a continuous dependent variable there was, however, a significant positive association between moderate-to-severe REM-AHI and both systolic and diastolic BP. These findings appear to suggest a possible positive association between REM-SDB and BP.

REM-SDB and depression

We did not find a significant association between depression and REM-SDB besides a trend in the NREM-AHI <10 events·h^{-1} subgroup. Our group and others have previously shown that patients with

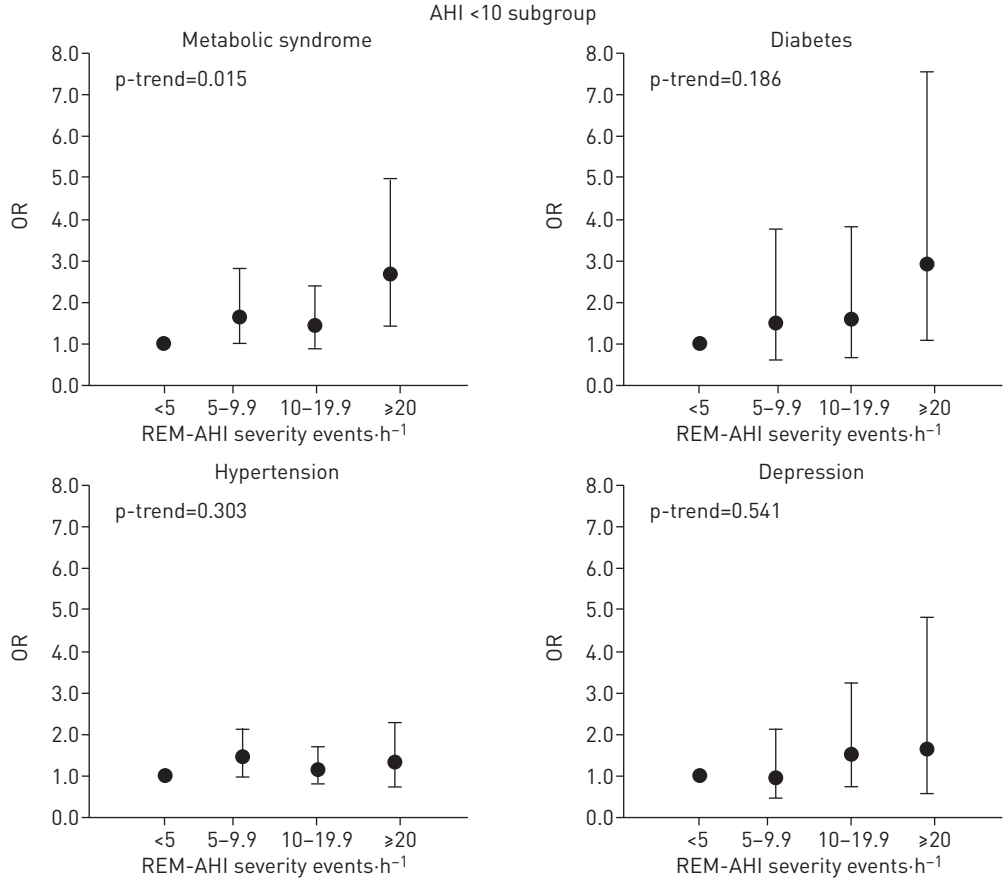

FIGURE 3 Odds ratios (ORs) and 95% CIs for rapid eye movement (REM) apnoea–hypopnoea index (AHI) severity categories (REM-AHI severity) in the subgroup with total AHI <10 events·h^{-1} (n=1047 polysomnographies (PSGs)). Circles represent the ORs and bars represent the 95% CIs. Logistic regression models were fitted to examine the associations for the entire cohort with metabolic syndrome, diabetes, hypertension and depression. Moderate-to-severe REM related sleep-disordered breathing (REM-SDB) was significantly associated with metabolic syndrome and diabetes. Diabetes, hypertension and depression showed no association with REM-SDB. Cardiovascular and metabolic comorbidities were adjusted for age, sex, body mass index, waist-to-hip ratio, total sleep time, smoking, alcohol consumption (weekly) and the logarithm of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, consumption of benzodiazepines, antidepressants and log-NREM-AHI. The number of participants with missing data in the models was as follows: metabolic syndrome (n=11), diabetes (n=11), hypertension (n=11), depression (n=189).

SDB are at higher risk of depressive disorders [1, 42–44] and have a greater prevalence of other psychiatric comorbidities [45–47]. However, the mechanisms underlying the possible association between REM-SDB and depression are not clear. Oxygen desaturation and hypoxia during sleep have been proposed as potential mechanisms for this association because interventional studies using oxygen or CPAP therapies [48, 49] found that reversing hypoxaemia in SDB improved mood disorders. Moreover, due to its likely role in emotion processing, REM sleep fragmentation could have a negative impact on mood [50]. However, we did not find an independent association of depression with ODI, T90 or arousal index (data not shown).

Strengths and limitations

The main strength of this study is the inclusion of a large sample representative of the general population and the extensive phenotyping of participants, which allowed the creation of models controlling for the main confounding factors for each analysed outcome. However, our study also has limitations that need to be acknowledged. First, the cross-sectional design does not allow any causality relationships to be determined. Secondly, the study population was aged between 40 and 85 years and essentially of white European origin with a low prevalence of obesity. Thus, generalizability of our findings to younger, more obese populations of different ethnicity is not possible. Lastly, we did not use the dichotomised definition of REM-SDB proposed by others [2–4]. However, we believe that the use of REM-AHI severity categories allows more precise analysis than a dichotomous classification.

In conclusion, our findings show that moderate-to-severe REM-SDB is highly prevalent in the general population, even in individuals classified as having absent or mild SDB, and that REM-SDB is independently associated with important cardiovascular risk factors such as metabolic syndrome and diabetes. As CPAP use is often limited to the first part of the night, leaving most REM-SDB untreated, our results strengthen the concept that patients should be encouraged to use CPAP for the whole night to obtain maximum benefit.

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