REM sleep obstructive sleep apnoea

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Shareable abstract (@ERSpublications)
Obstructive sleep apnoea (OSA) occurring only in REM sleep (REM OSA) is often identified, especially in women with mild–moderate OSA. REM OSA appears consistently linked with hypertension but its overall impact on health is still poorly defined. https://bit.ly/3RFxIuB

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Abstract

Obstructive sleep apnoea (OSA) can occur in both rapid eye movement (REM) and non-REM sleep or be limited to REM sleep, when the upper airway is most prone to collapse due to REM sleep atonia. Respiratory events are usually longer and more desaturating in REM than in NREM sleep. The prevalence of REM OSA is higher in women than in men and REM OSA usually occurs in the context of mild–moderate OSA based on the apnoea–hypopnoea index calculated for the entire sleep study. Studies have highlighted some detrimental consequences of REM OSA; for example, its frequent association with systemic hypertension and a degree of excessive daytime sleepiness similar to that found in nonsleep-stage-dependent OSA. Moreover, REM OSA could increase cardiometabolic risk. Continuous positive airway pressure (CPAP) treatment aimed at preventing REM OSA should be longer than the 4 h usually considered as good compliance, since REM sleep occurs mostly during the second half of the night. Unfortunately, patients with REM OSA show poor adherence to CPAP. Alternative non-CPAP treatments might be a good choice for REM OSA, but data are lacking. This review summarises the available data on REM OSA and critically examines the weaknesses and strengths of existing literature.

Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent medical condition, with an estimated global prevalence of almost 1 billion people, and rates exceeding 50% in some countries [1]. The pathogenesis of OSA is complex and its clinical manifestations are heterogeneous. Many factors affect its expression, including age, sex, ethnicity, bodily characteristics, comorbidities and sleep posture, as well as sleep stage, all of which collectively contribute to defining the endotypic and phenotypic features of OSA.

OSA may deteriorate during rapid eye movement (REM) sleep [2, 3]. Often, the number and duration of apnoeas and hypopnoeas increase during REM sleep compared with non-REM (NREM) sleep. In some patients, respiratory events occur primarily during REM sleep, a condition called REM sleep-related OSA (REM OSA). These patients might be symptomatic, yet they may not be diagnosed with OSA because their overall apnoea–hypopnoea index (AHI) falls within the normal range [4]. At present, there is no generally accepted definition of REM OSA and several definitions have been proposed [5–7]. Some authors make a distinction between REM-predominant (REMp) and REM-isolated (REMi) OSA. Yet other investigators focus on NREM *versus* REM OSA to assess the differential effect of both conditions [8, 9]. A recent comprehensive review of REM OSA highlighted the differences between NREM and REM sleep,

and the features of respiratory events according to sleep stages [10]. The scope of this review is to examine the evidence underpinning the assertion that REM OSA may constitute a different phenotype in the heterogeneous constellation of OSA.

Physiology

NREM and REM stages alternate cyclically during nocturnal sleep. REM sleep constitutes on average 20–25% of total sleep time and is more prominent towards the later hours of the sleep period. It is a distinctive sleep state, characterised by low-amplitude, mixed-frequency electroencephalographic activity, general muscle atonia and episodic sequences of REMs [11], which define phasic REM sleep, as opposed to tonic REM sleep. Fluctuations in heart rate, blood pressure (BP) and sympathetic outflow appear during REM sleep [12]. Respiration is also unstable, with variations in respiratory frequency and tidal volume. Episodic reduction of ventilation often occurs in association with bursts of REMs and is related to the inhibition of the respiratory muscles, including the diaphragm [13, 14]. In that context, short central apnoeas and hypopnoeas are a common sign of the ventilatory instability of normal REM sleep.

Sleep is hallmarked by reduced ventilatory responses to hypoxaemia and hypercapnia, which are present during NREM sleep and become most pronounced during REM sleep, where reductions to less than a third of the wakefulness state responses may be observed [15, 16]. In OSA, this reduced ventilatory drive may explain why respiratory events last longer in REM sleep, thus leading to greater dips in oxygen saturation [2, 17]. Moreover, lung volumes are decreased in REM sleep, even in OSA patients treated with continuous positive airway pressure (CPAP) [18, 19]. The resultant reduction in pulmonary oxygen stores makes individuals more susceptible to rapid oxygen desaturation induced by respiratory events [20]. Knowing that hypoxia has potent pressor effects in OSA [21] and that hypoxia often exacerbates during REM sleep, it becomes clear why greater fluctuations in heart rate and BP can be observed in REM sleep as compared with NREM sleep.

The duration of obstructive apnoeas and hypopnoeas is determined by the chemical ventilatory drive and the arousal threshold [22]. The latter is linked to an incremental ventilatory effort that triggers a cortical arousal when a critical level of respiratory muscle force has been reached [23]. Ventilatory effort can be assessed by measuring oesophageal pressure, gauging intrathoracic pressure [24]. Using oesophageal pressure measurements, Gleeson *et al*. [23] demonstrated that the stimulus to arousal from sleep in normal subjects is independent of the source of the rising drive to breathe, be it hypoxia, hypercapnia or resistive loading. While large interindividual differences exist, the intraindividual arousal threshold proves fairly stable. In 116 consecutive OSA patients, indices of respiratory effort were significantly lower in REM than in NREM sleep [25], as shown by the values of peak negative intrathoracic pressure (39.6±1.9 mbar in REM sleep *versus* 50.9±2.5 mbar in NREM sleep). Less respiratory effort might allow apnoeas to last longer before reaching the arousal threshold, thus explaining the extended duration of respiratory events in REM sleep.

The loop gain of the ventilatory control system is a nonanatomical factor in the pathogenesis of OSA [22]. It has been shown that worse ventilatory control stability due to increased loop gain is present in NREM-predominant OSA. In contrast, patients with REMp OSA are more prone to passive upper airway (UA) collapsibility as compared with the NREM OSA phenotype [26].

The general suppression of the skeletal muscle tone during REM sleep also affects the dilating muscles of the UA. In particular, both phasic and tonic activity of the genioglossal muscle are decreased, predisposing to increased UA collapsibility [26–29]. Just like in healthy individuals of both genders, OSA patients under CPAP treatment showed a progressive decrease in the activity of the genioglossal muscle, transitioning from stable NREM to tonic REM and finally to phasic REM sleep [30]. From this observation, it was postulated that a generalised reduction in genioglossal activity during REM sleep predisposes to pharyngeal collapse, especially in those individuals who are critically dependent on UA dilator muscle activity for maintaining UA patency [30]. Recently, pharyngeal collapsibility, characteristic of REM sleep, was shown to be largely explained by ventilatory drive withdrawal rather than by particular decrements in muscle activity or responsiveness [31]. The final common pathway of these mechanisms is an increased propensity for complete REM sleep-related UA collapse of longer duration, as compared with NREM sleep.

Epidemiology

A high degree of heterogeneity exists in the definitions of REM OSA in epidemiological studies, as listed in table 1 and reported in tables 2 and 3.

TABLE 1 Definitions of rapid eye movement (REM) obstructive sleep apnoea (OSA) in epidemiological studies

Reference(s)	Definition of OSA_{REM}
[32]	Quartiles of AHI_{REM}, AHI_{NREM} ⩾ or <8 events·h^{-1}
[33]	AHI_{REM} ⩾5 events·h^{-1}, AHI <15 events·h^{-1}
[40]	No OSA_{REM}: AHI_{REM} <10 events·h^{-1}; mild OSA_{REM}: AHI_{REM} 10–19 events·h^{-1}; moderate OSA_{REM}: AHI_{REM} 20–29 events·h^{-1}; severe OSA_{REM}: AHI_{REM} >30 events·h^{-1}
[35]	REM sleep ⩾30 min; AHI_{REM} categories (>5, 5.0–9.9, 10–19.9 and ⩾20 events·h^{-1})
[41]	AHI_{NREM} <5 events·h^{-1}; AHI_{REM}: <5 (normal), 5.0–14.9 (mild), 15.0–29.9 (moderate) and ⩾30.0 events·h^{-1} (severe)
[36, 39]	REM sleep ⩾30 min; severe OSA_{REM}: AHI_{REM} >30 events·h^{-1}
[36]	REM sleep ⩾30 min; severe OSA_{REM}: AHI_{REM} >30 events·h^{-1}; total AHI <15 events·h^{-1}
[36]	REM sleep ⩾30 min; severe OSA_{REM}: AHI_{REM} >30 events·h^{-1}; total AHI <15 events·h^{-1} and AHI_{NREM} <5 events·h^{-1}
[38]	AHI_{REM} >5 events·h^{-1}; REM sleep ⩾15 min
[43, 44]	Overall AHI between 10 and 25 events·h^{-1}, AHI_{REM}/AHI_{NREM} >2 and AHI_{NREM} <10 events·h^{-1}
[45]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} >2, REM sleep ⩾15% of TST
[55]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2, REM sleep ⩾10 min
[46, 51, 56]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2, REM sleep ⩾10 min, AHI_{NREM} <15 events·h^{-1}
[53, 57, 42, 58, 48]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2, REM sleep >10.5 min, AHI_{NREM} <8 events·h^{-1}
[57, 42, 54, 58, 48, 52]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2
Predominant OSA_{REM} [57, 42, 58, 47, 48, 50, 52]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2, AHI_{NREM} <15 events·h^{-1}
Isolated OSA_{REM} [34, 37, 54, 49]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2, AHI_{NREM} <5 events·h^{-1}, AHI_{REM} >5 events·h^{-1}, REM sleep ⩾30 min
[49, 52]	Overall AHI ⩾5 events·h^{-1}, AHI_{REM}/AHI_{NREM} ⩾2, AHI_{NREM} <15 events·h^{-1}, REM sleep ⩾30 min

AHI: apnoea–hypopnoea index; NREM: non-REM; TST: total sleep time.

Several studies, in both the general population and OSA patient cohorts, assessed the prevalence of REM OSA, its main clinical features and its possible prognostic implications. The majority of the studies are cross-sectional analyses of large cohorts, but longitudinal studies have provided information on the potential health risks associated with REM OSA and the evolution of REM OSA over time.

Studies in the general population

The results of cross-sectional studies highlight differences in prevalence rates, likely attributable to the different definitions of REM OSA and the variable sex distribution in the samples (table 2). Nevertheless, there is agreement on some aspects since REM OSA:

1) shows a prevalence rate between 17 and 74% [32–39];
2) is more common in women than in men [32, 35, 37, 39];
3) occurs with decreasing frequency from mild to severe OSA [33, 37];
4) does not appear to be associated with daytime sleepiness [32–34], poor quality of life [32, 33] or subjective insomnia [32];
5) does not seem to be associated with the supine position [34].

On the other hand, the data on sleep quality in OSA REM show variable results, since one study in elderly men reported an association with poor sleep quality [33], while other studies found no change in sleep structure/duration [34, 36, 37, 39]. Decreased total sleep time and low percentage of slow-wave sleep were only found in subjects with moderate–severe REM OSA [35].

As for the role of REM OSA with regard to comorbidities, systemic hypertension, evaluated either cross-sectionally or longitudinally, was shown to be associated with REM OSA, but not with NREM OSA [34]. Another study reported that moderate–severe REM OSA was associated with hypertension and metabolic abnormalities such as metabolic syndrome and diabetes, but not with depression [35]. No association was shown between REM OSA and either prevalent or incident increase in glycosylated haemoglobin (HBA1c) in men [40] or lipid profile [37]. Increased carotid intima thickness was reported in women, but not in men, with severe OSA in REM sleep [36, 39], suggesting a possible relationship of REM OSA with increased cardiovascular risk. In this regard, a longitudinal analysis in the Sleep Heart Health study cohort examined the impact of REM OSA on the occurrence of a composite cardiovascular end-point, *i.e.* fatal and nonfatal myocardial infarction, coronary revascularisation, congestive heart failure and stroke, in patients with or without prevalent cardiovascular disease. Isolated severe REM OSA was associated with the composite outcome only in patients with prevalent cardiovascular disease and correlated marginally with hypoxia during REM sleep [41].

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TABLE 2 Studies on rapid eye movement (REM) obstructive sleep apnoea (OSA) in the general population

First author [ref.], year	Study type; sample	Diagnostic criteria	Outcomes	Results
Chami [32], 2010	Cross-sectional; 5649 subjects (mean age 62.5 years, 52.6% women), SHHS	Quartiles of AHI_{REM} in patients with AHI_{NREM} ⩾ or <8 events·h^{-1}	ESS score, QoL and subjective sleep disruption	Prevalence of OSA_{REM}: 74% in the analysed samples. In fully adjusted models, ESS scores associated with increasing AHI_{NREM} but not with AHI_{REM}. Similar results for mental and physical QoL and report of insomnia.
Khan [33], 2013	Cross-sectional; 2765 men (age ⩾65 years), outcomes of MrOS Sleep study	REM-predominant OSA: AHI <15 events·h^{-1}, with AHI_{REM} ⩾5; analysis stratified by AHI_{REM} <5, 5–<15, 15–<30 and ⩾30 events·h^{-1}	ESS, FOSQ, PSQI, SF-12, GDS and self-perceived health status	Prevalence of OSA_{REM} (2044 subjects): 58% for AHI <15 (mild OSA_{REM}: 31.5%, moderate OSA_{REM}: 20%, severe OSA_{REM}: 6.5%). REM-predominant OSA associated with PSG indices of poor sleep quality, but not with daytime sleepiness or QoL.
Mokhlesi [34], 2014	Cross-sectional and longitudinal with follow-up 24 years; 4385 sleep studies in 1451 subjects (mean age 54 years, 46% women); ABPM studies in 742 subjects, Wisconsin Sleep Cohort	At least 30 min of REM sleep at PSG; AHI_{REM} stratified by severity (<1, 1–4.9, 5–14.9 and ⩾15 events·h^{-1}); subsample of subjects with AHI_{NREM} <5 events·h^{-1} (n=1216)	Cross-sectional analysis: association of OSA_{REM} with prevalent HT Longitudinal analysis: association of OSA_{REM} with incident HT	Prevalence of OSA_{REM} in the subsample of REM-predominant OSA: 33% of the total studies. Cross-sectional: significant association of AHI_{REM} and prevalent HT, confirmed in the sample of patients with ABPM data; no association with AHI_{NREM} or supine position. AHI_{REM} not associated with daytime sleepiness. Longitudinal: AHI_{REM} >15 events·h^{-1} associated HT. Similar results in the sample with ABPM measurements.
Appleton [40], 2016	Longitudinal; 837 nondiabetic men from the MAILES study	AHI_{REM}: <10 events·h^{-1} no OSA_{REM}; 10–19 events·h^{-1} mild OSA_{REM}; 20–29 events·h^{-1} moderate OSA_{REM}; >30 events·h^{-1} severe OSA_{REM}	Association with prevalent and incident HbA1c >6% in 2010–2011 compared to 2002–2006 (MAILES 1) and 2007–2010 (MAILES 2)	No estimate of REM-predominant OSA. AHI_{REM} not associated with either prevalent or incident HbA1c >6%.
Acosta-Castro [35], 2018	Cross-sectional; 2074 subjects (mean age 57 years, 51.7% women), HypnoLaus Sleep cohort	At least 30 min of REM sleep at PSG; AHI_{REM} according to four categories (>5, 5.0–9.9, 10–19.9 and ⩾20 events·h^{-1}) Analysis in the entire cohort and in patients with no–mild SDB (total AHI <10 events·h^{-1}, n=1047) and with exclusive REM-SDB (AHI_{NREM} <10 events·h^{-1}, n=1241)	Association of AHI_{REM} with CV, metabolic and psychiatric comorbidities	Overall prevalence of AHI_{REM} ⩾20 events·h^{-1}: 40.8%. Dose–response association of AHI_{REM} with metabolic syndrome, but not with diabetes or depression. AHI_{REM} ⩾20 events·h^{-1} associated with systolic and diastolic blood pressure. In no–mild SDB, prevalence of AHI_{REM} ⩾20 events·h^{-1}: 21.2%. AHI_{REM} ⩾20 events·h^{-1} associated with metabolic syndrome and diabetes. In exclusive REM-SDB, prevalence of AHI_{REM} ⩾20 events·h^{-1}: 9.1%. Dose–response association of AHI_{REM} with metabolic syndrome and diabetes.
Ljunggren [36], 2018	Cross-sectional; 201 women, mean age 49.8 years, from the SHE study; exclusion of subjects with CV events or CPAP treatment in the previous 10 years	At least 30 min of REM sleep at PSG: severe OSA_{REM} defined as AHI_{REM} >30 events·h^{-1} Analysis in the subgroups with total AHI <15 events·h^{-1} and with total AHI <15 events·h^{-1}+AHI_{NREM} <5 events·h^{-1}	Association of OSA_{REM} with carotid intima thickness	Increased carotid intima, but not media, thickness in women with severe OSA_{REM}, even after multiple adjustments including blood pressure, lipid levels and diabetes. Apnoea duration but not hypoxic markers were associated with intima thickness. Similar results in the subgroups with total AHI <15 events·h^{-1} (n=139, 69% of the sample) and with total AHI <15 events·h^{-1}+AHI_{NREM} <5 events·h^{-1} (n=99, 49% of the sample).

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TABLE 2 Continued

First author [ref.], year	Study type; sample	Diagnostic criteria	Outcomes	Results
Aurora [41], 2018	Longitudinal; 3265 subjects (mean age: 62 years, 63.1% women) with baseline AHI_{NREM} <5 events·h^{-1} (with prevalent CVD n=452, without prevalent CVD n=2813) followed for 9.5 years, SHHS	AHI_{REM} categorised according to clinical cut-off points: <5 (normal), 5.0–14.9 (mild), 15.0–29.9 (moderate) and ⩾30.0 events·h^{-1} (severe disease)	Composite CV end-point, *i.e.* occurrence of nonfatal or fatal events, including myocardial infarction, coronary artery revascularisation, congestive heart failure and stroke	Composite CV in 53.5% and 18.0% of participants with and without prevalent CVD at baseline. AHI_{REM} >30 events·h^{-1} associated with higher risk, but only in patients with prevalent CVD at baseline. Marginal association with time spent at S_{pO_2} <90% during REM sleep, no association with arousals.
Bikov [37], 2019	Cross-sectional; 94 volunteers (mean age 49 years, 68% women) free from lipid-modifying medications	REM-dependent OSA: AHI_{REM} ⩾5 events·h^{-1} and AHI_{NREM} <5 events·h^{-1}	Relationship between OSA_{REM} or OSA_{NREM} and lipid profile	OSA diagnosed in 41 subjects (21 mild, 13 moderate, seven severe). REM-dependent OSA in 17% of the sample, no differences in lipid profile compared to controls.
Aurora [38], 2020	Longitudinal; 1908 subjects with OSA_{REM} and AHI_{NREM} <5 at baseline (mean age 60.7 years, 64% women), with follow-up PSG study about 5 years after enrolment, and complete data from the SHHS	AHI_{REM} >5 events·h^{-1} at baseline and at least 15 min of REM sleep both at baseline and follow-up PSG Analysis performed also with cut-off values for AHI_{REM} >10 and >15 events·h^{-1}	Natural history or OSA_{REM} during a median follow-up of 5.3 years Development of OSA in NREM sleep and determinants of progression Association with incident CVD	At baseline OSA_{REM} in 44.9% of women and 46.1% of men. The majority of the sample did not show progression of AHI_{NREM} to values >5 events·h^{-1}. OSA progression was associated with age and AHI_{REM} in both men and women, while increased BMI was predictive only in men. Resolution of OSA_{REM} during follow-up was associated with younger age, lower BMI at baseline and decreased BMI at follow-up. An increased risk for incident CV event was only shown in women with baseline AHI_{REM} ⩾5 events·h^{-1} with AHI_{NREM} ⩾5 events·h^{-1} at follow-up.
Ljunggren [39], 2022	Cross-sectional; 253 women (SHE study) and 338 age- and BMI-matched men (MUSTACHE study)	At least 30 min of REM sleep at PSG: Severe OSA_{REM} defined as AHI_{REM} >30 events·h^{-1} Analysis in the subgroups with total AHI <15 events·h^{-1} and with AHI_{NREM} <5 events·h^{-1}	Association of OSA_{REM} with carotid intima thickness	Prevalence of severe OSA_{REM}: 26.6% in the entire sample, 37.9% in women and 18% in men. Mean AHI_{REM} higher in women (17.6 events·h^{-1}) than in men (6.5 events·h^{-1}), minor differences in mean AHI_{NREM} (5.2 events·h^{-1} in women, 3.9 events·h^{-1} in men). Severe OSA_{REM} associated with carotid intima thickness, persistent significance after adjustments. In sex-stratified analysis, significant association only in women. Subgroup analysis not significant but very small number of observations.

AHI: apnoea–hypopnoea index; ABPM: ambulatory blood pressure; BMI: body mass index; CV: cardiovascular; CVD: cardiovascular disease; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; GDS: Geriatric Depression Scale-15; HbA1c: glycosylated haemoglobin; HT: hypertension; MAILES: Men Androgen Inflammation Lifestyle Environment and Stress; MrOS Sleep: Sleep Disorders in Older Men; MUSTACHE: Men in Uppsala; a Study of sleep, Apnea and Cardiometabolic Health; NREM: non-REM; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; QoL: quality of life; SDB: sleep-disordered breathing; SF-12: Short Form-12; SHE: Sleep and Health in Women; SHHS: Sleep Heart Health Study; S_{pO_2}: oxygen saturation measured by pulse oximetry; TST: total sleep time.

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TABLE 3 Studies on rapid eye movement (REM) obstructive sleep apnoea (OSA) in clinical samples

First author [ref.], year	Study type; sample	Diagnostic criteria	Outcomes	Results
O'Connor [43], 2000	Cross-sectional retrospective in 838 OSA patients (mean age: men 48.6 years; women 50.8 years; women 24.6%)	OSA_{REM}: overall AHI between 10 and 25 events·h^{-1}, AHI_{REM}/AHI_{NREM} >2 and AHI_{NREM} <10 events·h^{-1}	Sex-related differences in OSA	Prevalence of OSA_{REM}: 24% in men, 62% in women. Lower overall AHI in women secondary to low AHI_{NREM}, AHI_{REM} not different between sexes. Largest difference between men and women in the mild–moderate OSA range. No relationship with age in both men and women.
Resta [44], 2005	Observational; 45 severely obese OSA patients (20 women age- and weight-matched to 25 men), mean age 44 years, BMI 40 kg·m^{-2}	OSA_{REM}: overall AHI between 10 and 25 events·h^{-1}, AHI_{REM}/AHI_{NREM} >2 events·h^{-1} and AHI_{NREM} <10 events·h^{-1}	Sex-related differences in sleep and OSA in severely obese patients	Prevalence of OSA_{REM}: 35% in women and 4% in men. Lower OSA severity and sleep efficiency and higher number of awakenings in patients with OSA_{REM}.
Haba-Rubio [45], 2005	Cross-sectional retrospective; 415 OSA patients (mean age 54.1 years, 73% men)	AHI_{REM}/AHI_{NREM} >2 Exclusion criteria: 1) AHI ⩽5 events·h^{-1} of TST; 2) previous treatment for SDB; 3) REM sleep <15% of TST during nocturnal recording	Frequency and clinical characteristics of OSA_{REM} including subjective (ESS) and objective (MWT, n=228) sleepiness	SDB_{REM} in 36.4% of the sample (women: 46.4%, men 53.6%). No difference in symptoms or sleepiness between SDB_{REM} and SDB_{NREM} groups, but OSA more severe in patients with SDB_{NREM}. Declining frequency of SDB_{REM} from mild to severe OSA. SDB_{REM} associated with higher BMI in mild–moderate OSA and more frequent in women except in severe OSA cases.
Koo [55], 2008	Observational; 2486 OSA patients (mean age 50.8 years, 67.1% men)	At least 10 min of REM sleep at PSG OSA_{REM} criteria: 1) overall AHI ⩾5 events·h^{-1}; 2) AHI_{NREM} <15 events·h^{-1}; and 3) AHI_{REM}/AHI_{NREM} ⩾2	Sex-related differences in OSA	Prevalence of OSA_{REM}: 21% in men, 40.8% in women. Patients with OSA_{REM} were younger and showed longer REM sleep duration. Prevalence of OSA_{REM} decreased with age and increasing BMI in both men and women. No difference in positional AHI was found for any sleep stage between sexes.
Koo [56], 2008	Cross-sectional retrospective; 221 patients with OSA_{REM} (mean age 50 years, 33.5% men)	OSA_{REM} criteria: 1) age ⩾18 years; 2) overall AHI ⩾5 events·h^{-1}; 3) AHI_{NREM} <15 events·h^{-1}; 4) AHI_{REM}/AHI_{NREM} >2; and 5) time spent in REM sleep >10 min	Effects of age and sex in OSA_{REM}	Prevalence of OSA_{REM} in the entire sample of OSA patients (n=1540): 14.4% (24.5% of women, 7.9% of men in the entire sample). Comorbidities: depression in 41.2%, at least one cardiovascular risk factor in 67.7% and EDS in 68.1%. In both men and women, OSA_{REM} more frequent in patients younger than 55 years of age and directly related to BMI in women.
Pamidi [53], 2011	Cross-sectional; 931 consecutive OSA patients (mean age 50 years, 44.4% men)	Overall AHI ⩾5 events·h^{-1}, with AHI_{REM}/AHI_{NREM} ⩾2, AHI_{NREM} < 8 events·h^{-1} and REM duration >10.5 min	Association of OSA_{REM} with subjective sleepiness (ESS) and QoL by SF-12	Prevalence of OSA_{REM}: 13.5%. OSA_{REM} patients were younger and more often women (76.2 *versus* 52.4%) compared to nonstage-specific OSA patients. AHI_{REM} did not predict sleepiness or QoL. Depressive symptoms and BMI predicted ESS and QoL in the OSA_{REM} group.

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TABLE 3 Continued

First author [ref.], year	Study type; sample	Diagnostic criteria	Outcomes	Results
Conwell [57], 2012	Cross-sectional; 931 consecutive OSA patients (mean age 50 years, 44.4% men)	Definition 1: overall AHI $\geqslant$5 events·h^{-1} and AHI_{REM}/AHI_{NREM} $\geqslant$2 Definition 2: overall AHI $\geqslant$5 events·h^{-1}, AHI_{REM}/AHI_{NREM} $\geqslant$2 and AHI_{NREM} <15 events·h^{-1} Definition 3: overall AHI $\geqslant$5 events·h^{-1}, AHI_{REM}/AHI_{NREM} $\geqslant$2, AHI_{NREM} <8 events·h^{-1} and at least 10.5 min of REM sleep duration	Prevalence of OSA_{REM} according to different definitions	Prevalence of OSA_{REM} varied according to the definition used (1: 36.7%; 2: 24.4%; 3: 13.5%). OSA_{REM} more prevalent in women (78 *versus* 48% in men), younger individuals (mean age 45 *versus* 52 years) and African Americans. Similar degrees of obesity and sleepiness, better sleep quality, and lower prevalence of diabetes and HT in OSA_{REM} compared to patients with nonsleep stage-dependent OSA.
Sakao [42], 2015	Cross-sectional; 468 patients with suspected OSA (mean age 54.9 years, 22.9% women)	Three definitions of OSA_{REM}: I: overall AHI $\geqslant$5 events·h^{-1} and AHI_{REM}/AHI_{NREM} $\geqslant$2 II: AHI_{NREM} <15 events·h^{-1} in addition to I III: AHI_{NREM} <8 events·h^{-1} and at least 10.5 min of REM sleep in addition to I	Prevalence and features of OSA_{REM} in Japanese subjects	Prevalence of OSA_{REM}: 24.8% (I), 17.6% (II) and 11% (III). In women, prevalence of OSA_{REM} increased from 33.6 to 40.1% from definition I to III and was higher than the prevalence of OSA_{NREM}. Subjects with OSA_{REM} showed lower BMI and HbA1c levels than subjects with OSA_{NREM}.
Lee [46], 2016	Cross-sectional retrospective; 1281 Korean OSA patients (mean age 54 years, 18% women)	Overall AHI $\geqslant$5 events·h^{-1}, AHI_{NREM} <15 events·h^{-1} and AHI_{REM} to AHI_{NREM} ratio >2	Association of OSA_{REM} with sleepiness (ESS), depressive symptoms (BDI) and health-related QoL (SF-36)	Prevalence of OSA_{REM}: 18% (32.6% in women, 14.1% in men). OSA_{REM} more frequent in mild–moderate than severe OSA. Significant association of OSA_{REM} with depressive symptoms only in men. Sleepiness or QoL similar in OSA_{REM} and non-REM related OSA groups.
Al Oweidat [54], 2018	Cross-sectional; 478 Jordanian patients with OSA (mean age 55.3 years, 44.6% women)	Overall AHI $\geqslant$5 events·h^{-1} Broad definition of OSA_{REM}: AHI_{REM}/AHI_{NREM} $\geqslant$2; strict definition: AHI_{NREM}<5 events·h^{-1}, AHI_{REM} >5 events·h^{-1} and at least 30 min of REM sleep; OSA_{NREM}: AHI_{REM}/AHI_{NREM} <2	Differences in demographic and PSG features between REM- and NREM-related OSA	Severe OSA in 72% of the sample. Prevalence of OSA_{REM}: 18% (31% in women, 7.5% in men) according to the broad definition, 2.7% (5.2% in women, 0.8% in men) according to the strict definition. Higher arousal index and time spent at S_{pO_2} <90% and lower S_{pO_2} nadir in patients with OSA_{NREM} compared to patients with OSA_{REM} for both broad and strict definitions. No differences in BMI, ESS and snoring between the two groups.
Mano [58], 2019	Retrospective cross-sectional; 3234 Japanese OSA patients (mean age: 52.5 years, 14.5% women)	Three definitions of OSA_{REM}: I: overall AHI $\geqslant$5 events·h^{-1} and AHI_{REM}/AHI_{NREM} $\geqslant$2 II: AHI_{NREM} <15 events·h^{-1} in addition to I III: AHI_{NREM} <8 events·h^{-1} and at least 10.5 min of REM sleep in addition to I	Effect of sex and age on OSA_{REM} In women, analysis of the effects of menopause, defined as age >50 years	Overall prevalence of OSA_{REM} 24.6%, 18.6% and 12.2% according to definitions I–III. In men, prevalence of OSA_{REM} decreased with age, from 22.8 in men under 50 years to 19.1% in men over 50 years (definition I). Corresponding values in women were 44.3% under 50 years and 47.7% over 50 years (definition I). In multivariate analysis, adjustment for BMI and CT90 slightly decreased significance, whereas further adjustment for AHI_{NREM} strongly reduced the difference between sexes, both below and above age 50.

Continued

TABLE 3 Continued

First author [ref.], year	Study type; sample	Diagnostic criteria	Outcomes	Results
Bahammam [47], 2020	Prospective observational; 2169 OSA patients (mean age: 46.7 years, 38% women)	Predominant OSA_{REM}: overall obstructive AHI $\geqslant$5 events·h^{-1}, AHI_{NREM} <15 events·h^{-1} and AHI_{REM}/AHI_{NREM} $\geqslant$2. OSA_{NSS}: AHI $\geqslant$5 events·h^{-1}, criteria for OSA_{REM} not fulfilled	Analysis of clinical and sleep features, and of comorbidities	Prevalence of OSA_{REM}: 17% (25% in women, 12% in men). OSA_{REM} was more frequent at younger age but was unrelated to menopause at multivariate analysis. In OSA_{REM}, frequent nocturnal chest pain, headache at awakening, nocturnal awakening with palpitations and higher prevalence of bronchial asthma, while snoring and overall prevalence of HT and ischaemic heart disease were lower than in OSA_{NSS}. In men, OSA_{REM} was independently associated with younger age, HT, bronchial asthma, high sleep efficiency, low amount of NREM sleep stage 1 and lower AHI and S_{pO_2} nadir. In women, OSA_{REM} was independently associated with younger age, higher BMI, less HT, hypothyroidism, less sleepiness, low amount of NREM sleep stage 1 and lower amount of time spent at S_{pO_2}: <90%.
Sasai-Sakuma [48], 2021	Retrospective cross-sectional; 1458 Japanese OSA patients (median age 48 years, 9.7% women)	Three definitions of OSA_{REM}: I: overall AHI $\geqslant$5 events·h^{-1} and AHI_{REM}/AHI_{NREM} $\geqslant$2 II: AHI_{NREM} <15 events·h^{-1} in addition to I III: AHI_{NREM} <8 events·h^{-1} and at least 10.5 min of REM sleep in addition to I	Effects of gender and OSA severity on OSA_{REM} prevalence	Prevalence of OSA_{REM} (definition II) was 0% in severe OSA, 18.9% in moderate and 47% in mild OSA. Compared with OSA_{NSS}, patients with OSA_{REM} showed higher BMI and female predominance, lower AHI and ODI, and higher sleep efficiency, but no difference in prevalence of daytime sleepiness or cardiometabolic comorbidities.
Chiu [49], 2022	Retrospective cross-sectional; 1331 Korean OSA patients aged >20 years (median age 53 years, 20.5% women)	REM sleep: at least 30 min. OSA_{REM}: AHI_{REM}/AHI_{NREM} >2 and AHI_{NREM} <15 events·h^{-1}; OSA_{NREM}: AHI_{REM}/AHI_{NREM} $\leqslant$2; OSA_{NSS}: AHI_{REM}/AHI_{NREM} >2 and AHI_{NREM} $\geqslant$15 events·h^{-1}; isolated OSA_{REM}: AHI_{REM} >5 events·h^{-1} with AHI_{NREM} <5 events·h^{-1}	Clinical demographics, OSA-related symptoms, PSG results and medical comorbidities in OSA_{REM}, OSA_{NREM} and OSA_{NSS}	Prevalence of OSA_{REM}: 31.1%, OSA_{NREM}: 60.7%, OSA_{NSS}: 8.2%. OSA_{REM} more frequent in women (53.1 *versus* 25.4% in men), mild–moderate than severe OSA based on overall AHI and associated with longer duration of desaturations and lower S_{pO_2} nadir. No difference in ESS score or prevalence of comorbidities compared to the other groups.
Lee [50], 2022	Retrospective cross-sectional; 692 Korean OSA patients (mean age 50.3 years, 28.2% women)	REM sleep: at least 30 min; OSA_{REM}: overall AHI >5 events·h^{-1}, AHI_{REM}/AHI_{NREM} $\geqslant$2 and AHI_{NREM} <15 events·h^{-1}	Prevalence and clinical characteristics of OSA_{REM}	Prevalence of OSA_{REM}: 20.2% (38.4% of women, 13% of men). In the OSA_{REM} group, females represented 53.6%. OSA_{REM} present in 69.3% of patients with mild OSA and 30% of patients with moderate OSA. Prevalence of HT and diabetes lower in patients with OSA_{REM} than in patients with OSA_{NREM}.

Continued

TABLE 3 Continued

First author [ref.], year	Study type; sample	Diagnostic criteria	Outcomes	Results
Sattaratpaijit [51], 2022	Retrospective cross-sectional; 408 Thai OSA patients (mean age 49.7 years, 39.9% women)	At least 10.5 min of REM sleep; OSA_{REM}: overall AHI $\geqslant$5 events·h^{-1}, AHI_{REM}/AHI_{NREM} >2 and AHI_{NREM} <15 events·h^{-1}	Prevalence and clinical characteristics of OSA_{REM}	Prevalence of OSA_{REM}: 21.6% (29.4% of women, 16.3% of men). OSA_{REM} significantly associated with female sex (OR 2.35), age <60 years (OR 2.52) and mild OSA (OR 17.46).
Qanash [52], 2023	Retrospective cross-sectional; 609 Saudi OSA patients (mean age 49 years, 42% women)	Strict definition: AHI $\geqslant$5 events·h^{-1}, AHI_{REM}/AHI_{NREM} $\geqslant$2, AHI_{NREM} <15 events·h^{-1}, at least 30 min of REM sleep Intermediate definition AHI $\geqslant$5 events·h^{-1}, AHI_{REM}/AHI_{NREM} $\geqslant$2, AHI_{NREM} <15 events·h^{-1} Lenient definition: AHI $\geqslant$5 events·h^{-1}, AHI_{REM}/AHI_{NREM} $\geqslant$2	Prevalence and clinical characteristics of OSA_{REM}	Prevalence of OSA_{REM}: 26% (women 36%, men 18%) according to the strict definition, 33% (women 48.4%, men 21.8%) according to the moderate definition and 52% (women 69.5%, men 35.4%) according to the lenient definition. Milder OSA and desaturation severity in OSA_{REM} compared to OSA_{NREM}. No differences in ESS or prevalence of comorbidities between OSA_{REM} and OSA_{NREM}.
Huang [61], 2023	Cross-sectional; 4152 subjects with suspected OSA (mean age 49 years, 21% women), Shangai Sleep Health Study cohort	Stratification of the sample according to AHI_{REM} in the no OSA and mild, moderate and severe OSA ranges Analysis in the subgroup with AHI_{NREM} <5 events·h^{-1}	Association of OSA_{REM} with cardiovascular risk, assessed as FRS and autonomic imbalance, assessed as HRV parameters in both subjects with and without prevalent CVD	Severe OSA_{REM} associated with increased FRS, but not with prevalent CVD, in the multivariate analysis. High LF/HF, high LF and high HF associated with AHI_{REM} in the subgroup with AHI_{NREM}<5 events·h^{-1}. HRV parameters mediated the relationship between AHI_{REM} and both prevalence of CVD and high FRS.

AHI: apnoea–hypopnoea index; BDI: Beck Depression Inventory; BMI: body mass index; CT90: cumulative time spent at S_{pO_2} <90%; CVD: cardiovascular disease; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; FRS: Framingham Risk Score; HbA1c: glycosylated haemoglobin; HF: high-frequency spectrum; HRV: heart rate variability; HT: hypertension; LF: low-frequency spectrum; MWT: maintenance of wakefulness test; ODI: oxygen desaturation index; NREM: non-REM; OR: odds ratio; OSA_{NSS}: nonstage-specific OSA; PSG: polysomnography; QoL: quality of life; SDB: sleep-disordered breathing; SF-12: Short Form-12; SF-36: Short Form-36; S_{pO_2}: oxygen saturation measured by pulse oximetry; TST: total sleep time.

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An interesting question concerns the evolution of isolated REM OSA over time, since the occurrence of REM OSA might evolve towards a progressive extension to events in NREM sleep. In patients with isolated REM OSA, *i.e.* with NREM AHI <5 events·h^{-1} at baseline, progression of OSA in NREM sleep to an AHI >5 events·h^{-1} occurred in a minority of patients and was associated with age and REM AHI in both men and women, and with increased body mass index (BMI) only in men. On the other hand, regression of REM OSA was observed in younger nonobese patients at baseline, who showed a decrease in BMI during follow-up [38].

Studies in OSA patient cohorts

The studies in OSA patients are mainly retrospective cross-sectional analyses of existing cohorts (table 3). The prevalence rates of REM OSA according to sex (figure 1) were variable, possibly due to different definitions of REM OSA, variable sex distribution in the sample and different ethnicities of the OSA patients being examined. Nevertheless, REM OSA occurred more frequently in women than in men in all studies [42]. The results obtained in OSA patients confirmed the higher prevalence of REM OSA in mild–moderate than in severe OSA [43–52]. Sleep quality was quite preserved in patients with REM OSA compared to patients with NREM OSA, *i.e.* lower arousal index and/or lower percentage of stage 1 NREM sleep [45, 47, 50, 51, 53, 54], except in a study on severely obese OSA patients [44].

REM OSA frequently occurred in young to middle-aged patients [51, 53, 55–58] and the differences between men and women progressively decreased at older age [55]. The seminal study by O'Connor *et al.* [43], however, did not find any relationship between age and REM OSA in both sexes. Some studies addressed the question of the possible role of menopause. The study by Mano *et al.* [58] reported that the risk of REM OSA was higher in women aged >50 years. Conversely, Bahammam *et al.* [47] found a progressive decrease in the prevalence of REM OSA in ageing women; in multivariate analysis age remained significant, while menopausal status did not. Short-term hormone replacement in post-menopausal women with OSA did not affect overall OSA severity and decreased AHI in REM sleep nonsignificantly [59]. In a prospective study in women during the menopausal transition, respiratory events

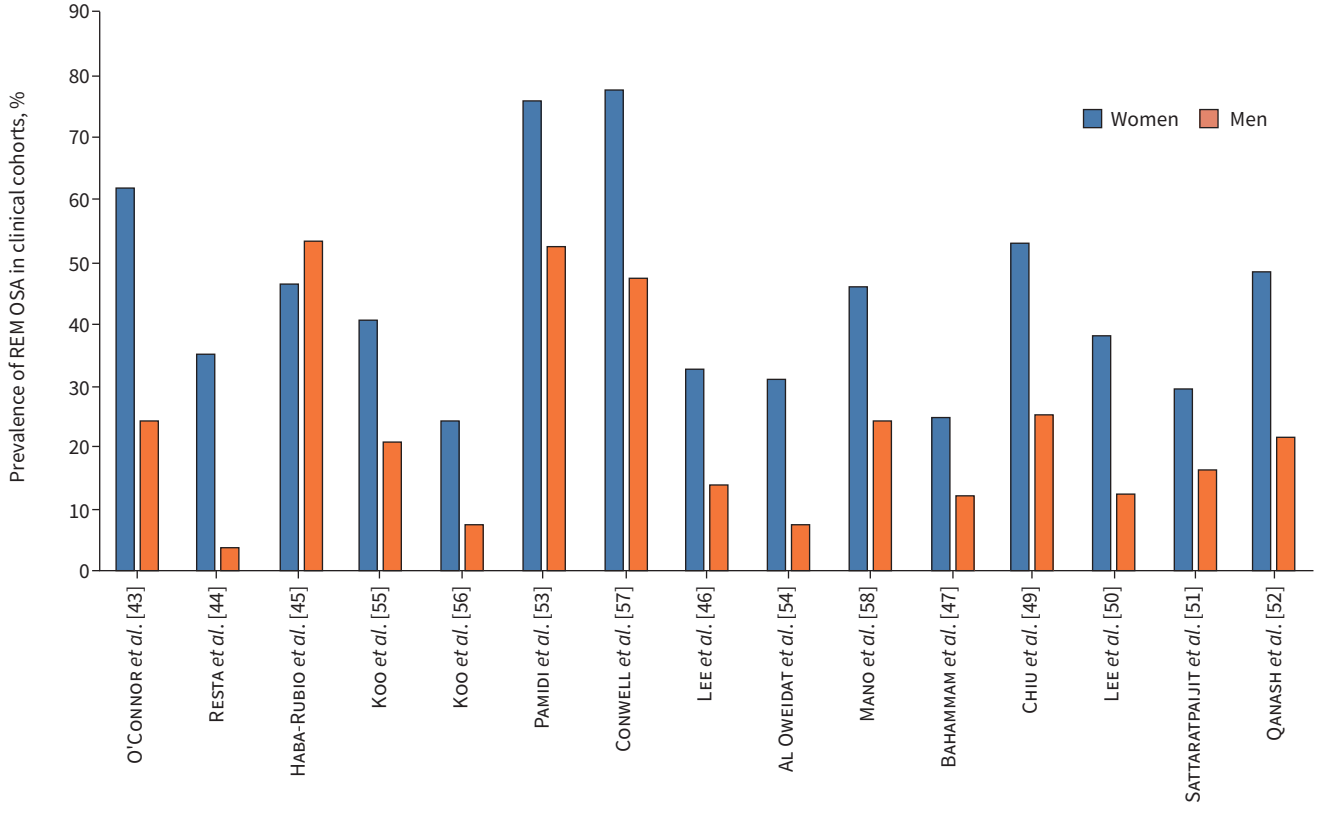

FIGURE 1 Prevalence of rapid eye movement obstructive sleep apnoea (REM OSA) in clinical cohorts. Prevalence of REM OSA is reported in women (blue) and men (orange) for different studies. All studies, but one, found a higher prevalence of REM OSA in women than in men.

in REM sleep at baseline predicted hypertension, increased at follow-up and were independent of hormone replacement therapy use [60]. More data are necessary to understand the relative role of hormonal status and ageing in female REM OSA.

Although REM OSA usually occurs in the context of less severe OSA, *i.e.* lower overall AHI, compared to NREM OSA [45, 54], the frequency of daytime sleepiness was similar in patients with REM OSA and NREM OSA [45, 46, 48, 49, 52, 54, 57]. This finding is intriguing and would suggest that OSA REM is not as mild as it would seem. On the other hand, a recent study found evidence of abnormal autonomic modulation in severe REM OSA, suggesting a possible detrimental effect of REM OSA on cardiovascular risk [61]. Sympathetic activation in OSA is particularly prominent in REM sleep [62] and was found to be associated with excessive daytime sleepiness (EDS) [63–65]. These findings possibly account, at least partly, for the similar degree of sleepiness in REM OSA and NREM OSA.

Some of the differences in results may be accounted for by the characteristics of the patient samples and/or the definition of REM OSA used. Yet, the overall findings in patient cohorts seem to confirm the data in the general population, *i.e.* predominant or isolated REM OSA is present mainly in women and in young rather than old subjects (figure 1). Differences in BMI and symptoms between REM OSA and NREM OSA were not highly relevant and, when present, they could be at least partly explained by the usually worse severity of NREM OSA compared to REM OSA.

REM OSA in other diseases

REM OSA has been reported to occur in the context of other diseases. Adult narcoleptic patients with OSA were older and had a higher BMI than patients without OSA and showed a high prevalence of REM OSA independent of the presence of cataplexy [66].

REM sleep behaviour disorder (RBD) is characterised by loss of general muscle atonia during REM sleep. Attention has been drawn to the possibility that RBD may protect against REM OSA because UA muscle tone is usually preserved in RBD. On the other hand, sleep apnoea-induced movement arousals accompanied with vocal sounds may mimic features of RBD [67]. In a case–control study, 109 patients with idiopathic RBD and OSA (RBD-OSA) were consecutively enrolled and compared with matched OSA controls without RBD. In the latter group, the AHI was significantly higher during REM than during NREM sleep ($p<0.01$). However, in RBD-OSA patients, the AHI was significantly lower during REM sleep as compared with non-RBD controls, the prevalence of REM OSA being 9.2 *versus* 33.0%, respectively [68]. Another study showed significantly less oxygen desaturation during REM sleep in RBD-OSA patients in comparison with non-RBD controls [69]. In proven RBD with associated OSA, symptoms of RBD may improve under CPAP therapy [70]. Thus, the relation between RBD and REM OSA may be reciprocal, as RBD may protect against REM OSA and treatment of OSA may alleviate RBD symptoms. More extensive research is needed, however, to corroborate this hypothesis.

A retrospective study in untreated patients with allergic rhinitis, sensitised to house dust mites (HDMs) or other allergens, found that the overall AHI or respiratory disturbance index (RDI) was on average low and similar to that recorded in controls. However, the REM RDI was higher in patients with rhinitis than in nonallergic subjects [71] and highest in patients with HDM allergy. Although sleep quality was shown to improve after long-term treatment for allergic rhinitis [72], no study to date has objectively recorded sleep in patients treated for allergic rhinitis.

Prevalence of REM OSA was assessed in a cohort of patients with coronary artery disease (CAD). The results were similar to those recorded in non-CAD cohorts, since the prevalence of REM OSA was 25.5% (26% in women *versus* 9.9% in men) and more frequent in obese than nonobese patients (42.5 *versus* 24.4%). The Mental Component Summary of the Short-Form 36 Assessment of Quality of Life was the only outcome significantly and inversely correlated with REM AHI [73]. Another study in patients with percutaneous coronary intervention within the previous 6–36 months found an 81% prevalence of REM OSA, positively associated with BMI, systolic BP and diabetes mellitus at univariate analysis, whereas only diabetes was a significant predictor of REM OSA at multivariate analysis [74].

It is likely that the prevalence of REM OSA could be significant in other conditions besides the ones analysed, but further studies are needed. The difficulty in obtaining data on REM OSA is linked to the widespread use of cardiorespiratory polygraphy, which can only suggest occurrence of REM OSA without any objective evidence. More data will be provided by sleep recordings over several nights, since significant variability in OSA, especially in the mild–moderate range, has been shown over different nights [75, 76].

Clinical manifestations

EDS

In OSA patients, the severity of the disorder, graded by the AHI or arousal index, only explains a small part of the variance of EDS assessed by the multiple sleep latency test [77, 78]. Studies in clinical OSA patients comparing the relative contribution of NREM *versus* REM OSA were unable to identify any relevant additional impact of the latter when EDS was measured either subjectively [79] or objectively [80]. In experimentally induced REM OSA (by withdrawing CPAP therapy exclusively during REM sleep), the results of mean reaction time and psychomotor vigilance tests were not significantly changed [81]. Moreover, REMp OSA did not seem to affect EDS differently from NREM OSA in the general population. This lack of significance has been observed in cross-sectional studies in adults [32, 48] and in a prospective study in children [82]. Thus, evidence to suggest that REMp or REMi OSA independently impairs daytime vigilance is lacking.

Insomnia

Whether REMp or REMi OSA may show stronger associations with insomnia than NREM or nonsleep-stage-dependent OSA has not been studied extensively. Only one study using the Pittsburgh Sleep Quality Index (PSQI) addressed this issue and found that REM-related OSA was significantly associated with an increased PSQI in all adjusted models [83]. In the subgroup analysis, the coefficients of all models were higher in female than in male patients with REM-related OSA. Because insomnia is much more prevalent in women, sex may be an important factor, potentially confounding the interpretation of these results [84]. Further research is awaited to clarify the effects of REM OSA on insomnia symptoms. Furthermore, better tools to specifically assess insomnia should be applied in this area of investigation.

Anxiety and depression

Studies investigating how REM OSA relates to anxiety and depression are also scarce. An observational study comparing healthy controls (n=18), patients with nonsleep-stage-dependent OSA (n=18) and REMi OSA patients (n=17) found significant differences in results from the Profile of Mood State test (43.8±2.6, 51±4.0 and 65.6±7.7, respectively; p=0.019) [85]. From this small sample of subjects, it was inferred that REMi OSA could be deleterious for emotional health. In an observational study of 72 patients with mild REMi OSA and 94 patients with mild NREM OSA, anxiety and depression scores were significantly higher in the former group. In a large sample of 1281 consecutively recruited OSA patients, linear regression analysis showed that the presence of REMp OSA was significantly associated with higher scores on the Beck Depression Inventory questionnaire [46]. Remarkably, this association was only present in men, not in women. Furthermore, no significant associations could be demonstrated between REM OSA and indices of anxiety or depression in older men from the general population [33] or in a clinical sample of OSA patients [86]. To summarise, studies on the association between REM OSA and anxiety/depression are hampered by methodological limitations and are overall inconclusive.

Arterial hypertension

Associations between elevated BP and REM OSA, but not NREM OSA, were documented in different cross-sectional and prospective general population studies using home polysomnography.

In the Wisconsin Sleep Cohort, the REM AHI, either defined as a categorical or continuous variable, had predictive value for prevalent hypertension, after controlling for common confounding factors [34]. This was also the case in subjects with REMi OSA, in whom the NREM AHI was below 5 events·h^{-1}. In contrast, NREM AHI did not predict hypertension in any of the models. A separate prospective study in the same cohort revealed that there was a greater risk of developing systolic and diastolic nondipping BP with greater severity of REM OSA in a dose-dependent manner [87]. When controlling for NREM AHI and other covariates, subjects with REM AHI $\geqslant$15 events·h^{-1} showed a higher relative risk of incident systolic and diastolic nondipping than those with REM AHI <1 event·h^{-1}.

In the Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) study, longitudinal and cross-sectional associations of previously unrecognised OSA with hypertension were examined. Severe REM OSA (AHI $\geqslant$30 events·h^{-1}) was associated independently with prevalent and recent-onset hypertension [40]. In addition, in subjects not considered to have OSA (AHI <10 events·h^{-1}), an REM AHI $\geqslant$20 events·h^{-1} was significantly associated with prevalent hypertension. The relationship with recent-onset hypertension was positive but not significant. No such associations with the NREM AHI were seen.

Data from the population-based HypnoLaus Sleep Cohort (48.3% men, mean age 57±11 years) were analysed to assess REM AHI *versus* NREM AHI as predictors for prevalent hypertension and other

common diseases. The prevalence of REM AHI ⩾20 events·h^{-1} was 40.8% in the entire cohort. Systolic and diastolic BP were positively associated with REM OSA, defined as REM AHI ⩾20 events·h^{-1}.

Associations between REM OSA and hypertension have also been demonstrated in patient populations. One study assessed REM AHI and morning *versus* evening BP levels in a patient sample [88]. The probability of morning hypertensive BP levels was significantly and independently associated with age, BMI and REM AHI, but not NREM AHI. REM AHI was not associated with evening hypertensive BP levels. In a recent study in a cohort with >10 000 OSA patients, fully adjusted models demonstrated a significant dose–response relationship between arousal index during REM sleep (REM AI) and prevalent hypertension [89]. The highest odds ratio of prevalent hypertension was found in a subgroup with an REM AI >40 events·h^{-1}. On the contrary, NREM AI did not predict hypertension in any model. However, in another study on OSA in patients with type 2 diabetes, a statistically significant association was found between NREM OSA and hypertension, which was not the case for REM OSA [90].

To summarise, associations between REM OSA and prevalent hypertension have been demonstrated in both general and clinical population studies. Thus, an increased REM AHI could be clinically relevant even in the presence of a global AHI <10 events·h^{-1} or an REMi OSA condition (defined by an NREM AHI <5 events·h^{-1}). Contemporary guidelines recommend that CPAP therapy should be used at least 4 h per night [91]. However, if CPAP therapy is limited to the first half of the sleep period, most of the nocturnal REM sleep will be left untreated. Therefore, REM OSA would require that CPAP treatment should be used during the entire sleep period.

Cardiovascular and metabolic complications

Besides its link with hypertension, REM OSA may also be implicated in cardiovascular and metabolic comorbidities. In a sample of the Sleep Heart Health Study (SHHS) [41], the incidence of cardiovascular events was assessed in subjects with and without prevalent cardiovascular disease during an average follow-up of 9.5 years. In stratified analyses, the postulated association could be confirmed only in those with prevalent cardiovascular disease and severe REM OSA, with an adjusted hazard ratio of 2.56 (95% CI 1.46–4.47). In another follow-up survey using SHHS data, it was evaluated whether subjects with REMi OSA would also develop NREM OSA in the course of time. Also, it was assessed whether the development of OSA during NREM sleep was associated with incident cardiovascular disease [38]. The majority of the participants did not develop OSA during NREM sleep. However, the likelihood of progression of OSA into NREM sleep did increase with higher baseline REM AHI. Obesity was a significant contributing factor. The relative risk for incident cardiovascular events among those who developed an NREM AHI of ⩾5 events·h^{-1} at the follow-up visit was elevated only in women with REMi OSA at baseline. Another study, however, showed different results indicating that REM OSA could not be related to an increased cardiovascular risk. REM OSA was identified as a separate entity from a cluster analysis study of a multisite, observational US veteran cohort [92]. These findings indicate that differences in population samples and applied methodology may affect risk assessment in REM OSA patients.

It is known that OSA may compromise glycaemic health. OSA has been implicated as an independent risk factor for insulin resistance in subjects who may not be obese [93, 94]. Furthermore, the degree of OSA-related hypoxaemia seems to correlate with HbA1c levels in subjects without diagnosed diabetes [95]. The question whether REM OSA by itself may worsen glucose metabolism has been addressed in a limited number of studies. The naturally occurring decline of interstitial glucose concentrations during sleep was reversed in REM OSA, whereas NREM OSA had no appreciable effect [96]. In a prospective study of obese type 2 diabetes patients, incremental quartiles of REM AHI were significantly associated with increasing levels of HbA1c after adjusting for common confounders [97]. Associations between REM OSA and insulin resistance have also been investigated in the SHHS. The REM AHI was significantly associated with increasing levels of insulin resistance after controlling for common confounders. In this study, however, NREM AHI also played a role as it correlated significantly with fasting and post-prandial glucose levels [98].

A recent study demonstrated that correlations between lipid profiles and REM AHI *versus* NREM AHI were no longer present after adjustment for BMI. Furthermore, there was no difference in the lipid profile of REM OSA subjects as compared with healthy controls [37].

Considering the effects on hypertension and cardiometabolic disorders, there may be a causal role for REM OSA in the development of the metabolic syndrome. Preliminary evidence seems to confirm this hypothesis, as REM OSA was shown to be significantly associated with key features of this syndrome, independently of the effect of covariates such as age and obesity [99].

Treatment

CPAP therapy

Adequate compliance with CPAP therapy is important to prevent REM OSA. CPAP use for at least 6 h per night (thus also covering REM sleep in the second half of the sleep period) is associated with a reduction in the incidence of cardiovascular events. This has been shown in an observational study in 5138 OSA patients who were treated with long-term CPAP therapy followed for a median of 6.6 years [100, 101].

Some studies addressed the question of CPAP effectiveness in REM OSA and compliance to treatment. In the series by Conwell *et al.* [57], CPAP titration was recommended in 88% of patients with REM OSA, but only 66% of them underwent titration of fixed CPAP and 30-day compliance was available in 27% of the sample. Although no difference in compliance was observed compared to patients with NREM OSA, the large majority of patients with REM OSA did not accept, or comply with, CPAP treatment. In the study by Su *et al.* [102], CPAP treatment appeared equally effective in patients with REM (n=130) and NREM OSA (n=200), with objective data available in 68 and 65% of the patients, respectively. Automatic CPAP was more often prescribed to patients with REM OSA and average pressure was lower in patients with REM OSA compared to patients with NREM OSA. Changes in functional outcome measures were similar in the two groups after treatment.

More recent studies reported lower CPAP use in patients with REM OSA compared to patients with NREM OSA. Almeneessier *et al.* [103] prospectively followed 175 OSA patients, 30 of them with REM OSA, at 1, 6 and 12 months, and documented lower CPAP use at 1 year in patients with REM OSA compared to the rest of the sample (3.8 *versus* 5.1 h·night^{-1}). Side-effects such as mask discomfort, facial skin irritation and nasal congestion were reported more often by patients with REM OSA (86.7 *versus* 35.2%). Good and partial adherence were recorded in 23.3 and 56.7%, respectively, of patients with REM OSA at 1 year, and adherence was lower than in NREM OSA at all time points. Hoshino *et al.* [104] found that a diagnosis of REM OSA was a strong predictor of drop-out from CPAP therapy. In the study by Hu *et al.* [105], only 48% of REM OSA patients prescribed CPAP were adherent to treatment after 1 year and showed decreased sleepiness and improved quality of life.

Non-CPAP treatments

Since patients with REM OSA poorly accept CPAP treatment, the clinical dilemma whether or not to treat is still an open problem [106]. Choosing a treatment other than CPAP may be appropriate since OSA REM often occurs in the mild–moderate AHI range. Effectiveness of oral appliances was similar in REM and NREM OSA, and the success rate was negatively influenced by BMI, especially in REM OSA patients [107]. REM OSA was successfully treated in a middle-aged woman by use of an intra-oral neuromuscular stimulation device [108]. It is possible that non-CPAP treatment of REM OSA may obtain better results than CPAP, but a lack of studies to date prevents any conclusion.

There are at present no published data on the effects of drugs specifically prescribed for the treatment of REM OSA.

Lifestyle interventions

Some studies suggest that lifestyle interventions may be useful in the treatment of REM OSA. Exercise and educational measures over 8 weeks did not affect overall AHI in patients with moderate–severe OSA, but decreased AHI in REM sleep, daytime sleepiness and body weight [109]. A 4-year follow-up study in patients with type 2 diabetes and REM OSA indicated that weight reduction obtained by lifestyle interventions was significantly related to changes in HbA1c. However, reductions in REM AHI (or NREM AHI) were not associated with improved glycaemic control in diabetic patients with OSA [110]. These results indicate that the role of confounders must be considered in treatment outcome studies on REM OSA.

Discussion

In summary, predominant or isolated REM OSA occurs frequently, especially in women with OSA in the mild–moderate AHI range and in younger patients. REM OSA has been convincingly associated with systemic hypertension, especially when the REM AHI is >20 events·h^{-1}, both in cross-sectional and longitudinal studies. REM OSA does not always worsen over time and progression of OSA to NREM sleep has only been found in women with severe REM OSA and obesity at baseline.

Since OSA shows major sex-related differences, it is currently difficult to ascertain whether the relative contribution of different factors implied in REM OSA might be due to sex-related differences or if the features of REM OSA are independent of sex. Obesity appears to play a role in REM OSA, but the possible sex-related effects of the central *versus* peripheral distribution of adipose tissue in REM OSA are

still unknown. Similarly, insomnia and depression occur more often in women than in men. Large population studies have reported sex-related differences but neither the prevalence of hypertension nor other outcomes have been analysed according to sex [34, 35, 41]. Therefore, the independent role of REM OSA should be explored in studies specifically designed to address these outcomes.

Current areas of uncertainty regard cardiometabolic changes and prognosis in predominant or isolated REM OSA. More long-term longitudinal studies are needed to clarify this question. The feasibility and effects of CPAP treatment remain a major issue in the management of patients with REM OSA. Currently, if a patient with REM OSA is symptomatic for sleepiness, CPAP treatment appears indicated and could be accepted. However, the high rate of treatment interruption or insufficient adherence would suggest that efforts to identify specific phenotypes of REM OSA with good CPAP adherence are necessary. Nevertheless, in the case of REM OSA, CPAP use for $4\ h \cdot night^{-1}$ would be insufficient, given the occurrence of REM sleep in the early morning hours [97]. On the other hand, very little evidence is available to indicate the effectiveness of alternative treatments or lifestyle interventions, which need to be verified by clinicians on a case-to-case basis.

Animal models do not appear useful to increase our knowledge on REM OSA. Obstructive apnoeas naturally occur in REM sleep in mice, especially in a model of Down syndrome [111]. However, reliable polysomnography signals during sleep are hard to obtain in rodents [112]. The widely used OSA model of intermittent hypoxia exposure in mice is known to decrease REM sleep compared to sleep fragmentation or control conditions [113]. The English bulldog could be another natural model of REM OSA anatomy [114], but it is uncertain if research in these animals is still ongoing.

The major limitation emerging from our analysis of the literature is the already underlined lack of standardisation of the definition for REM OSA: “Given the significant heterogeneity in defining REM-related OSA, it is not surprising that its epidemiology, natural history, and clinical significance are not well defined” [6]. Moreover, differences in the methodology used for the assessment of the AHI may have a significant impact on REM OSA case-finding [115].

Posture-dependent occurrence of apnoeas and hypopnoeas is frequent in OSA patients. Most often, the supine posture predisposes to sleep-disordered breathing, whereas the nonsupine position may alleviate obstructive breathing. In an observational study, supine-only OSA was common, occurring in 23–63% of a standard OSA population, whereas REMi OSA was much less common (approximately 10%). Supine-only OSA showed a greater impact on the overall severity of OSA than REMi OSA [116]. Both sleep state and postural mechanisms may affect the appearance and frequency of respiratory events. These effects should not be considered independently as they may, together, determine the severity of OSA [117]. Most publications on REM OSA, while requiring a recorded REM sleep time of at least 30 min, do not report data on position dependency. Studies based on polysomnography in which sufficient REM sleep is recorded in both the supine and nonsupine postures are scarce. Controlling for the confounding effect of body position on the phenotypic aspects of REM OSA implies the implementation of new studies with a sufficiently powered design.

In the vast majority of studies, the definition of REM OSA is based on the AHI, for which values are increased in this sleep state as compared with NREM sleep. Knowing that the AHI is an unprecise metric and a poor measure of clinical correlates of OSA, this approach may be misleading [118]. Discrimination between REM and NREM OSA should also consider the type of respiratory events (apnoeas *versus* hypopnoeas), their duration, as well as the concomitant systemic effects. The degree of hypoxaemia that is associated with respiratory events is an important systemic effect. The compilation of all hypoxaemic events during sleep, commonly known as the “hypoxic burden”, has been shown to better predict cardiovascular outcomes that the mere AHI [119, 120]. Novel indices of OSA severity should be utilised to assess the postulated discrepancies between REM and NREM OSA in terms of clinical manifestations and treatment outcomes.

Similar to Janus of the Roman myth, REM OSA appears double-faced. On one hand, it could be a rather benign form of OSA, due to its mild–moderate severity and the scarce tendency to progression. On the other hand, it could be symptomatic like NREM OSA, at least in terms of sleepiness, and be associated with cardiometabolic consequences, at least in some patient subgroups. This, coupled with the need for prolonged nightly treatment and the reported poor adherence to CPAP, leaves unsolved the clinical dilemma of REM OSA management. More well-designed studies, including testing of alternative non-CPAP treatments, are definitely needed. Prior to this endeavour, however, the sleep medicine community should decide on a standardised working definition of REM OSA. This would have to include

not only the frequency and type of respiratory events, but also their systemic effects (*e.g.* the degree of hypoxaemia) and the loss (or preservation) of positional dependency. Differences in end-organ impact between NREM and REM OSA will only become clear if NREM and REM OSA can be described in unequivocal pathophysiological concepts.

Questions for future research

- Reach a unified definition of REM OSA, allowing comparisons of results obtained by different studies.
- Assess the contribution of sex-related features of OSA to the epidemiology, clinical presentation and outcomes of REM OSA.
- Understand the role of REM OSA in the pathogenesis of daytime sleepiness and hypertension.
- Include hypoxic and other markers of OSA severity beyond the usual AHI-based definition.
- Address the potential of non-CPAP treatment in predominant or isolated REM OSA.

Provenance: Commissioned article, peer reviewed.

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