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Obstructive sleep apnea during REM sleep: Clinical relevance and therapeutic implications

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Abstract

Purpose of review—Obstructive sleep apnea (OSA) is a highly prevalent condition that has been associated with cardiovascular morbidity and mortality, impaired glucose metabolism and daytime functional impairment. Compared with non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep is associated with higher sympathetic activity and cardiovascular instability in healthy individuals and more so in patients with OSA.

Recent findings—Recent studies have indicated that REM OSA is independently associated with prevalent and incident hypertension, non-dipping of nocturnal blood pressure, increased insulin resistance and impairment of human spatial navigational memory.

Summary—These findings have significant clinical implications for the duration of continuous positive airway pressure (CPAP) use that is needed to decrease the health risks associated with OSA. Further research is needed to establish the duration of CPAP needed to effectively treat REM OSA and to evaluate patients with REM OSA with an overall normal apnea-hypopnea index (AHI).

Keywords

Treatment; Rapid Eye Movement Sleep; Obstructive Sleep Apnea; Hypertension; Diabetes

Introduction

In 1953, University of Chicago investigators Nathaniel Kleitman and Eugene Aserinsky discovered rapid eye movement (REM) sleep [1]. In healthy adult humans, REM sleep accounts for approximately 20% of total sleep time and it is mostly concentrated in the second half of the sleep period. To date, the majority of research on REM sleep has focused on memory, affect and cognition. However, there are important autonomic nervous system and cardiorespiratory changes that occur in REM sleep compared to non-REM (NREM) sleep that, taken together, support the view that obstructive sleep apnea (OSA) during REM sleep may have worse cardiometabolic consequences than during NREM sleep.

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Conflicts of Interest MA has no conflict of interest to declare.

OSA is a highly prevalent disorder that is associated with significant morbidity and mortality [2, 3]. It is characterized by intermittent partial (hypopnea) or complete (apnea) upper airway collapse that leads to recurring episodes of hypoxemia and hypercapnia, sleep fragmentation and increased sympathetic activity. OSA during REM sleep is a condition where hypopneas and apneas occur primarily during REM sleep. The clinical significance of REM OSA remains controversial [4, 5]. Our knowledge of the prevalence and clinical implications of REM OSA has increased in recent years. What follows is an overview of the most current research findings regarding REM OSA.

Pathophysiology of REM OSA

Upper airway obstruction can occur in both non-rapid eye movement (NREM) sleep and during REM sleep. However, there is an increased tendency for upper airway collapse during REM sleep due to the decreased genioglossus muscle tone secondary to the cholinergic mediated inhibition of the hypoglossal nerve [6–8]. Increased sympathetic activity is widely considered to be the major putative mechanism by which OSA increases cardiovascular risk [9]. REM sleep is associated with greater sympathetic activity and cardiovascular instability than NREM sleep in healthy subjects and in patients with OSA [10, 11]. Indeed, using beat-to-beat BP measurements and recordings of sympathetic nerve activity via microneurography in patients with OSA, Somers *et al* found an increase in mean blood pressure (BP) from 92±4.5 mm Hg during quiet wakefulness to 116±5 mm Hg in NREM sleep and 127±7 mm Hg during REM sleep. Moreover, sympathetic activity was highest during REM sleep [10]. In another study of 16 patients with OSA and untreated hypertension, beat-to-beat BP measured invasively revealed a higher systolic BP in REM sleep compared to NREM sleep (148±29 mm Hg vs. 134±24 mm Hg, respectively) [12]. Furthermore, obstructive apneas and hypopneas in REM are longer in duration and are associated with significantly greater oxygen desaturation [13–15]. This is partly due to the decreased hypoxic and hypercapnic respiratory drive during REM sleep [16, 17]. Hence, these acute changes in hemodynamics and ventilatory control during REM sleep in patients with OSA could play a part in triggering ischemic events in patients with cardiovascular disease [11, 18–20]. Therefore, OSA during REM sleep may confer a higher cardiovascular risk than OSA during NREM sleep.

Prevalence of REM related OSA

The reported prevalence of REM OSA has been based mostly on clinical studies with small cohorts. Due to the inconsistent definitions used in the literature the reported prevalence has ranged between 10–36% [21–24]. REM OSA has been defined in a variety of ways including: 1) overall apnea-hypopnea index (AHI) ≥5 with AHI_{REM}/AHI_{NREM} ≥2; 2) overall AHI ≥5 with AHI_{REM}/AHI_{NREM} ≥2 and with AHI_{NREM} <15; 3) overall AHI ≥5, AHI_{REM}/AHI_{NREM} ≥2 and with AHI_{NREM} <8. In a cross-sectional study evaluating 1,019 consecutive adults who were referred for their first in-laboratory full night polysomnogram (PSG) for suspected OSA the prevalence of REM OSA ranged from 13.5% to 36.7% depending on the used definition, which is similar to the prevalence rates reported in previous clinical studies [25]. In this large cross-sectional study REM OSA was more prevalent in women, younger individuals and African Americans [25].

The prevalence of OSA during REM sleep is also similarly high in community-based cohorts. In the Wisconsin Sleep Cohort, 18% of the sleep studies with no evidence of OSA (i.e. AHI <5) demonstrated moderate or severe OSA during REM sleep (i.e. REM AHI ≥15). Also, 70% of the sleep studies with an overall AHI <15 (i.e. no OSA and mild OSA) had a REM AHI ≥15 [26]. Likewise, in the Sleep Heart Health Study, 25% of individuals with a NREM AHI <8 had a REM AHI ≥13 [27]. Furthermore, in a recent study by Appleton et al involving the Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) Study, 15% of the community-dwelling men without "clinically significant" OSA (i.e. AHI <10) had a REM AHI ≥ 20 [28]. Taken together, these findings suggest that REM predominant OSA is prevalent in clinical populations as well as in the community.

REM OSA and Hypertension

Longitudinal studies have had contradicting evidence regarding the association of OSA with incident hypertension. An increased risk of incident hypertension from OSA was observed in the Wisconsin Sleep Cohort Study [29] while the Sleep Heart Health Study [30] and the Vitoria Sleep Cohort [31] found the relationship was not significant after adjusting for covariates such as BMI and age.

However, a recent report from an extended follow-up of the Wisconsin Sleep Cohort demonstrated that REM OSA is independently associated with prevalent hypertension in cross-sectional analysis and with incident hypertension in longitudinal analysis. These associations became more robust in a subset of patients in whom ambulatory blood pressure monitoring (ABPM) was used to define hypertension. Importantly, AHI during NREM sleep had no significant association with prevalent or incident hypertension after adjusting for REM AHI. Moreover, to further validate the relationship between REM OSA and hypertension, the investigators performed additional analysis in a subset of participants who had no disease in NREM sleep (i.e. NREM AHI < 5). In this subset, increasing quartiles of REM AHI was strongly associated with hypertension, suggesting a dose-relationship between REM AHI and hypertension *[26]. Specifically, the risk of hypertension increased significantly when REM AHI was greater than or equal to 15. In individuals with NREM AHI ≤5, a twofold increase in REM AHI was associated with 24% higher odds of hypertension.

Appleton et al most recently examined the temporal associations of previously unrecognized or undiagnosed OSA, including REM OSA, with hypertension **[28]. This was examined in 739 middle-aged and elderly community-dwelling men enrolled in the Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) Study, a population-based longitudinal cohort from Adelaide, Australia. REM OSA (REM AHI ≥30/h) demonstrated an independent association with prevalent and recent-onset hypertension (OR 2.40, 95% CI 1.42–4.06, and OR 2.24, 95% CI 1.04–4.81, respectively). In contrast, and similar to the Wisconsin Sleep Cohort analysis, NREM AHI was not associated with hypertension after adjusting for REM AHI. In men with AHI<10, REM AHI ≥20/h was significantly associated with prevalent hypertension (OR 2.67, 95% CI 1.33–5.38).

In healthy individuals BP normally varies during different physiologic states and declines by more than 10–20% at nighttime during sleep compared with daytime waking BP. Non-dipping has important clinical implications because it is a marker for future development of hypertension in those who are normotensive. Moreover, non-dipping BP has been associated with worse cardiovascular prognosis and increased target organ damage, including left ventricular hypertrophy, myocardial infarction, angina, ischemic stroke and cardiovascular death [32]. Another longitudinal analysis of the Wisconsin Sleep Cohort assessed 269 adults who completed two or more 24-hour ABPM studies over an average of 6.6 years of follow-up. The goal of the study was to evaluate the association of REM-related OSA and incident non-dipping of BP in a sample selected regardless of the presence of OSA symptoms or co-morbidities *[33]. The study demonstrated that OSA in REM sleep, independent of NREM OSA, was associated with the development of nocturnal systolic and diastolic non-dipping of BP over an average follow-up period of 6.6 years among participants who initially were normal nocturnal BP dippers. The association also showed a dose-response gradient: individuals with a baseline REM AHI ≥15 had an approximately threefold greater relative risk of developing systolic non-dipping and a fourfold greater relative risk of developing diastolic non-dipping compared with those with REM AHI <1.

Therefore, there is a convergence of data from two population-based studies from distinct geographical regions demonstrating a significant and clinically relevant association between OSA during REM sleep and prevalent hypertension, incident hypertension as well as incident nocturnal non-dipping of BP.

REM OSA and Glucose Metabolism

From a metabolic standpoint, elevated REM AHI has been independently associated with insulin resistance. In the community-based Sleep Heart Health Study, increased REM AHI was associated with increased insulin resistance but not with impaired fasting glucose or glucose intolerance after adjustment for multiple potential confounders, including age, sex, race, adiposity, self-reported sleep duration and NREM AHI. In contrast, increased NREM AHI was associated with impaired fasting glucose and glucose intolerance after adjusting for adiposity. This finding suggests that REM-related OSA may impact glucose metabolism even in the absence of NREM OSA **[34].

Two studies that performed continuous interstitial glucose monitoring simultaneously with polysomnography (PSG) directly support the hypothesis that REM-related OSA may have adverse metabolic consequences [35, 36]. One of these studies included 13 obese patients with type 2 diabetes and severe OSA and compared them to 13 obese patients with type 2 diabetes without OSA with similar demographic characteristics. The mean glucose level was 38% higher during REM sleep in those with OSA [35]. The second study included 11 non-diabetic subjects. They found that in the absence of OSA, REM sleep leads to a larger decline in interstitial glucose concentration than NREM sleep. OSA during REM sleep, however, abolished the expected decline in interstitial glucose concentration. In contrast, OSA during NREM sleep had no impact on interstitial glucose concentrations [36].

Increasing severity of disordered breathing during REM sleep is also associated with worse glycemic control in type 2 diabetes. In a prospective study of 115 subjects with type 2 diabetes enrolled from the community (65 women, age 55.2 ± 9.8 years; BMI 34.5 ± 7.5 kg/m^2), REM AHI was independently associated with increasing levels of hemoglobin A1c (HbA1c) (p=0.008). In contrast, NREM AHI was not associated with HbA1c (p=0.762). The mean adjusted HbA1c increased from 6.3% in subjects in the lowest quartile of REM AHI to 7.3% in subjects in the highest quartile of REM AHI, a clinically significant effect size *[37]. To obtain definite evidence regarding the clinical efficacy of CPAP treatment to improve glucose control in T2DM, we recently completed a proof-of-concept study that was designed to test the hypothesis that one week of full night CPAP treatment of OSA in the laboratory, as compared to sham-CPAP (placebo), results in improvement in glycemic control as assessed by mean plasma glucose levels from 24-h blood sampling *[38]. In this study we employed a rigorous methodology of 24-h blood sampling, adherence to standardized meals during 24-h blood sampling, and ensuring CPAP adherence in order to address important limitations faced by several prior studies such as solely relying on fasting measures of glucose and insulin or HbA1c or being limited by low CPAP adherence. In this study adherence to CPAP was monitored nightly in the sleep laboratory. The 24-h mean plasma glucose decreased significantly more after one week of active vs. sham CPAP treatment (−13.7 ± 3.6 mg/dL vs. −2.9 ± 1.4 mg/dL; p=0.013). This decrease in mean plasma glucose was associated with a trend for lower 24-hour mean insulin levels (−25.8 ± 16.5 pmol/L vs. 28.4 ± 21.6 pmol/L; p=0.071). Improvement in glucose levels was most prominent during the overnight period, resulting in lower morning fasting glucose levels. The degree of improvement seen with one week of full adherence to CPAP was similar to that achieved by oral pharmacologic agents and equivalent to a drop of 0.4–0.5% in the HbA1c levels. This improvement in glycemic control without an increase in serum insulin levels suggests that elimination of OSA decreases insulin resistance. Our study demonstrates that if CPAP is used during the entire eight hour sleep period, and therefore covering all REM sleep, it can lead to significant glycemic improvement in patients with OSA and type 2 diabetes *[38].

Collectively, these studies support the notion that OSA during REM sleep is adversely associated with glucose metabolism. However, despite these important associations between REM OSA and glusose metabolism, there is a need for additional research.

OSA during REM sleep and neurocognitive function

Several studies have shown that OSA during REM sleep is not associated with excessive daytime sleepiness (based on a subjective sleepiness questionnaire or multiple sleep latency test) or quality of life [27, 39–42]. However, sleepiness questionnaires and the multiple sleep latency test are not designed to detect impairments of neurocognitive function [5]. Studies in rodents have shown that REM sleep suppression leads to impairment of spatial memory [43, 44]. These findings were confirmed in the human in a recent study where 18 subjects with severe OSA on chronic CPAP therapy underwent 1-night of CPAP withdrawal only during REM sleep (i.e. creating a model of REM-specific OSA by lowering the CPAP pressure to non-therapeutic settings during REM sleep) [45]. This condition of CPAP withdrawal during REM sleep led to reemergence of severe OSA during REM sleep (REM AHI of 46.1±3.5

events/h) accompanied by REM sleep fragmentation without any effect on total sleep time, sleep efficiency and NREM slow wave sleep. The study showed that a normal overnight sleep while on CPAP consolidated spatial navigational memories. These benefits were completely lost when REM sleep was disrupted by 1-night of CPAP withdrawal exclusively during REM sleep. This finding suggests that fragmentation of REM sleep as occurs in REM OSA has deleterious effects on spatial navigational memory. However, additional studies are needed to better delineate the deleterious effect on untreated REM OSA on neurocognitive function.

Clinical Significance of REM OSA in the Context of CPAP Therapy

In clinical practice, 4 hours of nightly CPAP use for 70% of the nights is considered adequate adherence to therapy [46]. This translates into an average CPAP use of 2.8 hours every night. Indeed, it is plausible that reduced CPAP adherence and the predominantly untreated OSA during REM sleep (which prevails during the latter hours of normal nocturnal sleep) may explain the negative or modest effects of CPAP therapy on BP and glycemic control in randomized clinical trials. In a recent randomized controlled trial examining the effect of CPAP on incidence of hypertension or cardiovascular events in nonsleepy OSA patients, the investigators found that CPAP did not improve outcomes based on intention-to-treat analysis [47]. However, in post-hoc analyses, the investigators reported a significant reduction in incident hypertension or cardiovascular events in those that were adherent to CPAP therapy (median use of 6 hours/night). In another randomized controlled trial of patients with OSA and resistant hypertension, there was a significant positive correlation between hours of CPAP use and the decrease in 24-hour mean BP [48]. In a prospective study of 115 participants with type 2 diabetes, we reported that 3 and 4 hours of CPAP use after lights were turned off would leave 75% and 60% of obstructive events during REM sleep untreated, respectively [37]. Therefore, based on our data, the failure to treat REM OSA due to insufficient CPAP use may have clinical relevance in the context of mitigating its adverse cardiovascular and metabolic consequences [26, 33, 37]. In this context, it would of clinical interest to explore effectiveness of oral appliances in treating OSA during REM sleep, particularly that adherence to oral appliances tends to be better than with CPAP.

REM OSA, defined by REM AHI thresholds that are strongly associated with hypertension, is quite prevalent in the community at large and in individuals that would not be considered as having “clinically significant” OSA using current clinical definitions. Further research is needed to establish whether treatment can decrease the cardiovascular and metabolic risk associated with REM OSA. More attention should be given to increasing adherence to CPAP treatment in patients with OSA to cover the early morning hours before awakening in order to more effectively treat OSA during REM sleep. Those findings also emphasize the need to personalize OSA therapy. Not all patients with OSA fit into one phenotype. Further research and larger studies focusing on REM OSA are needed to redefine treatment strategies for REM OSA.

Conclusion

REM OSA is quite prevalent and is associated with adverse cardiovascular and metabolic outcomes. Current CPAP adherence guidelines may leave the majority of REM OSA untreated. Clinicians should emphasize the need for more prolonged CPAP usage that includes the early morning hours before awakening in patients with REM predominant OSA. Further research is needed to address treatment of patients with REM OSA who have an overall normal AHI.

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Key Points

- Rapid eye movement (REM) predominant OSA is a prevalent disorder that is independently associated with adverse cardiometabolic outcomes and impairment of human spatial navigational memory.
- Prolonged CPAP usage that includes the early morning hours before awakening in patients with REM predominant OSA should be emphasized by clinicians.
- Further research is needed to address treatment of patients with REM OSA who have an overall normal AHI.

Table 1

The relationship between REM OSA and risk of cardiometabolic disease

First Author (reference), year of publication	Study Participants	Study Design	Measure of Outcome	Results	Conclusion
Mokhlesi (*26), 2014	Wisconsin Sleep Cohort Study The total sample consisted of 1,451 subjects who underwent a total of 4,385 sleep studies Analyses performed for the entire sample were repeated for the subset of 742 participants who also had 24-hour ambulatory blood pressure monitoring (ABPM) with a total of 1,085 sleep studies	Cross-sectional analysis of a population-based study	Prevalent hypertension	Adjusted odds ratio (95% confidence interval) for prevalent hypertension in participants with REM AHI ≥15 plus non-REM AHI ≤5 relative to REM AHI <1 plus non-REM AHI ≤5 For the enitre sample: 1.32 (0.97–1.79) For ABPM subset: 3.38 (1.70–6.72)	REM OSA is cross-sectionally and longitudinally associated with hypertension. Non-REM AHI is not associated with hypertension.
		Longitudinal analysis of a population-based study	Incident hypertension	Adjusted odds ratio (95% confidence interval) for incident hypertension in participants with REM AHI ≥15 relative to REM AHI <1 For the entire sample: 1.76 (1.08–2.92) For the subset with non-REM AHI ≤5: 1.98 (1.01–3.88)	
Appleton (**28), 2016	739 men from the Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) Study	Cross-sectional analysis of a population-based study	Prevalent hypertension	Adjusted odds ratios (95% confidence interval) for prevalent hypertension In men with REM AHI ≥30/h: 2.40 (1.42–4.06) In men with total AHI<10, REM AHI ≥20/h: 2.67 (1.33–5.38)	Moderate-severe REM OSA was independently associated with prevalent and recent onset hypertension. Non-REM AHI is not associated with hypertension.
		Longitudinal analysis of a population-based study	Recent onset hypertension	Adjusted odds ratios (95% confidence interval) for recent onset hypertension In men with REM AHI ≥30/h: 2.24 (1.04–4.81) In men with AHI<10, REM AHI ≥20/h: 2.32 (0.79–6.84)	
Mokhlesi (*33), 2015	Wisconsin Sleep Cohort Study 199 and 215 participants in the systolic and diastolic non-dipping groups from ABPM, respectively	Longitudinal analysis of a population-based study	Incident non-dipping of nocturnal blood pressure	Relative Risk of incident systolic and diastolic non-dipping (95% confidence interval) in participants with REM AHI ≥15 to those with REM AHI<1 event/h, Systolic non-dipping: 2.84 (1.10–7.29) Diastolic non-dipping: 4.27 (1.20–15.13)	REM OSA is independently associated with incident non-dipping of BP. Non-REM AHI is not associated with non-dipping.

First Author (reference), year of publication	Study Participants	Study Design	Measure of Outcome	Results	Conclusion
Chami (**34), 2015	Sleep Heart Health Study 3,110 participants with full montage home-polysomnography and fasting glucose Fasting and 2-hour post-challenge glucose levels were assessed during an oral glucose tolerance test in 2,264 participants The homeostatic model assessment index for insulin resistance (HOMA-IR) was calculated in 1,543 participants	Cross-sectional analysis of a community-based study	-Fasting glucose -Fasting and 2-hour post-challenge glucose levels assessed during oral glucose tolerance test -The homeostatic model assessment index for insulin resistance (HOMA-IR)	REM AHI was only associated with HOMA-IR (beta = 0.04; 95% CI, 0.1–0.07; P = 0.01)	REM AHI is associated with insulin resistance but not with fasting glycemia or glucose intolerance
Grimaldi(*37), 2014	115 participants with type 2 diabetes	Cross-sectional analysis	Hemoglobin A1C	REM AHI was independently associated with increasing levels of hemoglobin A1c (HbA1c) (p=0.008)	OSA during REM sleep may influence long-term glycemic control. Non-REM AHI was not associated with HbA1c.
Mokhlesi (*38), 2016	19 participants with type 2 diabetes and OSA (13 treated with CPAP, 6 treated with sham CPAP)	Clinical trial	Plasma glucose levels by 24 hour blood sampling. Nightly CPAP (or sham CPAP) therapy in the sleep laboratory to ensure adherence to therapy	The 24-h mean plasma glucose decreased significantly more after one week of active vs. sham CPAP treatment (−13.7 ± 3.6 mg/dL vs. −2.9 ± 1.4 mg/dL; p=0.013)	If CPAP is used during the entire eight hour sleep period, and therefore covering all REM sleep, it can lead to significant glycemic improvement in patients with OSA and type 2 diabetes

Table 2

The relationship between REM OSA and daytime dysfunction

First Author (reference), year of publication	Study Participants	Study Design	Measure of Outcome	Results	Conclusion
Chami (27), 2010	5,649 participants from Sleep Heart Health Study	Cross-sectional analysis of a community-based study	Sleepiness measured based on Epworth Sleepiness Scale (ESS) Sleep maintenance based on Sleep Heart Health Study Sleep Habit Questionnaire QOL based on physical and mental composites scales of the Medical Outcomes Study Short Form (SF)-36.	REM AHI was not associated with the ESS scores, frequent difficulty maintaining sleep or early awakening from sleep, or the physical and mental components scales scores of the SF-36 after adjusting for demographics, body mass index, and non-REM AHI.	REM-predominant sleep disordered breathing is not independently associated with daytime sleepiness, self-reported sleep disruption, or impaired health-related QOL
Chervin (39), 1998	1,146 patients referred for a polysomnogram and multiple sleep latency test	Cross-sectional analysis of a clinical population	Sleepiness measured by Multiple Sleep Latency Test (MSLT)	In linear regression models, the AHI explained 11.0% of the variance in MSLT results. Non-REM AHI explained 10.8%, and REM AHI explained only 6.0% ($P \leq 0.001$ for each). REM AHI/non-REM AHI ratio had no influence on the overall relationship between AHI and sleepiness ($p=0.23$).	REM and non-REM AHI contribute equally to sleepiness as measured by the MSLT.
Punjabi (40), 2002	1,821 patients referred for a polysomnogram and multiple sleep latency test	Cross-sectional analysis of a clinical population	Sleepiness measured by Multiple Sleep Latency Test (MSLT)	REM AHI was not associated with daytime sleepiness (Relative Risk: 1.01; 95%CI: 0.94–1.10) Non-REM AHI was associated with daytime sleepiness	Sleep-disordered breathing during non-REM sleep, but not REM sleep, is associated with increased risk of daytime sleepiness
Pamidi (41), 2011	1,019 consecutive patients that were referred for their first polysomnogram for suspected OSA	Cross-sectional analysis of a clinical population	Subjective sleepiness using the Epworth Sleepiness Scale (ESS) Quality of Life (QoL) using the short-form quality of life questionnaire-12 (SF-12)	In adjusted linear regression models, non-REM AHI was a significant predictor of sleepiness in the entire cohort of patients with OSA REM AHI was not a significant predictor of ESS or QoL Greater depressive symptoms and body mass index were significant independent predictors of ESS and reduced QoL in the REM-related OSA group.	Sleep-disordered breathing during non-REM sleep, but not REM sleep, is associated with daytime sleepiness and QoL
Khan (42), 2013	3135 participants from the Osteoporotic Fractures in Men (MrOS) Sleep Study	Cross-sectional analysis of a community-based study	Daytime somnolence using Epworth Sleepiness Scale (ESS) Sleep-related quality of life using Functional Outcomes of Sleep Questionnaire (FOSQ) Sleep disturbance using Pittsburgh Sleep Quality Index (PSQI) General quality of life using Short Form-12 (SF-12)	REM AHI was not associated with subjective sleep measures (ESS, FOSQ, PSQI), lower quality of life (SF-12), or greater depressive symptoms	REM-predominant OSA was highly prevalent and was associated with objective indices of poorer sleep quality on polysomnography but not with subjective measures of daytime sleepiness or quality of life.

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First Author (reference), year of publication	Study Participants	Study Design	Measure of Outcome	Results	Conclusion
			Depressive symptoms using Geriatric depression Scale-15 (GDS) Health status using self-perceived health status		
Vargas (*45), 2014	18 subjects with severe OSA on chronic CPAP therapy underwent 1-night of CPAP withdrawal only during REM sleep	Prospective cohort study	Spatial navigational memory impairment measured by performance in 3 dimensional spatial mazes	The study showed that a normal overnight sleep while on CPAP consolidated spatial navigational memories. These benefits were completely lost when REM sleep was disrupted by 1-night of CPAP withdrawal exclusively during REM sleep.	This study suggests that fragmentation of REM sleep, despite normal sleep efficiency, total sleep time and slow wave sleep, may have adverse effects on spatial navigational memory