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

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Dear Prof. M. Kolb,

We thank the Journal and Reviewers for their positive feedback. The minor modifications were integrated into our manuscript as listed below.

Yours sincerely,

Prof. Heinzer for the coauthors

Reviewer: 1

The authors have done an excellent job addressing my concerns. I only found a few minor errors that the authors should correct.

1) In the abstract, please change "AHI10<10/h" to AHI<10/h.

The change was done.

2) In the Results, the description of Figure 2 is a bit confusing. The authors provide the p-values and odds ratio for just the moderate-to-severe REM SDB (REM AHI > 20). However, the figure also has a p for trend. In other words, the highest category of REM AHI is associated with diabetes and a trend for depression, but the p-value for trend (which compares all the four groups) is not significant for diabetes and depression. Perhaps what the authors can do is to rephrase the paragraph so it is more clear. For example, they could state the following: "Although the p-value for trend was not significant for diabetes or depression, the subgroup with the highest severity of REM SDB (i.e. REM AHI > 20/h) had significantly higher odds of diabetes

(OR=3.12 [1.35-7.20], p=0.008) and 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/h)." This way, the readers will not be confused by the differing p values in the text and in the figure.

We thank the Reviewer for the suggestion. The p-value for trend was significant for diabetes (p trend=0.039). Thus, we have incorporated the suggestion with some modification as follows: "Increasing REM-AHI severity was significantly associated with metabolic syndrome and diabetes, while hypertension and 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/h) 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/h)."

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

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"Take Home" Message: REM sleep-disordered breathing is highly prevalent and is associated with metabolic syndrome and diabetes.

ABSTRACT

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

Methods: 2074 home polysomnography (PSG) recordings from the population-based HypnoLaus Sleep Cohort (48.3% men, 57±11 years old) were analysed. The apnoea–hypopnoea index was measured during REM (REM-AHI) and non-REM (NREM-AHI) sleep. Regression models were used to explore the association between REM-SDB and hypertension, diabetes, metabolic syndrome and depression in the entire cohort and in subgroups with NREM-AHI<10/h and total AHI<10/h.

Results: Prevalence of REM-AHI≥20/h 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 subgroups (p-trend=0.014, <0.0001 and 0.015, respectively). An association was also found between REM-AHI≥20/h and diabetes in both NREM-AHI<10/h (OR=3.12 [1.35-7.20]) and AHI<10/h (OR=2.92 [1.12-7.63]) subgroups. Systolic and diastolic blood pressure were positively associated with REM-AHI≥20/h.

Conclusions: 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.

Keywords: REM, sleep apnea, sleep-disordered breathing, metabolic syndrome, diabetes, depression, hypertension.

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 and heart rate. SDB during rapid eye movement 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 compared with 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 blood pressure and hypertension [18-20], and REM-SDB has further 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 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-second epochs according to the 2007 AASM criteria [27]. Apnoeas, hypopnoeas, and respiratory effort-related arousals were scored according to the 2012 AASM criteria [28].

The average number of apnoeas-hypopnoeas per hour of sleep (apnoea–hypopnoea index [AHI]) was calculated for the whole night, and for REM and NREM sleep separately. Percentage of total sleep time (TST) with oxygen saturation below 90% (T90) and the number of ≥3% oxygen desaturations per hour (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 100g using a Seca® scale, 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. Hip was measured at the largest part of the hips. For waist and hip, two measures were made and the mean (expressed in centimeters) was used to assess waist-to-hip ratio (WHR). Neck circumpherence was measured at the middle of the neck between the mid-cervical spine and superior line of the cricothyroid membrane.

Blood pressure was measured thrice on the left arm in the morning and the average of the last two readings was considered. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive drugs. Diabetes was defined as fasting blood glucose ≥7 mmol/L or current antidiabetic drug treatment. Metabolic syndrome was defined according to the Adult Treatment Panel III (ATP-III) report [29]. 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) [30]. 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 Corporation, Armonk, NY, USA). Bivariate analyses were performed using Chi-squared test for categorical variables and Kruskal-Wallis for continuous variables. Pairwise comparisons were performed using 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. REM-AHI was classified into four severity categories (REM-AHI <5/h [reference group]; 5–9.9/h; 10–19.9/h; and ≥20/h) for the primary analysis (according to previous results of the HypnoLaus cohort) and used as continuous variable for a sensitivity analysis. A linear regression model was also used to assess the association between REM-AHI (as continuous and dummy variable) and diastolic and systolic blood pressure.

Analyses were performed on the entire cohort and in two subgroups: one restricted to subjects with a total AHI<10/h (absent or mild SDB), and another in those with NREM-AHI<10/h (exclusive REM-SDB). For hypertension, diabetes and metabolic syndrome, the models were adjusted for age, sex, BMI, WHR, TST, logarithme of NREM-AHI (log-NREM-AHI), smoking and alcohol consumption. An additional adjustment for antihypertensive treatment was added when SBP and DBP 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 ratio (OR) and 95% confidence interval. Statistical significance was condidered for a two-sided test $p<0.05$ and $p<0.008$ for multiple comparisons in univariate analysis.

Results

Study population

Of the 2168 subjects (48.3% men, 59±11 y.o, range 40-85, body mass index 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 with less than four hours of TST were excluded to avoid the risk of unbalanced representation of different sleep stages. We also excluded 47 patients with <30 minutes of REM sleep 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/h) was 40.8% in 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 ODI and arousal index and spent more time with oxygen saturation <90% (T90), but there was no difference in the ESS score between the REM-SDB severity categories.

Figure 1 shows the results for the association of REM-SDB with metabolic syndrome, diabetes, hypertension and depression. REM-AHI categories of 5-9.9/h (OR=1.78 [1.13-2.81], p=0.013), 10-19.9/h (OR=1.69 [1.12-2.57], p=0.013), and ≥20/h (OR=1.94 [1.29-2.92], p=0.001) were independently associated with metabolic syndrome, but not diabetes and depression. Although we found no association between hypertension and REM-SDB, there was a significant association of REM-AHI≥20/h with both systolic and diastolic blood pressure (Table 4).

NREM-AHI <10/h (exclusive REM-SDB)

A subgroup of 1241 subjects (59.8%) with NREM-AHI<10/h was analysed to better define the specific influence of REM-SDB (Table 2). In this subgroup, the prevalence of moderate-to-severe REM-SDB (REM-AHI≥20/h) 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, and a higher prevalence of hypertension, diabetes and metabolic syndrome.

TST and REM sleep time were reduced only in the REM-AHI≥20/h group, while arousal index, ODI and T90 was increased in all REM-SDB subgroups. No significant differences were found in SWS time and ESS score among the REM-SDB severity categories.

The same multivariate models were applied to this subgroup (Figure 2). Increasing REM-AHI severity was significantly associated with metabolic syndrome and diabetes, while hypertension and 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/h) 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/h).

Total AHI<10/h (absent or mild SDB)

A second subgroup of 1047 subjects (50.5%) with total AHI<10/h was analysed to evaluate the prevalence and significance of REM-SDB in subjects with absent or mild SDB (Table 3). In this subgroup the prevalence of moderate-to-severe REM-SDB (REM-AHI≥20/h) was 9.1% (n=95). As observed in the exclusive REM-SDB subgroup and the overall population, increasing REM-AHI severity was associated with higher mean age, BMI, WHR, neck circumference, and a higher prevalence of metabolic syndrome, diabetes and hypertension in univariate analysis.

Only the REM-AHI≥20/h group presented lower TST and REM sleep time compared to the other groups, while all REM-SDB subgroups presented increased arousal index compared to REM-AHI<5/h. Subjects with higher REM-AHI showed increased ODI and T90. No significant differences were found in SWS time and ESS score across the REM-AHI categories.

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

We performed the same analysis using REM-AHI as continuous variable instead of REM-AHI categories with the same covariables previously described. Using these models, we also found significant associations between REM-AHI and metabolic syndrome in the entire cohort and the two subgroups, and with diabetes in both NREM-AHI<10/h and AHI<10/h subgroups (Table S1). However, no association was significant for hypertension and 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/h) in this middle to older age general population sample was 40.6%, and that nearly 10% of patients with a global AHI of <10/h 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, 31, 32], 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/h) and in those with exclusive REM-SDB (NREM-AHI<10/h). This suggests that apnoeas and hypopnoeas occurring during REM sleep may have a specific association with the 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 (T2DM) 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/h and AHI<10/h. Recently, Mokhlesi et al described an improvement in glycaemic control in patients with T2DM and SDB after one week of 8-hour nightly continuous positive airway pressure (CPAP) [33]. However, another study, in which CPAP was used for a mean of 4.3

hours per night, showed no significant improvement in glycaemic control in patients with T2DM and SDB [34]. The better results obtained by Mokhlesi and colleagues could be related to the longer duration of CPAP usage resulting in better control of REM-SDB, because 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 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 was present only in patients with moderate-to-severe sleep apnoea and coronary or cerebrovascular disease who used CPAP for more than four hours per night [34, 35]. It is howerver unclear why this association was found mainly in the group with NREM-AHI<10 in our study.

Different hypotheses can be proposed regarding the underlying mechanisms of the associations between REM-SDB and metablic 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 shown to acutely increase insulin resistance in healthy volunteers [36]. 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 [37-39]. Furthermore, SDB in REM reversed the physiological nocturnal decline of interstitial glucose concentration (IGC), while NREM-SDB had no effect on IGC [40]. Lastly, nocturnal hyperglycaemia associated with SDB in patients with diabetes was shown to be specifically accentuated during REM sleep [41].

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 nor in the subgroups with REM-AHI<10/h or global AHI<10/h. The reason for these differences between our 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 [42]. 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 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 by Mokhlesi and colleagues on the Wisconsin cohort used 24-hour blood pressure 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 blood pressure as a continuous dependent variable, there was however a significant positive association between moderate-to-severe REM-AHI and both systolic and diastolic blood pressure. These findings appear to suggest a possible positive association between REM-SDB and blood pressure.

REM-SDB and depression

We did not find a significant association between depression and REM-SDB, besides a trend in the NREM-AHI<10/h subgroup. Our group and others have previously shown that patients with SDB are at higher risk of depressive disorders [1, 43-45] and have a greater prevalence of other psychiatric comorbidities [46-48]. 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 [49, 50] 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 [51]. However, we did not find an independent association of depression with ODI, T90, and 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 aknowledged. First, the cross-sectional design does not allow any causality relationships to be determined. Second, 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 dichotomized 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. Because CPAP use is often limited to the first part of the night (leaving the most REM-SDB untreated), our results strenghten the concept that patients should be encouraged to use CPAP for the whole night to obtain maximum benefit.

Financial support

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Table 1. Subject's characteristics in the entire cohort based on REM-AHI severity.

REM-AHI severity categories in the entire cohort						
	All	<5/h	5-9.9/h	10-19.9/h	≥20/h	p-value
Number of subjects, % (n)	100 (2074)	22.0 (456)	16.0 (331)	21.3 (441)	40.8 (846)	
Female, % (n)	52.0 (1079)	69.7 (318)*	57.1 (189)*	49.9 (220)	41.6 (352)	**<0.0001**
Age, years, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, % (n)	40.8 (846)	24.3 (111)	34.7 (115)	37.4 (165)	53.9 (455)*	**<0.0001**
Type 2 diabetes, % (n)	9.7 (200)	3.3 (15)	5.4 (18)	6.8 (30)	16.2 (137)*	**<0.0001**
Metabolic syndrome, % (n)	30.0 (623)	12.3 (56)	19.3 (64)	27.2 (120)	45.3 (383)	**<0.0001**
Depression, % (n)	6.2 (107)	6.3 (23)	4.6 (13)	6.6 (25)	6.6 (46)	0.668
Antihypertensive medication, % (n)	25.7 (532)	14.5 (66)	19.9 (66)	21.5 (95)	36.1 (305)*	**<0.0001**
Antidepressant medication, % (n)	5.7 (115)	7.1 (31)	3.4 (11)	4.6 (20)	6.4 (53)	0.096
Benzodiazepines, % (n)	8.4 (171)	7.4 (33)	8.5 (28)	8.1 (35)	8.9 (75)	0.815
Current smoking, %, (n)	18.5 (379)	20.3 (92)	18.3 (60)	17.8 (78)	17.9 (149)	0.063
Alcohol consumption before PSG, mean (SD)	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, mean (SD)	6.5 (7.9)	5.5 (7.2)	5.8 (6.9)	6.7 (8.2)	7.1 (8.4)*	**0.007**
TST, min, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, mean (SD)	4.1 (12.3)	7.2 (1.1)	9.3 (1.4)*	13.0 (3.5)*+	14.3 (7.0)*+#	**<0.0001**
ESS score, Median (IQR)	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

Definition of abbreviations: AHI = apnoea–hypopnoea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; Min = minutes; NREM = non-rapid eye movement; ODI = oxygen desaturation index per hour of 3% or greater; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SWS = slow wave sleep; T90 = percentage of total sleep time with oxygen saturation below 90%; TST = total sleep time; WHR = waist-to-hip ratio. Alcohol consumption = mean consumption of standard drink containing 10 g of alcohol.

Data analyzed by Pearson's chi-square or Kruskal-Wallis followed by Mann-Whitney pairwise comparisons. *p<0.008 compared to <5/h; #p<0.008 compared to 10-19.9/h; +p<0.008 compared to 5-9.9/h. Number of participants with missing data: alcohol consumption before PSG (31), antidepressant medication (49), benzodiazepines (27), BMI (12), smoking (22), depression (353), diabetes (2), hypertension (2), neck circumference (57), REM-AHI non-supine (89), REM-AHI supine (394), REM time in supine (1), T90 (28), WHR (2).

Table 2. Patient characteristics in NREM-AHI<10 subgroup based on REM-AHI severity.

REM-AHI severity categories in NREM-AHI<10 subgroup						
	All	<5/h	5-9.9/h	10-19.9/h	≥20/h	p-value
Number of subjects, % (n)	100 (1241)	33.2 (412)	22.2 (275)	23.4 (291)	21.2 (263)	
Female, % (n)	63.7 (790)	73.5 (303)*	60.7 (167)	58.8 (171)	56.7 (149)	**<0.0001**
Age, years, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, % (n)	32.1 (398)	22.3 (92)	32.7 (90)	33.7 (98)	45.0 (118)*	**<0.0001**
Type 2 diabetes, % (n)	5.4 (67)	2.2 (9)	3.6 (10)	5.5 (16)	12.2 (32)*	**<0.0001**
Metabolic syndrome, % (n)	20.7 (257)	10.7 (44)	17.1 (47)	22.0 (64)	38.8 (102)*	**<0.0001**
Depression, % (n)	7.0 (72)	6.6 (22)	5.4 (13)	7.3 (18)	8.8 (19)	0.547
Antihypertensive medication, % (n)	18.7 (232)	11.9 (49)	18.5 (51)	18.6 (54)	29.7 (78)	**<0.0001**
Antidepressant medication, % (n)	4.7 (57)	6.8 (27)	3.7 (10)	4.2 (12)	3.1 (8)	0.100
Benzodiazepines, % (n)	7.5 (92)	6.2 (25)	9.2 (25)	5.9 (17)	9.6 (25)	0.192
Current smoking, %, (n)	20.0 (246)	20.3 (83)	19.5 (53)	19.7 (57)	20.3 (53)	0.832
Alcohol consumption before PSG, mean (SD)	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, mean (SD)	5.7 (7.3)	5.3 (7.1)	5.8 (7.1)	6.1 (7.2)	5.9 (7.8)	0.380
TST, min, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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 3%, events/h, Median (IQR)	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, mean (SD)	2.5 (11.1)	1.1 (7.6)	1.5 (10.1)	2.9 (13.7)*+	5.2 (13.0)*+#	**<0.0001**
ESS score, Median (IQR)	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

Definition of abbreviations: AHI = apnoea–hypopnoea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; Min = minutes; NREM = non-rapid eye movement; ODI = oxygen desaturation index per hour of 3% or greater; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SWS = slow wave sleep; T90 = percentage of total sleep time with oxygen saturation below 90%; TST = total sleep time; WHR = waist-to-hip ratio. Alcohol consumption = mean consumption of standard drink containing 10 g of alcohol.

Data analyzed by Pearson's chi-square or Kruskal-Wallis followed by Mann-Whitney pairwise comparisons. *p<0.008 compared to <5/h; #p<0.008 compared to 10-19.9/h; +p<0.008 compared to 5-9.9/h.

Number of participants with missing data: alcohol consumption before PSG (20), antidepressant medication (28), benzodiazepines (16), BMI (3), smoking (9), depression (206), hypertension (1), neck circumference (35), REM-AHI non-supine (44), REM-AHI supine (213), T90 (14), WHR (1).

Table 3. Patient characteristics in AHI<10 subgroup based on REM-AHI severity.

REM-AHI severity categories in AHI<10 subgroup						
	All	<5/h	5-9.9/h	10-19.9/h	≥20/h	p-value
Number of subjects, % (n)	100 (1047)	40 (419)	26.3 (275)	24.6 (258)	9.1 (95)	
Female, % (n)	65.2 (683)	72.8 (305)*	61.5 (169)	59.3 (153)	58.9 (56)	**<0.0001**
Age, years, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, % (n)	29.8 (312)	22.9 (96)	32.4 (89)	33.7 (87)	42.1 (40)*	**<0.0001**
Type 2 diabetes, % (n)	4.3 (45)	2.4 (10)	3.6 (10)	5.4 (14)	11.6 (11)*	**0.001**
Metabolic syndrome, % (n)	17.9 (187)	11.5 (48)	17.1 (47)	21.3 (55)	17.9 (187)*	**<0.0001**
Depression, % (n)	6.4 (56)	6.5 (22)	5.4 (13)	7.2 (16)	6.3 (5)	0.887
Antihypertensive medication, % (n)	16.9 (177)	12.2 (51)	18.2 (50)	19.0 (49)	28.4 (27)*	**0.001**
Antidepressant medication, % (n)	4.9 (50)	6.9 (28)	3.7 (10)	4.3 (11)	1.1 (1)	0.058
Benzodiazepines, % (n)	7.7 (79)	6.1 (25)	9.2 (25)	6.3 (16)	13.8 (13)*	**0.045**
Current smoking, %, (n)	20.9 (217)	20.7 (86)	19.5 (53)*	21.8 (56)*	23.2 (22)*+	0.858
Alcohol consumption before PSG, mean (SD)	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, mean (SD)	5.7 (7.2)	5.4 (7.3)	5.8 (7.1)	6.0 (7.3)	5.6 (6.7)	0.497
TST, min, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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 3%, events/h, Median (IQR)	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, mean (SD)	2.1 (11.1)	1.1 (7.5)	1.5 (10.1)	2.9 (14.3)*+	5.6 (15.7)*+#	**<0.0001**
ESS score, Median (IQR)	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

Definition of abbreviations: AHI = apnoea–hypopnoea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; Min = minutes; NREM = non-rapid eye movement; ODI = oxygen desaturation index per hour of 3% or greater; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SWS = slow wave sleep; T90 = percentage of total sleep time with oxygen saturation below 90%; TST = total sleep time; WHR = waist-to-hip ratio. Alcohol consumption = mean consumption of standard drink containing 10 g of alcohol.

Data analyzed by Pearson's chi-square or Kruskal-Wallis followed by Mann-Whitney pairwise comparisons. *p<0.008 compared to <5/h; #p<0.008 compared to 10-19.9/h; +p<0.008 compared to 5-9.9/h.

Number of participants with missing data: alcohol consumption before PSG (19), antidepressant medication (27), benzodiazepines (15), BMI (3), smoking (7), depression (169), neck circumference (33), NREM-AHI supine (58), REM-AHI supine (194), T90 (12), WHR (1).

Table 4. Associations between REM-AHI and blood pressure.

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

Definition of abbreviations: AHI = apnoea–hypopnoea index; β = linear regression coefficient beta; NREM = non-rapid eye movement; REM = rapid eye movement.

Data analyzed by linear regression using REM-AHI as 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 and log-NREM-AHI.

Number of participants with missing data in the models (entire cohort, NREM-AHI<10, AHI<10): systolic blood pressure and diastolic blood pressure (16, 6, 5).

Figure captions

Figure 1. Odds ratios and 95% confidence intervals (CI) for rapid eye movement (REM) apnoea-hypopnoea index (AHI) severity categories in the entire cohort (n=2074 polysomnographies). Circles represent the odds ratio and bars the 95% CI**.** Logistic regression models 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-sleep-disordered breathing (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 logarithme of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, and consumption of benzodiazepines, antidepressants, and log-NREM-AHI. Number of participants with missing data in the models: metabolic syndrome (35), diabetes (37), hypertension (37), depression (389).

Figure 2. Odds ratios and 95% confidence intervals (CI) for rapid eye movement (REM) apnoea-hypopnoea index (AHI) severity categories in the subgroup with non-REM-AHI<10/h (n=1241 polysomnographies). Circles represent the odds ratio and bars the 95% CI**.** Logistic regression models 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-sleep-disordered breathing (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 logarithme of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, and consumption of benzodiazepines, antidepressants, and log-NREM-AHI. Number of participants with missing data in the models: metabolic syndrome (13), diabetes (13), hypertension (14), depression (226).

Figure 3. Odds ratios and 95% confidence intervals (CI) for rapid eye movement (REM) apnoea-hypopnoea index (AHI) severity categories in the subgroup with total AHI<10/h (n=1047 polysomnographies). Circles represent the odds ratio and bars the 95% CI**.** Logistic regression models fitted to examine the associations for the entire cohort with metabolic syndrome, diabetes, hypertension and depression. Moderate-to-severe REM 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 logarithme of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, and consumption of benzodiazepines, antidepressants, and log-NREM-AHI. Number of participants with missing data in the models: metabolic syndrome (11), diabetes (11), hypertension (11), depression (189).

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

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“Take Home” Message: REM sleep-disordered breathing is highly prevalent and is associated with metabolic syndrome and diabetes.

ABSTRACT

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

Methods: 2074 home polysomnography (PSG) recordings from the population-based HypnoLaus Sleep Cohort (48.3% men, 57±11 years old) were analysed. The apnoea–hypopnoea index was measured during REM (REM-AHI) and non-REM (NREM-AHI) sleep. Regression models were used to explore the association between REM-SDB and hypertension, diabetes, metabolic syndrome and depression in the entire cohort and in subgroups with NREM-AHI<10/h and total AHI<10/h.

Results: Prevalence of REM-AHI≥20/h 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 subgroups (p-trend=0.014, <0.0001 and 0.015, respectively). An association was also found between REM-AHI≥20/h and diabetes in both NREM-AHI<10/h (OR=3.12 [1.35-7.20]) and AHI<10/h (OR=2.92 [1.12-7.63]) subgroups. Systolic and diastolic blood pressure were positively associated with REM-AHI≥20/h.

Conclusions: 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.

Keywords: REM, sleep apnea, sleep-disordered breathing, metabolic syndrome, diabetes, depression, hypertension.

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 and heart rate. SDB during rapid eye movement 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 compared with 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 blood pressure and hypertension [18-20], and REM-SDB has further 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 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-second epochs according to the 2007 AASM criteria [27]. Apnoeas, hypopnoeas, and respiratory effort-related arousals were scored according to the 2012 AASM criteria [28].

The average number of apnoeas-hypopnoeas per hour of sleep (apnoea–hypopnoea index [AHI]) was calculated for the whole night, and for REM and NREM sleep separately. Percentage of total sleep time (TST) with oxygen saturation below 90% (T90) and the number of ≥3% oxygen desaturations per hour (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 100g using a Seca® scale, 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. Hip was measured at the largest part of the hips. For waist and hip, two measures were made and the mean (expressed in centimeters) was used to assess waist-to-hip ratio (WHR). Neck circumpherence was measured at the middle of the neck between the mid-cervical spine and superior line of the cricothyroid membrane.

Blood pressure was measured thrice on the left arm in the morning and the average of the last two readings was considered. Arterial hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive drugs. Diabetes was defined as fasting blood glucose ≥7 mmol/L or current antidiabetic drug treatment. Metabolic syndrome was defined according to the Adult Treatment Panel III (ATP-III) report [29]. 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) [30]. 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 Corporation, Armonk, NY, USA). Bivariate analyses were performed using Chi-squared test for categorical variables and Kruskal-Wallis for continuous variables. Pairwise comparisons were performed using 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. REM-AHI was classified into four severity categories (REM-AHI <5/h [reference group]; 5–9.9/h; 10–19.9/h; and ≥20/h) for the primary analysis (according to previous results of the HypnoLaus cohort) and used as continuous variable for a sensitivity analysis. A linear regression model was also used to assess the association between REM-AHI (as continuous and dummy variable) and diastolic and systolic blood pressure.

Analyses were performed on the entire cohort and in two subgroups: one restricted to subjects with a total AHI<10/h (absent or mild SDB), and another in those with NREM-AHI<10/h (exclusive REM-SDB). For hypertension, diabetes and metabolic syndrome, the models were adjusted for age, sex, BMI, WHR, TST, logarithme of NREM-AHI (log-NREM-AHI), smoking and alcohol consumption. An additional adjustment for antihypertensive treatment was added when SBP and DBP 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 ratio (OR) and 95% confidence interval. Statistical significance was condidered for a two-sided test p<0.05 and p<0.008 for multiple comparisons in univariate analysis.

Results

Study population

Of the 2168 subjects (48.3% men, 59±11 y.o, range 40-85, body mass index 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 with less than four hours of TST were excluded to avoid the risk of unbalanced representation of different sleep stages. We also excluded 47 patients with <30 minutes of REM sleep 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/h) was 40.8% in 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 ODI and arousal index and spent more time with oxygen saturation <90% (T90), but there was no difference in the ESS score between the REM-SDB severity categories.

Figure 1 shows the results for the association of REM-SDB with metabolic syndrome, diabetes, hypertension and depression. REM-AHI categories of 5-9.9/h (OR=1.78 [1.13-2.81], p=0.013), 10-19.9/h (OR=1.69 [1.12-2.57], p=0.013), and ≥20/h (OR=1.94 [1.29-2.92], p=0.001) were independently associated with metabolic syndrome, but not diabetes and depression. Although we found no association between hypertension and REM-SDB, there was a significant association of REM-AHI≥20/h with both systolic and diastolic blood pressure (Table 4).

NREM-AHI <10/h (exclusive REM-SDB)

A subgroup of 1241 subjects (59.8%) with NREM-AHI<10/h was analysed to better define the specific influence of REM-SDB (Table 2). In this subgroup, the prevalence of moderate-to-severe REM-SDB (REM-AHI≥20/h) 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, and a higher prevalence of hypertension, diabetes and metabolic syndrome.

TST and REM sleep time were reduced only in the REM-AHI≥20/h group, while arousal index, ODI and T90 was increased in all REM-SDB subgroups. No significant differences were found in SWS time and ESS score among the REM-SDB severity categories.

The same multivariate models were applied to this subgroup (Figure 2). Increasing REM-AHI severity was significantly associated with metabolic syndrome and diabetes, while hypertension and 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/h) 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/h).

Total AHI<10/h (absent or mild SDB)

A second subgroup of 1047 subjects (50.5%) with total AHI<10/h was analysed to evaluate the prevalence and significance of REM-SDB in subjects with absent or mild SDB (Table 3). In this subgroup the prevalence of moderate-to-severe REM-SDB (REM-AHI≥20/h) was 9.1% (n=95). As observed in the exclusive REM-SDB subgroup and the overall population, increasing REM-AHI severity was associated with higher mean age, BMI, WHR, neck circumference, and a higher prevalence of metabolic syndrome, diabetes and hypertension in univariate analysis.

Only the REM-AHI≥20/h group presented lower TST and REM sleep time compared to the other groups, while all REM-SDB subgroups presented increased arousal index compared to REM-AHI<5/h. Subjects with higher REM-AHI showed increased ODI and T90. No significant differences were found in SWS time and ESS score across the REM-AHI categories.

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

We performed the same analysis using REM-AHI as continuous variable instead of REM-AHI categories with the same covariables previously described. Using these models, we also found significant associations between REM-AHI and metabolic syndrome in the entire cohort and the two subgroups, and with diabetes in both NREM-AHI<10/h and AHI<10/h subgroups (Table S1). However, no association was significant for hypertension and 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/h) in this middle to older age general population sample was 40.6%, and that nearly 10% of patients with a global AHI of <10/h 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, 31, 32], 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/h) and in those with exclusive REM-SDB (NREM-AHI<10/h). This suggests that apnoeas and hypopnoeas occurring during REM sleep may have a specific association with the 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 (T2DM) 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/h and AHI<10/h. Recently, Mokhlesi et al described an improvement in glycaemic control in patients with T2DM and SDB after one week of 8-hour nightly continuous positive airway pressure (CPAP) [33]. However, another study, in which CPAP was used for a mean of 4.3

hours per night, showed no significant improvement in glycaemic control in patients with T2DM and SDB [34]. The better results obtained by Mokhlesi and colleagues could be related to the longer duration of CPAP usage resulting in better control of REM-SDB, because 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 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 was present only in patients with moderate-to-severe sleep apnoea and coronary or cerebrovascular disease who used CPAP for more than four hours per night [34, 35]. It is howerver unclear why this association was found mainly in the group with NREM-AHI<10 in our study.

Different hypotheses can be proposed regarding the underlying mechanisms of the associations between REM-SDB and metablic 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 shown to acutely increase insulin resistance in healthy volunteers [36]. 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 [37-39]. Furthermore, SDB in REM reversed the physiological nocturnal decline of interstitial glucose concentration (IGC), while NREM-SDB had no effect on IGC [40]. Lastly, nocturnal hyperglycaemia associated with SDB in patients with diabetes was shown to be specifically accentuated during REM sleep [41].

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 nor in the subgroups with REM-AHI<10/h or global AHI<10/h. The reason for these differences between our 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 [42]. 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 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 by Mokhlesi and colleagues on the Wisconsin cohort used 24-hour blood pressure 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 blood pressure as a continuous dependent variable, there was however a significant positive association between moderate-to-severe REM-AHI and both systolic and diastolic blood pressure. These findings appear to suggest a possible positive association between REM-SDB and blood pressure.

REM-SDB and depression

We did not find a significant association between depression and REM-SDB, besides a trend in the NREM-AHI<10/h subgroup. Our group and others have previously shown that patients with SDB are at higher risk of depressive disorders [1, 43-45] and have a greater prevalence of other psychiatric comorbidities [46-48]. 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 [49, 50] 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 [51]. However, we did not find an independent association of depression with ODI, T90, and 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 aknowledged. First, the cross-sectional design does not allow any causality relationships to be determined. Second, 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 dichotomized 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. Because CPAP use is often limited to the first part of the night (leaving the most REM-SDB untreated), our results strenghten the concept that patients should be encouraged to use CPAP for the whole night to obtain maximum benefit.

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Table 1. Subject's characteristics in the entire cohort based on REM-AHI severity.

REM-AHI severity categories in the entire cohort						
	All	<5/h	5-9.9/h	10-19.9/h	≥20/h	p-value
Number of subjects, % (n)	100 (2074)	22.0 (456)	16.0 (331)	21.3 (441)	40.8 (846)	
Female, % (n)	52.0 (1079)	69.7 (318)*	57.1 (189)*	49.9 (220)	41.6 (352)	**<0.0001**
Age, years, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, % (n)	40.8 (846)	24.3 (111)	34.7 (115)	37.4 (165)	53.9 (455)*	**<0.0001**
Type 2 diabetes, % (n)	9.7 (200)	3.3 (15)	5.4 (18)	6.8 (30)	16.2 (137)*	**<0.0001**
Metabolic syndrome, % (n)	30.0 (623)	12.3 (56)	19.3 (64)	27.2 (120)	45.3 (383)	**<0.0001**
Depression, % (n)	6.2 (107)	6.3 (23)	4.6 (13)	6.6 (25)	6.6 (46)	0.668
Antihypertensive medication, % (n)	25.7 (532)	14.5 (66)	19.9 (66)	21.5 (95)	36.1 (305)*	**<0.0001**
Antidepressant medication, % (n)	5.7 (115)	7.1 (31)	3.4 (11)	4.6 (20)	6.4 (53)	0.096
Benzodiazepines, % (n)	8.4 (171)	7.4 (33)	8.5 (28)	8.1 (35)	8.9 (75)	0.815
Current smoking, %, (n)	18.5 (379)	20.3 (92)	18.3 (60)	17.8 (78)	17.9 (149)	0.063
Alcohol consumption before PSG, mean (SD)	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, mean (SD)	6.5 (7.9)	5.5 (7.2)	5.8 (6.9)	6.7 (8.2)	7.1 (8.4)*	**0.007**
TST, min, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, mean (SD)	4.1 (12.3)	7.2 (1.1)	9.3 (1.4)*	13.0 (3.5)*+	14.3 (7.0)*+#	**<0.0001**
ESS score, Median (IQR)	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

Definition of abbreviations: AHI = apnoea–hypopnoea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; Min = minutes; NREM = non-rapid eye movement; ODI = oxygen desaturation index per hour of 3% or greater; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SWS = slow wave sleep; T90 = percentage of total sleep time with oxygen saturation below 90%; TST = total sleep time; WHR = waist-to-hip ratio. Alcohol consumption = mean consumption of standard drink containing 10 g of alcohol.

Data analyzed by Pearson's chi-square or Kruskal-Wallis followed by Mann-Whitney pairwise comparisons. *p<0.008 compared to <5/h; #p<0.008 compared to 10-19.9/h; +p<0.008 compared to 5-9.9/h. Number of participants with missing data: alcohol consumption before PSG (31), antidepressant medication (49), benzodiazepines (27), BMI (12), smoking (22), depression (353), diabetes (2), hypertension (2), neck circumference (57), REM-AHI non-supine (89), REM-AHI supine (394), REM time in supine (1), T90 (28), WHR (2).

Table 2. Patient characteristics in NREM-AHI<10 subgroup based on REM-AHI severity.

REM-AHI severity categories in NREM-AHI<10 subgroup						
	All	<5/h	5-9.9/h	10-19.9/h	≥20/h	p-value
Number of subjects, % (n)	100 (1241)	33.2 (412)	22.2 (275)	23.4 (291)	21.2 (263)	
Female, % (n)	63.7 (790)	73.5 (303)*	60.7 (167)	58.8 (171)	56.7 (149)	**<0.0001**
Age, years, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, % (n)	32.1 (398)	22.3 (92)	32.7 (90)	33.7 (98)	45.0 (118)*	**<0.0001**
Type 2 diabetes, % (n)	5.4 (67)	2.2 (9)	3.6 (10)	5.5 (16)	12.2 (32)*	**<0.0001**
Metabolic syndrome, % (n)	20.7 (257)	10.7 (44)	17.1 (47)	22.0 (64)	38.8 (102)*	**<0.0001**
Depression, % (n)	7.0 (72)	6.6 (22)	5.4 (13)	7.3 (18)	8.8 (19)	0.547
Antihypertensive medication, % (n)	18.7 (232)	11.9 (49)	18.5 (51)	18.6 (54)	29.7 (78)	**<0.0001**
Antidepressant medication, % (n)	4.7 (57)	6.8 (27)	3.7 (10)	4.2 (12)	3.1 (8)	0.100
Benzodiazepines, % (n)	7.5 (92)	6.2 (25)	9.2 (25)	5.9 (17)	9.6 (25)	0.192
Current smoking, %, (n)	20.0 (246)	20.3 (83)	19.5 (53)	19.7 (57)	20.3 (53)	0.832
Alcohol consumption before PSG, mean (SD)	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, mean (SD)	5.7 (7.3)	5.3 (7.1)	5.8 (7.1)	6.1 (7.2)	5.9 (7.8)	0.380
TST, min, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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 3%, events/h, Median (IQR)	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, mean (SD)	2.5 (11.1)	1.1 (7.6)	1.5 (10.1)	2.9 (13.7)$^{*+}$	5.2 (13.0)$^{*+\#}$	**<0.0001**
ESS score, Median (IQR)	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

Definition of abbreviations: AHI = apnoea–hypopnoea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; Min = minutes; NREM = non-rapid eye movement; ODI = oxygen desaturation index per hour of 3% or greater; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SWS = slow wave sleep; T90 = percentage of total sleep time with oxygen saturation below 90%; TST = total sleep time; WHR = waist-to-hip ratio. Alcohol consumption = mean consumption of standard drink containing 10 g of alcohol.

Data analyzed by Pearson's chi-square or Kruskal-Wallis followed by Mann-Whitney pairwise comparisons. *p<0.008 compared to <5/h; #p<0.008 compared to 10-19.9/h; +p<0.008 compared to 5-9.9/h.

Number of participants with missing data: alcohol consumption before PSG (20), antidepressant medication (28), benzodiazepines (16), BMI (3), smoking (9), depression (206), hypertension (1), neck circumference (35), REM-AHI non-supine (44), REM-AHI supine (213), T90 (14), WHR (1).

Table 3. Patient characteristics in AHI<10 subgroup based on REM-AHI severity.

REM-AHI severity categories in AHI<10 subgroup						
	All	<5/h	5-9.9/h	10-19.9/h	≥20/h	p-value
Number of subjects, % (n)	100 (1047)	40 (419)	26.3 (275)	24.6 (258)	9.1 (95)	
Female, % (n)	65.2 (683)	72.8 (305)*	61.5 (169)	59.3 (153)	58.9 (56)	**<0.0001**
Age, years, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, % (n)	29.8 (312)	22.9 (96)	32.4 (89)	33.7 (87)	42.1 (40)*	**<0.0001**
Type 2 diabetes, % (n)	4.3 (45)	2.4 (10)	3.6 (10)	5.4 (14)	11.6 (11)*	**0.001**
Metabolic syndrome, % (n)	17.9 (187)	11.5 (48)	17.1 (47)	21.3 (55)	17.9 (187)*	**<0.0001**
Depression, % (n)	6.4 (56)	6.5 (22)	5.4 (13)	7.2 (16)	6.3 (5)	0.887
Antihypertensive medication, % (n)	16.9 (177)	12.2 (51)	18.2 (50)	19.0 (49)	28.4 (27)*	**0.001**
Antidepressant medication, % (n)	4.9 (50)	6.9 (28)	3.7 (10)	4.3 (11)	1.1 (1)	0.058
Benzodiazepines, % (n)	7.7 (79)	6.1 (25)	9.2 (25)	6.3 (16)	13.8 (13)*	**0.045**
Current smoking, %, (n)	20.9 (217)	20.7 (86)	19.5 (53)*	21.8 (56)*	23.2 (22)*+	0.858
Alcohol consumption before PSG, mean (SD)	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, mean (SD)	5.7 (7.2)	5.4 (7.3)	5.8 (7.1)	6.0 (7.3)	5.6 (6.7)	0.497
TST, min, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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, Median (IQR)	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 3%, events/h, Median (IQR)	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, mean (SD)	2.1 (11.1)	1.1 (7.5)	1.5 (10.1)	2.9 (14.3)*+	5.6 (15.7)*+#	**<0.0001**
ESS score, Median (IQR)	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

Definition of abbreviations: AHI = apnoea–hypopnoea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; Min = minutes; NREM = non-rapid eye movement; ODI = oxygen desaturation index per hour of 3% or greater; PSG = polysomnography; REM = rapid eye movement; SD = standard deviation; SWS = slow wave sleep; T90 = percentage of total sleep time with oxygen saturation below 90%; TST = total sleep time; WHR = waist-to-hip ratio. Alcohol consumption = mean consumption of standard drink containing 10 g of alcohol.

Data analyzed by Pearson's chi-square or Kruskal-Wallis followed by Mann-Whitney pairwise comparisons. *p<0.008 compared to <5/h; #p<0.008 compared to 10-19.9/h; +p<0.008 compared to 5-9.9/h.

Number of participants with missing data: alcohol consumption before PSG (19), antidepressant medication (27), benzodiazepines (15), BMI (3), smoking (7), depression (169), neck circumference (33), NREM-AHI supine (58), REM-AHI supine (194), T90 (12), WHR (1).

Table 4. Associations between REM-AHI and blood pressure.

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

Definition of abbreviations: AHI = apnoea–hypopnoea index; β = linear regression coefficient beta; NREM = non-rapid eye movement; REM = rapid eye movement.

Data analyzed by linear regression using REM-AHI as 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 and log-NREM-AHI.

Number of participants with missing data in the models (entire cohort, NREM-AHI<10, AHI<10): systolic blood pressure and diastolic blood pressure (16, 6, 5).

Figure captions

Figure 1. Odds ratios and 95% confidence intervals (CI) for rapid eye movement (REM) apnoea-hypopnoea index (AHI) severity categories in the entire cohort (n=2074 polysomnographies). Circles represent the odds ratio and bars the 95% CI**.** Logistic regression models 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-sleep-disordered breathing (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 logarithme of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, and consumption of benzodiazepines, antidepressants, and log-NREM-AHI. Number of participants with missing data in the models: metabolic syndrome (35), diabetes (37), hypertension (37), depression (389).

Figure 2. Odds ratios and 95% confidence intervals (CI) for rapid eye movement (REM) apnoea-hypopnoea index (AHI) severity categories in the subgroup with non-REM-AHI<10/h (n=1241 polysomnographies). Circles represent the odds ratio and bars the 95% CI**.** Logistic regression models 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-sleep-disordered breathing (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 logarithme of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, and consumption of benzodiazepines, antidepressants, and log-NREM-AHI. Number of participants with missing data in the models: metabolic syndrome (13), diabetes (13), hypertension (14), depression (226).

Figure 3. Odds ratios and 95% confidence intervals (CI) for rapid eye movement (REM) apnoea-hypopnoea index (AHI) severity categories in the subgroup with total AHI<10/h (n=1047 polysomnographies). Circles represent the odds ratio and bars the 95% CI**.** Logistic regression models fitted to examine the associations for the entire cohort with metabolic syndrome, diabetes, hypertension and depression. Moderate-to-severe REM 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 logarithme of non-REM-AHI (log-NREM-AHI). Depression was adjusted for age, gender, and consumption of benzodiazepines, antidepressants, and log-NREM-AHI. Number of participants with missing data in the models: metabolic syndrome (11), diabetes (11), hypertension (11), depression (189).

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Supplementary Table S1. Impact of a 10 events per hour increase in REM-AHI on the prevalence of comorbidities.

	Metabolic Syndrome		Diabetes		Hypertension		Depression	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
REM-AHI, events/h								
Entire cohort	1.10 (1.02 - 1.18)	**0.012**	1.08 (1.00 - 1.18)	0.127	1.04 (1.00 - 1.11)	0.258	1.10 (1.00 - 1.25)	0.160
NREM-AHI<10 subgroup	1.26 (1.12 - 1.40)	**<0.0001**	1.26 (1.07 - 1.46)	**0.007**	1.08 (1.00 - 1.21)	0.195	1.18 (1.00 - 1.40)	0.117
AHI<10 subgroup	1.31 (1.08 - 1.55)	**0.009**	1.41 (1.05 - 1.79)	**0.024**	1.10 (0.99 - 1.30)	0.317	1.20 (0.98 - 1.60)	0.302

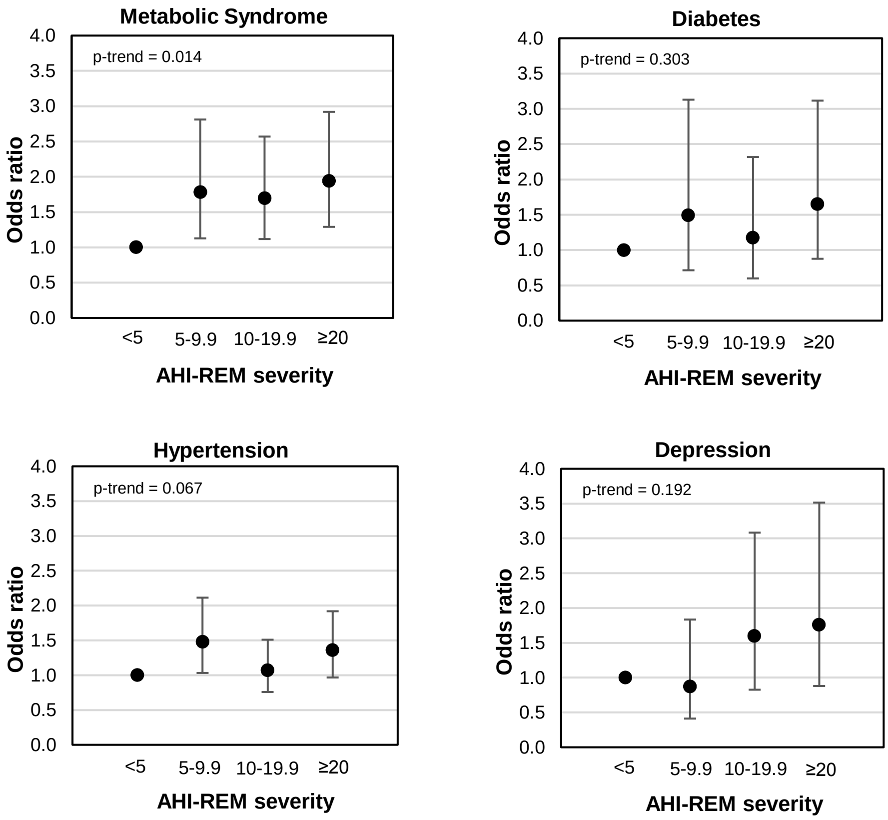
Definition of abbreviations: AHI = apnoea–hypopnoea index; CI = confidence interval; OR = Odds ratio; REM = rapid eye movement.
Data analyzed by multivariable-adjusted logistic regression. Cardiovascular and metabolic comorbidities were adjusted for age, sex, body mass index, waist-to-hip ratio, total sleep time, smoking, alcohol consumption (weekly) and non-REM AHI (NREM-AHI). Depression was adjusted for age, gender, consumption of benzodiazepines and antidepressants and log-NREM-AHI.
Number of participants with missing data in the models (entire cohort, NREM-AHI<10, AHI<10): systolic blood pressure and diastolic blood pressure (16, 6, 5).
Number of participants with missing data in the models of the entire cohort (REM-AHI, REM-AHI in supine, REM-AHI non-supine): metabolic syndrome (entire cohort: 35, 424, 35; NREM-AHI<10 subgroup: 13, 223, 13; AHI<10 subgroup: 11, 203, 11); diabetes (entire cohort: 37, 426, 37; NREM-AHI<10 subgroup: 13, 223, 13; AHI<10 subgroup: 11, 203, 11); hypertension (entire cohort: 37, 426, 37; NREM-AHI<10 subgroup: 14, 224, 14; AHI<10 subgroup: 11, 203, 11); depression (entire cohort: 389, 720, 389; NREM-AHI<10 subgroup: 226, 410, 226; AHI<10 subgroup: 189, 358, 189).

Supplementary Table S2. Associations between REM-AHI and blood pressure in participants free of antihypertensive drug use.

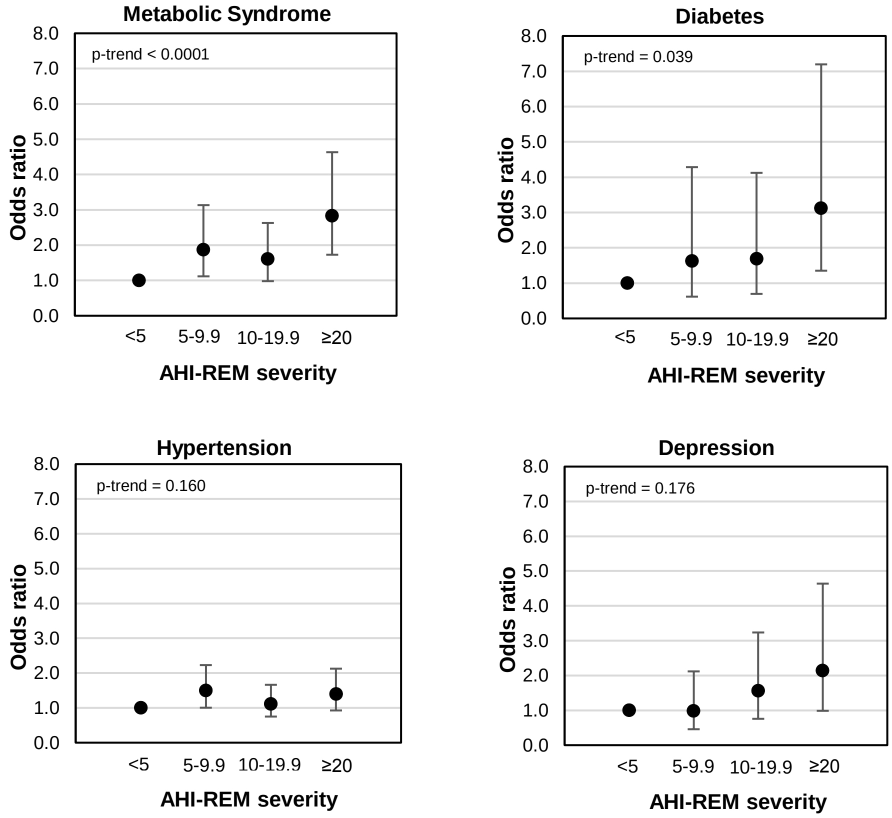
	Entire cohort n=1531		NREM-AHI<10 subgroup n=1004		AHI<10 subgroup n=866	
	β	**p-value**	**β**	**p-value**	**β**	**p-value**
Systolic blood pressure	0.02	0.285	0.00	0.864	0.01	0.772
REM-AHI (continuous)	0.01	0.785	-0.01	0.886	0.04	0.499
5-9.9/h	1.27	0.274	1.03	0.393	0.96	0.422
10-19.9/h	0.81	0.469	1.90	0.125	2.02	0.108
≥20/h	0.47	0.680	0.33	0.815	0.18	0.925
Diastolic blood pressure						
REM-AHI (continuous)	0.02	0.285	0.00	0.864	0.01	0.772
5-9.9/h	0.92	0.229	1.02	0.202	0.96	0.225
10-19.9/h	0.56	0.446	1.04	0.202	1.06	0.196
≥20/h	1.00	0.183	0.29	0.754	-0.35	0.779

Definition of abbreviations: AHI = apnoea–hypopnoea index; β = linear regression coefficient beta; NREM = non-rapid eye movement; REM = rapid eye movement.
Data analyzed by linear regression using REM-AHI as continuous or dummy variable with adjustment for age, sex, body mass index, waist-to-hip ratio, total sleep time, smoking, alcohol consumption (weekly), and log-NREM-AHI.
Number of participants with missing data in the models (entire cohort, NREM-AHI<10, AHI<10): systolic blood pressure and diastolic blood pressure (11, 5, 4).

ENTIRE COHORT



NREM-AHI<10 SUBGROUP



AHI<10 SUBGROUP