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SCIENTIFIC INVESTIGATIONS

Prevalence and Clinical Significance of Respiratory Effort-Related Arousals in the General Population

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Study Objectives: To determine the prevalence and clinical associations of respiratory effort-related arousals (RERA) in a general population sample.
Methods: A total of 2,162 participants (51.2% women, 58.5 ± 11.0 years old, body mass index [BMI] 25.6 ± 4.2 kg/m^2) of a general population-based cohort (HypnoLaus, Switzerland) underwent full polysomnography at home. Each subject with a RERA index ≥ 5 events/h was compared with an age-, sex- and apnea-hypopnea index (AHI)-matched control without RERA.
Results: A RERA index ≥ 5 events/h was present in 84 participants (3.8%; 95% confidence interval: 3.2–4.8%). In 17 participants (0.8%; 95% confidence interval: 0.5–1.3%), RERAs were the predominant sleep breathing disorder and only one of them complained of excessive daytime sleepiness. Compared to matched controls, subjects with a RERA index ≥ 5 events/h were similar in terms of BMI (26.5 ± 3.5 versus 26.3 ± 4.8 kg/m^2, P = .73), neck circumference (38.5 ± 3.3 versus 37.6 ± 3.7 cm, P = .10) and Epworth Sleepiness Scale score (6.7 ± 3.7 versus 6.0 ± 3.7, P = .22). Also, no differences were found for hypertension (21.4% versus 27.4%, P = .47), diabetes (7.1% versus 7.1%, P = 1.00), or metabolic syndrome (31.0% versus 23.8%, P = .39).
Conclusions: In a middle-aged population-based cohort, the prevalence of a RERA index ≥ 5 events/h was low (3.8%) and was not associated with negative clinical outcomes when using the currently recommended scoring criteria of the American Academy of Sleep Medicine.
Keywords: cardiovascular risk, excessive daytime sleepiness, general population, polysomnography, RERA, sleep apnea, sleep-disordered breathing, upper airway resistance syndrome
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BRIEF SUMMARY
Current Knowledge/Study Rationale: Several previous studies have tried to characterize respiratory effort-related arousals (RERAs), but their relevance as a specific disease and their cardiovascular consequences are still debated. We aimed to determine the prevalence and clinical associations of RERAs in a large, general population-based sample investigated by polysomnography.
Study Impact: The prevalence of RERAs was low (3.8%) and no association with sleepiness, hypertension, diabetes, and metabolic syndrome was found. This may be because of the current American Academy of Sleep Medicine criteria that include arousals in the definition of hypopneas.

INTRODUCTION

Sleep-disordered breathing (SDB) is increasingly recognized as a prevalent disease in the middle- to older-age adult population, affecting one in four women and up to one-half of men according to recent large general population-based studies.[1–3] In addition to the typical association with daytime sleepiness attributed to sleep fragmentation, SDB has been associated with hypertension and an increased cardiovascular risk in epidemiological studies.[1,4–7] Obstructive sleep apnea (OSA) represents the most severe form of the sleep breathing disturbances spectrum, which can be seen as a continuum, with simple snoring as its lightest form and repetitive respiratory effort-related arousals (RERAs) as an intermediate feature. RERAs are characterized by respiratory events without concomitant oxygen desaturation, which may lead to daytime sleepiness and functional impairment.[8] Several previous studies have attempted to characterize RERAs, but their relevance as a specific disorder and their cardiovascular consequences are still a matter of debate. Moreover, the prevalence of RERAs in the general population has not yet been described.[9]

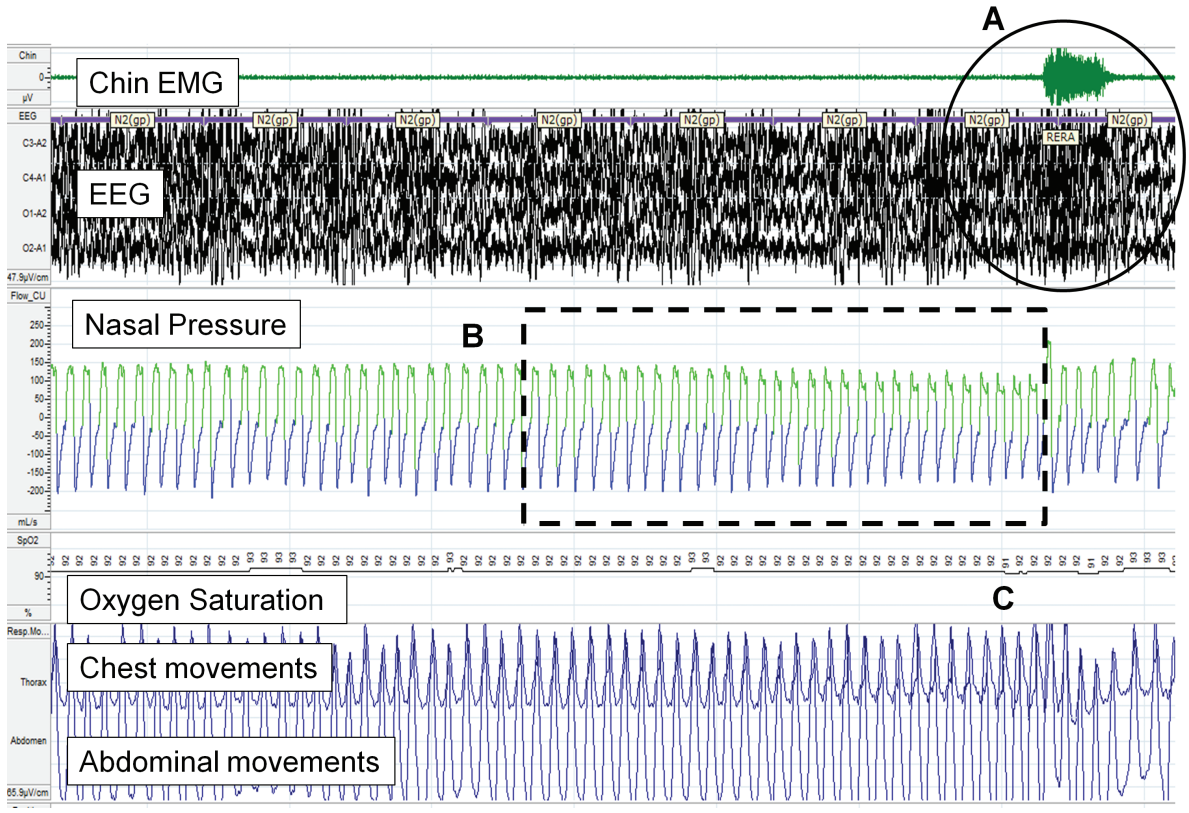
In this analysis, we aimed to determine the prevalence of RERAs and their association with cardiovascular risk factors in a large, general population-based sample investigated by polysomnography (PSG).

METHODS

Participants

Data from the population-based cross-sectional HypnoLaus study, performed between 2009 and 2013 as an ancillary study of the CoLaus/PsyCoLaus cohort were analyzed. CoLaus/PsyCoLaus is a population-based cohort, with the primary aim to

Figure 1—Polysomnography recording showing a RERA event.



Polysomnography sample from a study patient showing a RERA: EEG arousal **(A)** following an episode of flattening of the inspiratory portion of the nasal pressure **(B)**, which was not associated with oxygen desaturation **(C)**. EEG = electroencephalography, RERA = respiratory effort-related arousal.

explore the epidemiology and genetic determinants of cardiovascular risk factors.[10] It included participants aged 35 to 75 years at baseline, recruited by simple, nonstratified random selection of the inhabitants of the city of Lausanne, Switzerland.

The HypnoLaus cohort included a subgroup of 2,162 participants of the CoLaus/PsyCoLaus cohort, randomly selected to be representative of the general population of Lausanne. Details on participant selection, assessment process, and clinical data measurements have been described previously.[1]

The study complied with the Declaration of Helsinki and was approved by the local institutional ethics committee (Commission cantonale d'éthique de la recherche sur l'être humain, Lausanne). All participants provided written informed consent.

Measurements and Equipment

All participants underwent unattended home polysomnography (PSG), recorded with a digital system device (Titanium; Embla Systems, Flaga, Reykjavik, Iceland), manually scored by a trained technician using Somnologica software (Version 5.1.1, by Embla Flaga, Reykjavik, Iceland) and reviewed by a sleep expert MD (JHR). Random quality controls were also performed by a second sleep specialist (RH). Sleep stages and arousals were scored according to the American Academy of Sleep Medicine (AASM) 2007 criteria.[11–13] Chest and abdominal motion bands, finger pulse oximetry, and a nasal pressure cannula were applied to analyze respiration and to assess SDB according to the AASM 2012 consensus criteria[8]: hypopneas were scored when the nasal pressure signal dropped by ≥ 30% of pre-event baseline for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal; RERAs were defined as events lasting at least 10 seconds, characterized by flattening of the inspiratory portion of the nasal pressure followed by an arousal, which did not meet the flow criteria for an apnea or hypopnea and were not associated with an oxygen desaturation[8] (**Figure 1**). The apnea-hypopnea index (AHI) was computed as index of apneas and hypopneas per hour of sleep and the respiratory disturbance index (RDI) was computed as the index of respiratory events (AHI + RERA) per hour of sleep.[8] RERA was considered as the predominant sleep breathing disorder in the presence of a RERA index > 5 events/h accounting for > 50% of the RDI.[9]

Cardiovascular Risk Factors and Other Variables

Arterial hypertension was defined as a systolic blood pressure (BP) ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg during the study visit, or current use of antihypertensive medication. Diabetes was defined as a fasting blood glucose level ≥ 7 mmol/L (126 mg/dL) or current use of antidiabetic medication. The body mass index (BMI) was calculated from measured weight and height. The metabolic syndrome was defined according to the Adult Treatment Panel III report (ATP-III) in the presence of at least three of the following five factors: abdominal obesity

(waist circumference > 102 cm in men and > 88 cm in women), elevated triglycerides (≥ 1.70 mmol/L, > 150 mg/dL), reduced HDL cholesterol (< 1.03 mmol/L [40 mg/dL] in men and < 1.20 mmol/L [50 mg/dL] in women), elevated BP (≥ 130/ ≥ 85 mmHg) (or hypertension), or elevated fasting glucose (≥ 5.60 mmol/L or type 2 diabetes mellitus).

Smoking habit was self-reported and dichotomized as current smoker/ex-smoker or never smoker. Alcohol consumption was assessed by questionnaire. Data on medication taken before the sleep recording were collected using a questionnaire administered in the morning. Benzodiazepines and hypnotic agents were considered as sleep medications. Excessive daytime sleepiness was defined as an Epworth Sleepiness Scale score > 10.

Statistics

For each participant of the HypnoLaus cohort having a RERA index ≥ 5 events/h ("RERA cases"), one age-, sex- and AHI-matched (± 2 events/h) control with a RERA < 1 event/h was identified. Mean and standard deviation were used to describe continuous variables, and percentages to describe dichotomous or categorical variables. We used a *t* test and a chi-square test to compare the characteristics of groups as appropriate. The independent associations of AHI and RERA with cardiovascular comorbidities (hypertension, diabetes, and metabolic syndrome) were explored by multivariate logistic regression adjusting for BMI, smoking, alcohol consumption, and sleep medication use. A second age-, sex- and RDI-matched (± 2 events/h) control group was identified having RERA < 1 event/h, confirming the statistical power of the study to identify a difference in the prevalence of comorbidities between the study groups. Results are presented in the supplemental material (**Table S1**). Statistical analysis was conducted using R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was established for a two-sided test with $P < .05$.

RESULTS

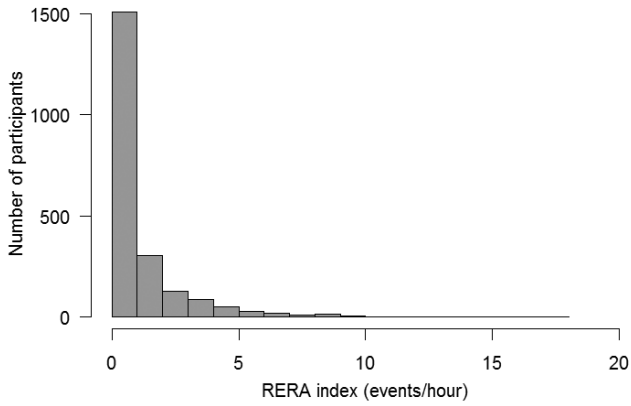
Prevalence of RERA in the General Population

In the 2,162 participants of the HypnoLaus general population-based sample, the mean RERA index was 1.6 ± 1.7 events/h (**Figure 2**). A RERA index ≥ 5 events/h was present in 84 subjects, corresponding to 3.8% of the sample (95% confidence interval [CI]: 3.2% to 4.8%). These subjects were included in the successive analysis as "RERA cases" and matched to controls. Demographic, anthropometric, and relevant medical data of cases and controls are detailed in **Table 1**.

The mean AHI of the RERA cases was 16.1 ± 12.5 events/h and the mean RDI was 24.7 ± 13.2 events/h. Among these 84 cases, 36 (42.9%) had moderate to severe SDB (AHI ≥ 15 events/h) and 10 (11.9%) had severe SDB (AHI ≥ 30 events/h) (**Figure 3**).

In 17 participants (0.8% of the general population; 95% CI: 0.5% to 1.3%), RERAs accounted for more than 50% of the RDI, and was thus considered as the predominant SDB. Among these 17 participants showing RERA as the predominant SDB, only 1 presented with excessive daytime sleepiness, corresponding to a prevalence of 0.5% in our sample.

Figure 2—Frequency of the RERA index in the HypnoLaus cohort.



RERA = respiratory effort-related arousal.

Characteristics of RERA Patients

There were no significant differences between RERA cases and control subjects regarding anthropometric characteristics such as BMI, neck circumference and Mallampati score, whereas waist to hip ratio was significantly higher in RERA cases than in controls (**Table 1**).

There was no significant difference in the prevalence of hypertension, metabolic syndrome, and diabetes between participants with RERA and matched control subjects (**Table 2**).

In the analyzed population, the risk of hypertension, metabolic syndrome, and diabetes increased significantly with increasing AHI, and the RERA index showed no additional independent association with any of the three cardiovascular or metabolic comorbidities (**Table 3**).

Participants with RERA had a higher arousal index and a greater amount of stage N1 sleep than controls, although we observed no significant difference in total sleep time (TST), sleep efficiency, and sleep latency. Furthermore, the Epworth Sleepiness Scale score and the prevalence of excessive daytime sleepiness were similar in the two groups (**Table 2**).

DISCUSSION

In this large population-based sample, we found that the prevalence of a RERA index > 5 events/h was 3.8% and that RERA was the predominant type of respiratory event in fewer than 1% of the population. Most of the participants were asymptomatic, as only 1 of 2,162 participants presented with excessive daytime sleepiness in association with RERAs as the predominant sleep breathing disorder, corresponding to a prevalence of 0.5%. Compared to AHI-matched controls, subjects with a RERA > 5 events/h were similar in terms of BMI, neck circumference and Epworth Sleepiness Scale score and they did not show an increased prevalence of hypertension, diabetes, or metabolic syndrome.

Table 1—Characteristics of the study population.

	RERA Cases (n = 84)	AHI-Matched Controls (n = 84)	*P*
Male sex, n (%)	52 (61.9)	52 (61.9)	1.000
Age (years)	52.7 (8.4)	53.2 (8.6)	.698
Anthropometric			
Mallampati	2.6 (1.0)	2.6 (0.9)	.700
Neck circumference (cm)	38.5 (3.3)	37.6 (3.7)	.102
BMI (kg/m^2)	26.5 (3.5)	26.3 (4.8)	.733
Waist-hip ratio	0.94 (0.06)	0.92 (0.07)	.041
Clinical Features			
Active smoking, n (%)	21 (25.0)	17 (20.2)	.580
Alcohol consumption ≥ 2 units/day, n (%)	9 (10.7)	9 (10.7)	1.000
Sleep medication use, n (%)	4 (4.8)	4 (4.8)	1.000
Current depression, n (%)	2 (3.0)	2 (2.8)	1.000
Sleep Breathing Disorders			
AHI (events/h)	16.1 (12.2)	16.0 (12.4)	.972
RDI (events/h)	23.2 (12.7)	16.4 (13.3)	.001
RERA index (events/h)	7.1 (2.1)	0.4 (0.3)	< .001
OAI (events/h)	2.4 (4.2)	2.3 (4.7)	.883
HI (events/h)	13.3 (9.5)	12.9 (8.8)	.801
ODI 3% (events/h)	13.8 (11.0)	16.2 (14.7)	.236
Mean SpO_2 (%)	94.3 (1.4)	94.0 (1.8)	.236
Time with SpO_2 < 90% (%)	1.7 (4.6)	4.2 (10.9)	.064
Sleep Characteristics			
TST (minutes)	401 (66)	405 (78)	.686
Sleep efficiency (%)	87.2 (8.8)	86.8 (9.1)	.778
Arousal index (events/h)	26.1 (9.2)	20.1 (9.0)	< .001
Sleep onset latency (minutes)	16.6 (16.5)	16.1 (24.2)	.866
Stage N1 sleep (minutes)	52.0 (22.7)	44.1 (23.2)	.027
Stage N1 sleep (% of TST)	13.3 (6.2)	11.1 (5.5)	.018
Slow wave sleep (minutes)	81 (30)	88 (36)	.165
Slow wave sleep (% of TST)	20.2 (7.1)	21.8 (8.5)	.212
REM sleep (minutes)	90 (27)	94 (32)	.354
REM sleep (% of TST)	22.4 (4.9)	22.9 (5.9)	.516
Periodic leg movements index (events/h)	5.8 (16.0)	7.9 (15.6)	.380

Values are presented as mean (standard deviation) unless otherwise indicated. *P* by Student *t* or chi-squared test. AHI = apnea-hypopnea index, BMI = body mass index, RDI = respiratory disturbance index, RERA = respiratory effort-related arousal, OAI = obstructive apnea index, HI = hypopnea index, ODI = oxygen desaturation index, SpO_2 = nocturnal oxygen saturation, REM = rapid eye movement, TST = total sleep time.

Prevalence of RERA in the General Population

Current knowledge on RERA is mainly based on descriptions of case series from sleep centers, including mainly selected, symptomatic populations. In a retrospective review of polysomnographies performed in an academic military sleep disorder center, Kristo et al. found an 8.4% prevalence of RERA as the predominant sleep breathing disorder among veterans referred for suspected sleep apnea with excessive daytime sleepiness.[14] We report here the first evaluation of the prevalence of RERA in an unselected general population sample. The results show an extremely low prevalence rate, suggesting that this condition is probably a rare independent cause of daytime sleepiness. In a previous Brazilian population study, Palombini et al. described that an inspiratory flow limitation (not specifically within the definition of RERA) is frequent even in asymptomatic individuals and may account for up to 30% of their TST.[15] However, the authors analyzed neither the prevalence of RERAs nor the associations of inspiratory flow limitation with symptoms or clinical outcomes.

The results of our study may reflect the evolution of the recording techniques and scoring rules in recent years. Previous studies on RERA used older scoring criteria in which arousals could not be used in the definition of hypopneas, whereas we used the AASM hypopnea definition that includes arousals. When a 4% O_2 desaturation was required to score hypopneas using the 2007 AASM recommended criteria, many of the respiratory events ending with an arousal but with a smaller O_2 desaturation were then classified as RERA, making the AHI lower and the RDI higher. The low prevalence of RERA we found may thus be caused by this change in the scoring criteria. However, the use of nasal pressure cannulas instead of thermistors has increased the sensitivity of the flow sensor[8] and episodes of inspiratory flow limitations are easier to detect than previously, which should conversely increase the RERA index compared with earlier studies. However, it seems that

most of these events are now classified as hypopneas with the updated AASM scoring criteria.

Clinical Significance of RERAs

Previous case series reported an increased rate of excessive daytime sleepiness and reduced psychomotor performances in patients presenting with increased upper airways resistance as the only sleep breathing disorder.[16–18] Some uncontrolled studies also found an improvement of daytime symptoms following the treatment of upper airways resistance syndrome with continuous positive air pressure.[19–21] In addition to the daytime symptoms, Guilleminault et al.[22] also described repetitive increases in blood pressure concomitant with RERA episodes during sleep, and suggested that this type of respiratory event may play a role in the development of cardiovascular comorbidities. In older studies on individuals without SDB, sleep fragmentation has been associated with hypertension[23,24] and with a decrease in insulin sensitivity.[25] Despite these interesting pathophysiological observations, more studies are needed to confirm the hypothesis of a causal association between RERAs and significant cardiovascular or metabolic disorders.[9,22,26,27]

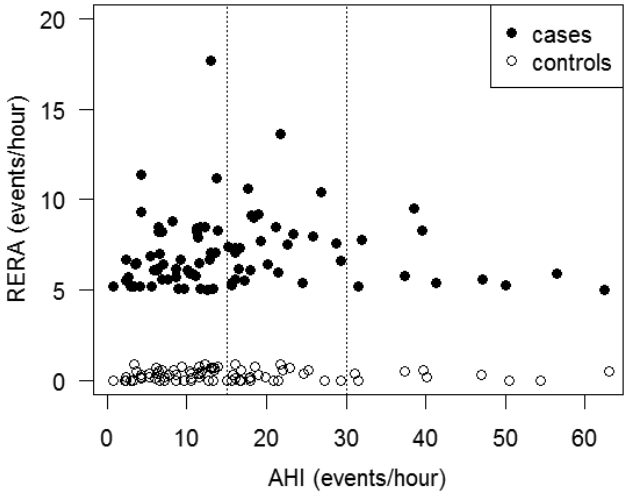
In the subgroup analysis comparing the RERA cases with AHI-matched controls there was no significant difference regarding clinical outcomes. When comparing the association between RERA and the other respiratory events included in the AHI, we could replicate the association between the severity of the SDB and cardiovascular and metabolic comorbidities as previously reported in the first analysis of the HypnoLaus population, in which the AHI was independently associated with the presence of hypertension, diabetes, and metabolic syndrome.[1] However, no independent association was found between the RERA index and the aforementioned comorbidities, suggesting that the presence of RERA on top of apneas and hypopneas does not have a significant association with neither daytime sleepiness nor with the prevalence of cardiovascular or metabolic comorbidities in our population.

The higher total arousal index observed in the RERA cases may be explained by the definition of this group, and may also explain the greater amount of stage N1 sleep we observed. We also observed a slightly higher waist to hip ratio in RERA cases compared to matched controls, suggesting a greater truncular obesity in this population yielding a possible decrease in lung volume and a higher upper airway compliance.[28] This should, however, be confirmed in future studies.

Scoring RERAs

According to the AASM 2007 guidelines,[13] upper airway resistance syndrome is subsumed under the diagnosis of OSA, and the RDI is defined as the sum of the AHI and RERA. The scoring of RERAs is, however, considered optional, and whether to use AHI or RDI to diagnose OSA remains a matter of debate. Although there is some evidence that inspiratory

Figure 3—Distribution of the RERA index according to AHI in cases and controls.



AHI = apnea-hypopnea index, RERA = respiratory effort-related arousal.

Table 2—Daytime symptoms, cardiovascular and metabolic comorbidities.

	RERA Cases (n = 84)	AHI-Matched Controls (n = 84)	*P*
Epworth Sleepiness Scale score, mean (SD)	6.7 (3.7)	6.0 (3.7)	.224
Excessive daytime sleepiness, n (%)	12 (15.4)	8 (10.8)	.553
Metabolic syndrome, n (%)	26 (31.0)	20 (23.8)	.387
Hypertension, n (%)	18 (21.4)	23 (27.4)	.472
Diabetes, n (%)	6 (7.1)	6 (7.1)	1.000

P by Student *t* or chi-square test. AHI = apnea-hypopnea index, RERA = respiratory effort-related arousal, SD = standard deviation.

Table 3—Association between AHI, RERA, and cardiovascular comorbidities (multivariate analysis).

	Hypertension		Metabolic Syndrome		Diabetes	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
AHI	1.589 (1.142–2.211)	.006	1.404 (1.001–1.970)	.049	1.800 (1.146–2.823)	.011
RERA	0.910 (0.348–2.823)	.986	1.753 (0.620–4.952)	.290	0.832 (0.134–5.184)	.844

OR (95% CI) for an increment of 10 events/h. Statistical analysis by multivariate logistic regression adjusting for body mass index, smoking, alcohol consumption and sleep medication use. AHI = apnea-hypopnea index, CI = confidence interval, OR = odds ratio, RERA = respiratory effort-related arousal.

flow limitation is abnormal and leads to pathologic changes in sleep and wakefulness, the controversy of whether to score or ignore RERAs is still a topic of debate and will only be solved by investigating prospectively the potential adverse outcomes associated with respiratory-related arousals.

Although our epidemiological data do not show clinical associations between RERAs and clinical outcomes, we obviously cannot exclude that individual patients exhibiting RERA and otherwise unexplained daytime sleepiness may benefit from a treatment. On the basis of the existing literature, an empirical treatment trial of RERAs seems reasonable in adults presenting with excessive daytime sleepiness without other identified causes. Such cases seem to be extremely rare in the general population (0.05% in our sample).

Strengths and Limitations

Our results should be interpreted in view of the study strengths and limitations: despite the use of a gold-standard sleep assessment technique on a large general population-based sample, the main limitation of our study is its cross-sectional design, which does not allow us to conclude a causal association between SDB and cardiovascular/metabolic comorbidities. A second limitation is that the prevalence of RERAs, and thus their clinical importance, may have been reduced compared to previous reports by the use the AASM 2012 hypopnea definition (including arousals as a scoring criterion) instead of the preceding definition (which did not include arousals in the definition of hypopneas), but this reflects the current state of the art and the exact framework in which the ongoing controversy takes place. The low rate of RERA we found could also be due a lower rate of arousals in general, because the recordings were obtained in the participant's home environment, which can be less stressful than a sleep laboratory. Third, it is possible that, considering the increase in the upper airway compliance with age, our middle- to older-age sample showed mainly full apneas and hypopneas and that the prevalence of RERA in younger individuals could have been higher. Finally, it should be noted that our results obtained from a population-based sample do not necessarily reflect the daily practice of a sleep disorder's center, where the attending patients are preselected. Two technical limitations should also be acknowledged: first, although the AASM definition of RERA was strictly applied by our trained certified technicians and sleep doctors, the detection of flow limitation as a criterion for RERA detection may still be subject to interobserver variations. Second, the original description of RERA depended on esophageal pressure signal to determine respiratory effort,[19] a measurement that was not available in the current study. It should be noted that flattening of the inspiratory portion of the nasal pressure signal is admitted as a diagnostic criterion according to the 2007 AASM guidelines.[8]

CONCLUSIONS

In our middle- to older-age population-based sample, only 3.8% showed a RERA index > 5 events/h and fewer than 1% of subjects exhibited RERA as predominant SDB. We found no significant clinical difference between RERA cases and AHI-matched controls in terms of BMI, neck circumference, daytime sleepiness, hypertension, diabetes, and metabolic syndrome. This suggests that when using the AASM guidelines that include arousals in the definition of hypopneas, the scoring of RERA may not have a significant clinical effect.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, index of apnea-hypopneas per hour of sleep
BMI, body mass index
OSA, obstructive sleep apnea
PSG, polysomnography
RDI, respiratory disturbance index (AHI + RERA index)
REM sleep, rapid eye movement sleep
RERA, respiratory effort-related arousal
RLS, restless legs syndrome
SDB, sleep-disordered breathing
TST, total sleep time

REFERENCES

1. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310–318.
2. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med*. 2010;11(5):441–446.
3. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):685–689.
4. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163(1):19–25.
5. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J*. 2004;25(9):735–741.
6. Kent BD, Grote L, Ryan S, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *Chest*. 2014;146(4):982–990.
7. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342(19):1378–1384.
8. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597–619.
9. Pepin JL, Guillot M, Tamisier R, Levy P. The upper airway resistance syndrome. *Respiration*. 2012;83(6):559–566.
10. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord*. 2008;8:6.
11. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*. Los Angeles, CA: UCLA Brain Information Service/Brain Research Institute; 1968.
12. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. 1992;15(2):173–84.

13. Iber C, Ancoli-Israel S, Chesson AL Jr, Qaun SF; For the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
14. Kristo DA, Lettieri CJ, Andrada T, Taylor Y, Eliasson AH. Silent upper airway resistance syndrome: prevalence in a mixed military population. *Chest.* 2005;127(5):1654–1657.
15. Palombini LO, Tufik S, Rapoport DM, et al. Inspiratory flow limitation in a normal population of adults in São Paulo, Brazil. *Sleep.* 2013;36(11):1663–1668.
16. Gold AR, Gold MS, Harris KW, Espeleta VJ, Amin MM, Broderick JE. Hypersomnolence, insomnia and the pathophysiology of upper airway resistance syndrome. *Sleep Med.* 2008;9(6):675–683.
17. Powers CR, Frey WC. Maintenance of wakefulness test in military personnel with upper airway resistance syndrome and mild to moderate obstructive sleep apnea. *Sleep Breath.* 2009;13(3):253–258.
18. Stoohs RA, Philip P, Andries D, Finlayson EV, Guilleminault C. Reaction time performance in upper airway resistance syndrome versus obstructive sleep apnea syndrome. *Sleep Med.* 2009;10(9):1000–1004.
19. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest.* 1993;104(3):781–787.
20. de Godoy LB, Palombini LO, Guilleminault C, Poyares D, Tufik S, Togeiro SM. Treatment of upper airway resistance syndrome in adults: Where do we stand? *Sleep Sci.* 2015;8(1):42–48.
21. Gold MS, Amdo T, Hasaneen N, Gold AR. Somatic arousal and sleepiness/fatigue among patients with sleep-disordered breathing. *Sleep Breath.* 2016;20(2):749–758.
22. Guilleminault C, Stoohs R, Shiomi T, Kushida C, Schnittger I. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. *Chest.* 1996;109(4):901–908.
23. Lofaso F, Coste A, Gilain L, Harf A, Guilleminault C, Goldenberg F. Sleep fragmentation as a risk factor for hypertension in middle-aged nonapneic snorers. *Chest.* 1996;109(4):896–900.
24. Lofaso F, Goldenberg F, d'Ortho MP, Coste A, Harf A. Arterial blood pressure response to transient arousals from NREM sleep in nonapneic snorers with sleep fragmentation. *Chest.* 1998;113(4):985–991.
25. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest.* 2010;137(1):95–101.
26. Exar EN, Collop NA. The upper airway resistance syndrome. *Chest.* 1999;115(4):1127–1139.
27. Asker M, Asker S, Kucuk U, Kucuk HO. An overlooked cause of resistant hypertension: upper airway resistance syndrome - preliminary results. *Clinics (San Paolo).* 2014;69(11):731–734.
28. Heinzer RC, Stanchina ML, Malhotra A, et al. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2005;172(1):114–117.

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