ORIGINAL ARTICLE

Obstructive Sleep Apnea during REM Sleep and Hypertension
Results of the Wisconsin Sleep Cohort

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Abstract

Rationale: Obstructive sleep apnea (OSA) is associated with hypertension.

Objectives: We aimed to quantify the independent association of OSA during REM sleep with prevalent and incident hypertension.

Methods: We included adults enrolled in the longitudinal community-based Wisconsin Sleep Cohort Study with at least 30 minutes of REM sleep obtained from overnight in-laboratory polysomnography. Studies were repeated at 4-year intervals to quantify OSA. Repeated measures logistic regression models were fitted to explore the association between REM sleep OSA and prevalent hypertension in the entire cohort (n = 4,385 sleep studies on 1,451 individuals) and additionally in a subset with ambulatory blood pressure data (n = 1,085 sleep studies on 742 individuals). Conditional logistic regression models were fitted to longitudinally explore the association between REM OSA and development of hypertension. All models controlled for OSA events during non-REM sleep, either by statistical adjustment or by stratification.

Measurements and Main Results: Fully adjusted models demonstrated significant dose-relationships between REM apnea–hypopnea index (AHI) and prevalent hypertension. The higher relative odds of prevalent hypertension were most evident with REM AHI greater than or equal to 15. In individuals with non-REM AHI less than or equal to 5, a twofold increase in REM AHI was associated with 24% higher odds of hypertension (odds ratio, 1.24; 95% confidence interval, 1.08–1.41). Longitudinal analysis revealed a significant association between REM AHI categories and the development of hypertension (P trend = 0.017). Non-REM AHI was not a significant predictor of hypertension in any of the models.

Conclusions: Our findings indicate that REM OSA is cross-sectionally and longitudinally associated with hypertension. This is clinically relevant because treatment of OSA is often limited to the first half of the sleep period leaving most of REM sleep untreated.

Keywords: sleep-disordered breathing; obstructive sleep apnea; rapid eye movement; REM-related sleep apnea; hypertension

Obstructive sleep apnea (OSA) is a highly prevalent chronic condition characterized by recurrent episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway causing intermittent hypoxemia and hypercapnia, cortical microarousals, increased oxidative stress, and sleep fragmentation (1, 2). These adverse effects of OSA are important mediators of cardiovascular risk (3, 4), even in milder forms of OSA (5–8). OSA has been independently associated with hypertension (9, 10), coronary heart disease, stroke, and cardiovascular mortality (11–15). Upper airway collapse can occur in both REM and non-REM sleep. However, during REM sleep, cholinergic-mediated inhibition of the

(Received in original form June 20, 2014; accepted in final form October 8, 2014)

Supported by National Institutes of Health grants R01HL062252 and1 UL1RR025011. B.M. is supported by R01HL119161.

Author Contributions: B.M., L.A.F., E.V.C., and P.E.P. designed the study and/or the analysis. B.M., E.W.H., L.A.F., and P.E.P. performed all analyses. T.Y. and P.E.P. obtained study funding. B.M., L.A.F., E.W.H., T.Y., K.M.H., E.V.C., and P.E.P. participated in data interpretation and manuscript preparation. B.M., L.A.F., and P.E.P. oversaw all analyses and take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. All authors approved this manuscript in its final form.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 190, Iss 10, pp 1158–1167, Nov 15, 2014

Originally Published in Press as DOI: 10.1164/rccm.201406-1136OC on October 8, 2014
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea has been associated with hypertension in community-based and clinical cohorts. To date, however, it remains unclear whether obstructive respiratory events during REM sleep have a different impact on cardiovascular health compared with events during non-REM sleep.

What This Study Adds to the Field: Our analysis of the Wisconsin Sleep Cohort participants shows for the first time that obstructive sleep apnea in REM sleep is cross-sectionally and longitudinally associated with hypertension. Because REM sleep predominates in the early morning hours before typical awakening, the cardiovascular benefits of therapy may not be achieved with the typical continuous positive airway pressure use of 3–4 hours at the beginning of the night.

hypoglossal nerve results in the suppression of genioglossus muscle tone, which substantially increases the propensity for upper airway collapse (16–18). This increased propensity for upper airway collapse can lead to REM-predominant OSA or simply OSA that becomes more severe during REM sleep (19–23). In patients with mild or moderate OSA, who represent more than 80% of individuals with OSA in the community (14, 15), obstructive events often cluster in REM sleep resulting in selective fragmentation of REM sleep (20).

Increased sympathetic activity is widely considered to be the major putative mechanism by which OSA increases cardiovascular risk (24). Moreover, it is well established that compared with non-REM sleep, REM sleep is associated with greater sympathetic activity and cardiovascular instability in healthy human subjects and in patients with OSA (25–27). Therefore, OSA during REM sleep may have more serious adverse consequences than OSA during non-REM sleep. The hemodynamic and sympathetic changes during REM sleep cause a surge in blood pressure and heart rate. These acute hemodynamic changes could play a part in triggering ischemic events in patients with cardiovascular disease (26, 28–30). Moreover, REM sleep is characterized by a reduction in the hypoxic and hypercapnic ventilatory drive (31, 32). This physiologic phenomenon may in part explain why obstructive apneas and hypopneas during REM sleep are longer in duration and are associated with significantly greater oxygen desaturation compared with events in non-REM sleep (33–35). Although OSA during REM sleep has not been associated with excessive daytime sleepiness or reduced quality of life (36–40), a recent study found that in type 2 diabetics, worse glycemic control was associated with obstructive apneas and hypopneas that occur in REM sleep but not in non-REM sleep (41). Whether REM-related respiratory events have more deleterious effects on cardiovascular health than non–REM-related events remains largely unexplored (42).

To that end, the primary objective of this study was to determine the association between REM apnea–hypopnea index (AHI) and hypertension. We hypothesized that OSA during REM sleep is cross-sectionally and longitudinally associated with hypertension. To test our hypothesis, we examined data from the Wisconsin Sleep Cohort Study (WSCS), a large community-based cohort selected independently of the presence of symptoms or comorbidities. Analyses of data from 709 participants in the WSCS published in 2000 (9) revealed a significant dose-response association between the presence and severity of OSA at baseline and hypertension during a 4-year follow-up. The present analyses seek to determine whether the association between OSA and hypertension is mainly driven by REM OSA, rather than non-REM OSA, using the currently available data on 1,451 participants who each underwent, on average, three polysomnographic studies at approximate 4-year intervals.

Methods

Study Population

The University of Wisconsin Health Sciences Institutional Review Board approved WSCS protocols and informed consent documents. Details of the WSCS are provided in the online supplement. Of the 2,940 individuals invited to undergo an initial overnight in-laboratory polysomnography study, 1,546 (53%) agreed to participate and were successfully studied. All participants had a baseline in-laboratory polysomnography study between 1988 and 2000. Participants were invited approximately every 4 years for follow-up in-laboratory polysomnography.

As previously described (9), we excluded subjects with unusable physiologic measurements or less than 4 hours of sleep. For the current study, we also excluded 510 polysomnography studies with less than 30 minutes of recorded REM sleep to ensure meaningful assessments of OSA during REM sleep. The threshold value of 30 minutes of REM sleep was based on previous clinical observations that most patients referred for diagnostic polysomnography have a REM sleep time of at least 30 minutes (42), and to allow for sufficient observation of REM sleep to characterize REM OSA. We also excluded 170 polysomnography studies that were performed while the participant was using their home continuous positive airway pressure (CPAP) therapy during the in-laboratory polysomnography. Consequently, for cross-sectional associations, our total sample consisted of 1,451 subjects who underwent a total of 4,385 sleep studies. Most participants had multiple sleep studies (*see* Table E1 in the online supplement). Analyses performed for the total sample were repeated for the subset sample of 742 participants who also had 24-hour ambulatory blood pressure monitoring (ABPM) with a total of 1,085 polysomnography studies.

Polysomnography

Details of the in-laboratory polysomnography technique are provided in the online supplement. Each 30-second epoch of recording was scored for sleep stage and apnea and hypopnea events by trained technicians. Scoring, reviewing, and interpretation of the respiratory data from the polysomnograms use previously described criteria (1, 2). Oxygen saturation metrics, such as 4% or greater oxygen desaturation index (ODI), and percent sleep time below 90% Sp_{O_2} (T90) and time spent in supine position are not available on the entire sample of 4,385 sleep studies used for analysis of the AHI. In particular, these metrics are available on only a small subset of the sleep studies performed before 2000, when fully

digitalized data collection was initiated in the WSCS. Therefore, for the present analyses, in total, 2,058 studies were available to examine the impact of ODI, 1,631 studies to examine the impact of T90, and 2,021 studies to examine the impact of body position. As such, the subanalyses of the oxygen saturation parameters and body position are significantly underpowered relative to those that use the AHI.

Outcome Variables

At each polysomnography study, hypertension was defined by one of two methods: clinically assessed auscultatory blood pressure equal to or above 140/90 mm Hg (measured as described in [9]) or use of antihypertensive medications ("clinical hypertension"); or ABPM-based mean wake systolic blood pressure of greater than or equal to 135 mm Hg or mean wake diastolic blood pressure greater than or equal to 85 mm Hg or use of antihypertensive medication ("ABPM hypertension"). Details of the ABPM study protocol have been previously published (43, 44) and are summarized in the online supplement. The use of antihypertensive medication (α-adrenergic antagonists, β-blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers) was determined based on the participants' self-report of current use at the time of each polysomnography study.

Covariates

Covariates included in the final models were age, sex, race, body mass index (BMI), waist-to-hip ratio, smoking habits, and alcohol use as assessed at the time of each polysomnography study. Covariate assessment is described in detail in the online supplement.

Statistical Analysis

The primary goal of the study was to estimate the association of OSA during REM sleep, independent of non-REM OSA and covariates, with prevalent hypertension and incident hypertension. Continuously distributed blood pressure measurements were not modeled because the common use of antihypertensive medication in the cohort obscures underlying blood pressure levels in those who use medications, therefore biasing associations. All data were analyzed with SAS software (SAS Institute Inc., Cary, NC) and two-sided *P* values of

Table 1. Sample Characteristics by REM AHI Severity Category for the Entire Sample of Sleep Studies in 1,451 Subjects (Multiple Studies per Subject)

	REM AHI Severity Category (*Events/h*)				
	<1	**1–4.9**	**5–14.9**	**⩾15**	**Total**
Number of sleep studies, n (%)	1,143 (26)	1,098 (25)	929 (21)	1,215 (28)	4,385
Female, %	52	42	43	45	46
Race/ethnicity, white, %	98	97	95	95	96
Current smoking, %	16	14	12	10	14
Prevalent hypertension, %	25	36	43	60	41
Type 2 diabetes, %	2	5	7	12	7
Age, yr, mean (SD)	50 (10)	53 (10)	55 (9)	58 (9)	54 (10)
Body mass index, kg/m^2, mean (SD)	28 (5)	29 (5)	30 (6)	35 (7)	30 (6)
Waist-to-hip ratio, mean (SD)	0.87 (0.09)	0.89 (0.09)	0.91 (0.09)	0.93 (0.09)	0.90 (0.09)
Total sleep time, min, mean (SD)	376 (60)	377 (57)	378 (57)	373 (56)	376 (57)
REM sleep time, min, mean (SD)	72 (25)	71 (25)	70 (24)	63 (23)	68 (25)
REM sleep time, percent of total sleep time, mean (SD)	19 (5)	19 (6)	18 (5)	17 (5)	18 (5)
Slow wave sleep, min, mean (SD)	42 (32)	39 (34)	35 (33)	31 (32)	37 (33)
Slow wave sleep, percent of total sleep time, mean (SD)	11 (9)	10 (9)	9 (8)	8 (8)	10 (9)
AHI, events/h, mean (SD)	0.9 (2.1)	2.5 (4.7)	4.9 (5.4)	14.0 (13.1)	5.8 (9.4)
non-REM AHI, events/h, mean (SD)	1.3 (3.0)	3.4 (6.7)	5.9 (8.4)	15.7 (17.2)	6.8 (12.0)
REM AHI, events/h, mean (SD)	0.2 (0.3)	2.6 (1.1)	9.1 (2.8)	34.8 (17.4)	12.3 (17.0)
Oxygen desaturation index, events/h, mean (SD)*	1.8 (3.6)	3.9 (6.2)	7.3 (8.1)	19.9 (15.5)	10.8 (13.4)
non-REM oxygen desaturation index, events/h, mean (SD)*	1.9 (4.1)	3.8 (6.8)	6.4 (9.0)	15.8 (15.9)	8.9 (12.8)
REM oxygen desaturation index, events/h, mean (SD)*	0.2 (0.3)	2.3 (1.3)	8.4 (3.1)	34.2 (16.8)	16.1 (18.3)
Time below 90% Sp_{O_2}, percent of total sleep time, mean (SD)†	0.4 (1.9)	1.3 (8.8)	0.8 (3.7)	3.8 (9.5)	2.4 (8.6)
Time below 90% Sp_{O_2}, percent of non-REM sleep time, mean (SD)†	0.3 (1.8)	1.3 (8.6)	0.7 (3.6)	2.6 (8.8)	1.9 (8.2)
Time below 90% Sp_{O_2}, percent of REM sleep time, mean (SD)†	0.5 (3.6)	1.6 (10.5)	1.4 (5.2)	10.8 (18.4)	5.8 (15.3)
Epworth Sleepiness Scale, mean (SD)‡	8.4 (4.0)	8.4 (4.0)	8.8 (4.1)	9.0 (4.1)	8.7 (4.1)
Excessive daytime sleepiness, %	20	18	22	23	21

Definition of abbreviations: AHI = apnea–hypopnea index; Sp_{O_2} = oxygen saturation by finger pulse oximetry.
*Available on a subset of studies (n = 2,058) after implementation of full digital polysomnography in the Wisconsin Sleep Cohort.
†Available on a subset of studies (n = 1,631) after implementation of full digital polysomnography in the Wisconsin Sleep Cohort.
‡Available on a subset of studies (n = 3,552).

less than 0.05 were considered to indicate statistical significance.

REM AHI was examined as the independent variable in two ways: as severity categories (REM AHI < 1 [reference category], 1–4.9, 5–14.9, ≥ 15, which corresponded roughly to quartiles of the distribution of REM AHI); and as a continuous variable, $\log_2$(REM AHI + 1), which allows for the coefficients to be interpreted as the "effect" of a twofold increase in REM AHI (1 was added to REM AHI in the argument of the logarithm to allow for analysis of zero values).

For cross-sectional analyses of "clinical" and "ABPM" hypertension, repeated measures logistic regression was used. Repeated measures analysis allows for the efficient use of multiple studies per person by adjusting for within-subject correlation of observations, and for computing robust standard errors for hypothesis testing and computing confidence intervals. These models were adjusted for $\log_2$(non-REM AHI +1), age, sex, race/ethnicity, BMI, waist-to-hip ratio, smoking status, and alcohol use. Interactions between REM AHI categories and both age and sex were tested for statistical significance. In supplementary analyses intended to comprehensively isolate the effects of REM from non-REM OSA, beyond statistical adjustment by $\log_2$(non-REM AHI +1), we also performed cross-sectional analyses in samples restricted to having non-REM AHI less than or equal to 5 (n = 2,953 such sleep studies for "clinical hypertension" and 572 sleep studies for "ABPM hypertension"). In these supplementary models, as with all others, we statistically adjusted for the remaining non-REM AHI variability.

Longitudinal models of intrasubject change in hypertensive status were fit using conditional logistic regression to estimate the increased likelihood of development of hypertension associated with REM AHI severity category. The conditional models use data only from individuals who transition from hypertension to no hypertension status or vice versa and implicitly control for fixed within-person characteristics, such as sex, race, and genetic profile. These models were adjusted for $\log_2$(non-REM AHI +1), age, BMI, waist-to-hip ratio, smoking status, and alcohol use. There were 428 subjects (1,775 sleep studies) that demonstrated a change in

Table 2. Sample Characteristics by REM AHI Severity Category for the Subsample of Sleep Studies with non-REM AHI ≤ 5 in 1,216 Subjects (Multiple Studies per Subject)

	REM AHI Severity Category				
	<1	1–4.9	5–14.9	⩾15	Total
Number of sleep studies, n (%)	1,067 (36)	912 (31)	621 (21)	353 (12)	2,953
Female, %	45	54	50	42	48
Race/ethnicity, white, %	98	97	95	96	97
Current smoking, %	17	16	12	15	15
Prevalent hypertension, %	24	33	37	50	33
Type 2 diabetes, %	2	4	6	6	4
Age, years, mean (SD)	49 (9)	52 (9)	54 (9)	56 (8)	52 (10)
Body mass index, kg/m^2, mean (SD)	27 (5)	28 (5)	30 (6)	33 (7)	29 (6)
Waist-to-hip ratio, mean (SD)	0.87 (0.09)	0.89 (0.09)	0.90 (0.09)	0.90 (0.08)	0.88 (0.09)
Total sleep time, min, mean (SD)	377 (59)	380 (57)	381 (56)	373 (56)	378 (57)
REM sleep time, min, mean (SD)	73 (25)	73 (25)	72 (24)	66 (23)	72 (25)
REM sleep time, percent of total sleep time, mean (SD)	19 (5)	19 (6)	19 (5)	18 (5)	19 (5)
Slow wave sleep, min, mean (SD)	43 (32)	41 (35)	37 (33)	37 (34)	40 (34)
Slow wave sleep, percent of total sleep time, mean (SD)	12 (5)	11 (9)	10 (8)	10 (9)	11 (9)
AHI, events/h, mean (SD)	0.4 (0.7)	1.1 (0.9)	2.4 (1.3)	5.2 (2.7)	1.6 (2.0)
non-REM AHI, events/h, mean (SD)	0.6 (0.9)	1.1 (1.2)	1.8 (1.3)	2.4 (1.3)	1.2 (1.3)
REM AHI, events/h, mean (SD)	0.2 (0.3)	2.5 (1.1)	9.0 (2.9)	27 (11)	5.9 (9.3)
Oxygen desaturation index, events/h, mean (SD)*	0.7 (0.9)	1.5 (1.1)	3.2 (1.5)	6.8 (2.9)	2.7 (2.6)
non-REM oxygen desaturation index, events/h, mean (SD)*	0.7 (1.0)	1.1 (1.2)	1.8 (1.3)	2.5 (1.2)	1.5 (1.3)
REM oxygen desaturation index, events/h, mean (SD)*	0.2 (0.3)	2.2 (1.2)	8.2 (3.2)	24.7 (10.8)	7.3 (9.7)
Time below 90% Sp_{O_2}, percent of total sleep time, mean (SD)†	0.4 (2.0)	1.3 (9.2)	0.6 (2.2)	1.4 (3.8)	0.9 (5.5)
Time below 90% Sp_{O_2}, percent of non-REM sleep time, mean (SD)†	0.3 (1.9)	1.2 (9.1)	0.5 (2.2)	0.9 (3.8)	0.8 (5.5)
Time below 90% Sp_{O_2}, percent of REM sleep time, mean (SD)†	0.5 (3.8)	1.6 (10.7)	1.0 (3.3)	3.6 (6.3)	1.5 (7.0)
Epworth Sleepiness Scale, mean (SD)‡	8.3 (4.0)	8.2 (4.0)	8.5 (4.0)	8.3 (3.9)	8 (4)
Excessive daytime sleepiness, %	20	17	22	20	20

Definition of abbreviations: AHI = apnea–hypopnea index; Sp_{O_2} = oxygen saturation by finger pulse oximetry.
*Available on a subset of studies (n = 1,155) after implementation of full digital polysomnography in the Wisconsin Sleep Cohort.
†Available on a subset of studies (n = 845) after implementation of full digital polysomnography in the Wisconsin Sleep Cohort.
‡Available on a subset of studies (n = 2,276).

Table 3. Percentage of Subjects with Hypertension by REM AHI Severity Category in the Subset of Subjects with Ambulatory Blood Pressure Monitoring Data

	REM AHI Severity Category				
	<1	1–4.9	5–14.9	⩾15	Total Studies
Total sample (n = 742)					
Number of sleep studies	350	281	217	237	1,085
Prevalent hypertension, %	23	36	40	58	37
Individuals with non-REM AHI ⩽ 5 (n = 572)					
Number of sleep studies	330	236	142	71	779
Prevalent hypertension, %	21	32	35	54	30

Definition of abbreviation: AHI = apnea–hypopnea index.

hypertension status in at least one 4-year interval.

All analyses described previously were repeated twice: first after excluding subjects who reported any CPAP use at home (n = 65); and second after excluding those who were adherent to CPAP therapy, where adherence was defined as subject report of use of CPAP on 70% of days for at least 4 hours per night (n = 51).

Results

Cross-Sectional Analyses

A total of 1,451 subjects with at least 30 minutes of REM sleep on their baseline polysomnography completed 4,385 sleep studies. Table 1 shows summary demographics and polysomnographic variables for this cohort by categories of REM AHI severity. The mean ± SD age and BMI were 54 ± 10 years and 30 ± 6 kg/m^2, respectively (46% female and 96% white). The mean total sleep time was 376 ± 57 minutes; REM sleep represented 18 ± 5% of total sleep time. As expected, there was an increase in total AHI and non-REM AHI across increasing REM AHI severity categories. There was no increase in mean scores on the Epworth Sleepiness Scale or reports of excessive daytime sleepiness with increasing REM AHI category. Participants in the highest REM AHI category were older, more obese, and had a higher prevalence of hypertension.

Table 2 summarizes demographic and polysomnography data of the subgroup of participants with non-REM AHI less than or equal to 5. This sample consisted of 1,216 subjects who had undergone a total of 2,953 sleep studies. This subgroup was slightly younger with lower mean BMI than the entire cohort (mean age, 52 ± 10 yr; BMI, 29 ± 6 kg/m^2) but had similar sex and race/ethnicity distributions. Mean total sleep time and percentage of REM sleep was also similar to the entire cohort and there was no increase in subjective sleepiness with increasing REM AHI categories. Similar to the entire cohort, participants in the highest REM AHI category were older, more obese, and had a higher prevalence of hypertension. Table 3 describes the prevalence of hypertension in the subset with available ABPM data. There were higher proportions of participants with hypertension with increasing REM AHI categories in the entire cohort (n = 742) and in the subgroup with non-REM AHI less than or equal to 5 (n = 572).

Table 4 summarizes the results from repeated measures logistic regression models estimating the risk of prevalent hypertension based on REM AHI categories after adjusting for age, sex, race, BMI, waist-to-hip ratio, smoking, alcohol consumption, and non-REM AHI (Figure 1). Models were constructed for the overall sample (n = 1,451) and for the subset with non-REM AHI less than or equal to 5 (n = 1,216) (Figures 1A and 1B). Higher REM AHI categories were significantly associated with higher risk of prevalent hypertension in the entire cohort (P trend = 0.04; Figure 1A). In the subgroup with non-REM AHI less than or equal to 5, higher REM AHI categories were associated with higher odds of hypertension but did not reach statistical significance (P trend = 0.09; Figure 1B). In contrast, in the subgroup with available ABPM data and non-REM AHI less than or equal to 5, the association between higher REM AHI categories and higher odds of prevalent hypertension was highly significant ($P < 0.001$; Figure 1D). Similar results were obtained when log REM AHI was used as a continuous variable in regression models; a twofold increase in the REM AHI was independently associated

Table 4. Logistic Regression Models Estimating the Risk of Prevalent Hypertension by REM AHI Severity Category

	Adjusted Odds Ratios (95% CI) for Prevalent Hypertension*			
	Total Sample		Subset with Ambulatory Blood Pressure Monitoring	
REM AHI Severity Category	All Sleep Studies (*n = 4,385*)	non-REM AHI ⩽ 5 (*n = 2,953*)	All Sleep Studies (*n = 1,085*)	non-REM AHI ⩽ 5 (*n = 779*)
<1 (reference)	NA	NA	NA	NA
1–4.9	1.11 (0.93–1.32)	1.14 (0.94–1.38)	1.54 (1.07–2.21)	1.70 (1.12–2.59)
5–14.9	1.16 (0.97–1.38)	1.12 (0.90–1.39)	1.28 (0.88–1.88)	1.58 (1.00–2.53)
⩾15	1.26 (1.01–1.57)	1.32 (0.97–1.79)	1.63 (1.02–2.61)	3.38 (1.70–6.72)
P trend	0.04	0.09	0.08	<0.001

Definition of abbreviations: AHI = apnea–hypopnea index; CI = confidence interval; NA = not applicable.
*All models are adjusted for age, sex, race, body mass index, waist-to-hip ratio, smoking alcohol, and $\log_2$(non-REM AHI + 1). In the model including all sleep studies in the total sample, the P value for $\log_2$(non-REM AHI + 1) was 0.20. In the model including all sleep studies in the subset with ambulatory blood pressure monitoring, the P value for $\log_2$(non-REM AHI + 1) was 0.47.

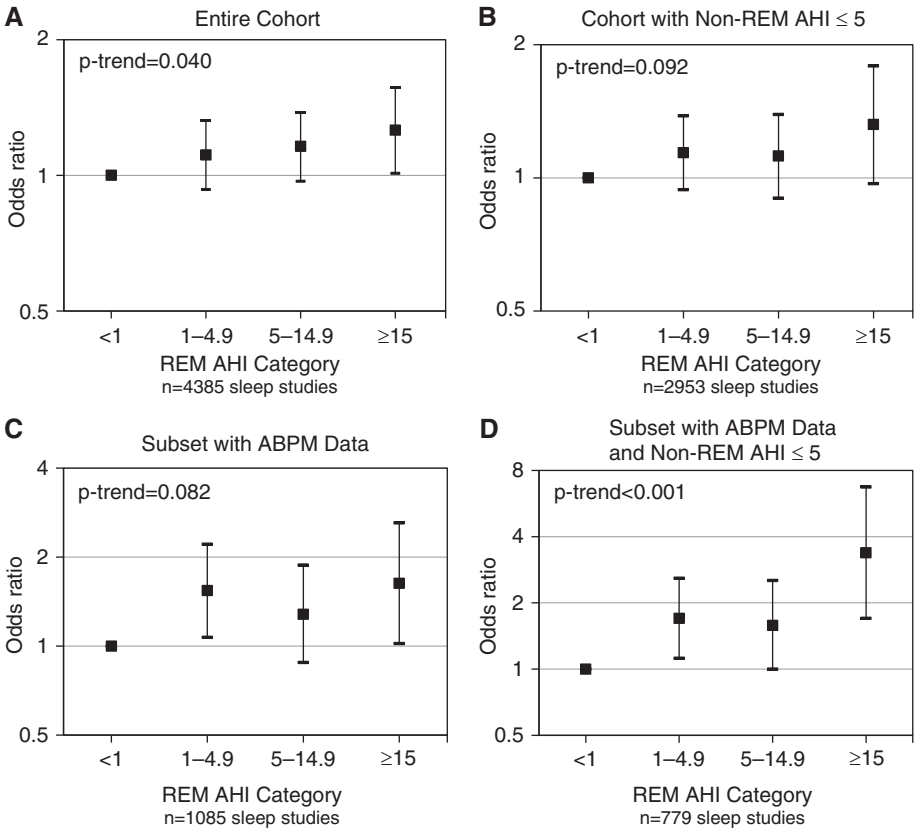

Figure 1. Odds ratios and 95% confidence intervals for REM apnea–hypopnea index (AHI) severity categories and prevalent hypertension. Repeated measures logistic regression models fitted to examine cross-sectional associations between obstructive sleep apnea during REM sleep based on REM AHI categories and prevalent hypertension. (*A*) Association for the entire cohort (n = 4,385 polysomnograms on 1,451 individuals). (*B*) Subsample with non-REM AHI less than or equal to 5 (n = 2,953 polysomnograms on 1,216 individuals). (*C*) Association between prevalent hypertension in the subset with available ambulatory blood pressure monitoring data (n = 1,085 polysomnograms on 742 individuals). (*D*) Subset of subjects with available ambulatory blood pressure monitoring data and non-REM AHI less than or equal to 5 (n = 779 polysomnograms on 572 individuals). Increasing REM AHI categories were associated with increased risk of hypertension in all models and it reached statistical significance in the entire cohort (*A*) and in the subsample of subjects who had ambulatory blood pressure monitoring data limited to non-REM AHI less than or equal to 5 (*D*). All estimates are adjusted for age, sex, race, body mass index, waist-to-hip ratio, smoking, alcohol, and $\log_2$(non-REM AHI + 1). In *A*, the *P* value for $\log_2$(non-REM AHI + 1) was 0.20. In *C*, the *P* value for log non-REM AHI was 0.5. ABPM = ambulatory blood pressure monitoring.

with 24% higher odds of prevalent hypertension using ABPM in the subset of participants with non-REM AHI less than or equal to 5 (Table 5). Importantly, non-REM AHI was not a significant predictor of prevalent hypertension in any of the models. Results were essentially unchanged when models were fitted after excluding participants on any home CPAP therapy (data not shown).

Although the prevalence of sleepiness did not vary across REM AHI categories (Tables 1 and 2), we examined whether the association between REM OSA and prevalent hypertension was influenced by sleepiness. Specifically, the *P* value for the interaction term between $\log_2$REM AHI (doubling of REM AHI) and sleepiness in the entire cohort was 0.55 and in the subset of individuals with non-REM AHI less than or equal to 5 was 0.92. Moreover, we also stratified the analysis based on sleepiness and there was no significant difference in prevalent hypertension or the likelihood of developing hypertension between sleepy and nonsleepy individuals.

In our analyses, we also confirmed that increasing severity of total AHI by category was significantly associated with prevalent hypertension in the overall sample (n = 1,451 with 4,385 sleep studies) (*see* Table E2). However, once total AHI was replaced by REM AHI and non-REM AHI, only REM AHI remained significant in our models.

Roles of Body Position and Hypoxemia

Additional analyses were performed taking into account time spent in supine position for both REM and non-REM sleep in the subset of participants who had available data on body position (2,021 sleep studies and 1,079 sleep studies with non-REM AHI ⩽5). The analysis revealed that the β coefficients for REM AHI categories, adjusted for body position, remained essentially unchanged.

In our study, hypopneas were scored based on greater than or equal to 4% oxygen desaturation. Not surprisingly, the ODI and AHI in non-REM and REM sleep were highly correlated when we examined studies with ODI data (n = 2,058 sleep studies). The Pearson correlation coefficient for REM AHI and REM ODI was 0.99 ($P < 0.001$). Similarly, the Pearson correlation coefficient for non-REM AHI and non-REM ODI was 0.99 ($P < 0.001$). As expected, when we replaced REM AHI and non-REM AHI with REM ODI and non-REM ODI in the regression models, the results were very similar. We did not find an independent association between T90 in REM sleep and prevalent hypertension. However, this analysis was limited by the fact that T90 was available in only 37% of the sleep studies in the entire cohort (1,631 out of 4,385 sleep studies) and 29% of the sleep studies in the subset with non-REM AHI less than or equal to 5 (845 out of 2,953 sleep studies).

Longitudinal Analyses

In 1,451 subjects who had undergone a total of 4,385 sleep studies over 24 years, there was a change in hypertension status in a subset of 428 subjects (i.e., subjects were observed both without hypertension and with hypertension at different time points). In this subset, we estimated the relative odds of developing hypertension with higher REM AHI using a conditional logistic regression model. There was a significant association between the development of hypertension and higher REM AHI categories (*P* trend = 0.02) after adjusting for $\log_2$(non-REM AHI + 1) and important confounders including age, BMI, waist-to-hip ratio, smoking, and alcohol consumption. In these models we did not

Table 5. Logistic Regression Models Estimating the Odds of Prevalent Hypertension Associated with $\log_2$(REM AHI + 1)

	Relative Odds of Prevalent Hypertension Associated with a 1-Unit Increment in $\log_2$(REM AHI + 1) (i.e., an Approximate Doubling of the REM AHI)	
	OR for Hypertension*	**95% CI**
Overall sample		
All sleep studies	1.05	(1.01–1.10)
Subset with non-REM AHI ⩽ 5	1.06	(1.00–1.12)
Subset with ambulatory blood pressure recordings		
All sleep studies	1.09	(0.99–1.20)
Subset with non-REM AHI ⩽ 5	1.24	(1.08–1.41)

Definition of abbreviation: AHI = apnea–hypopnea index; CI = confidence interval; OR = odds ratio.
*All models are adjusted for age, sex, race, body mass index, waist-to-hip ratio, smoking, alcohol, and $\log_2$(non-REM AHI + 1). In the model including all sleep studies in the total sample, the *P* value for $\log_2$(non-REM AHI + 1) was 0.29. In the model including all sleep studies in the subset with ambulatory blood pressure monitoring, the *P* value for $\log_2$(non-REM AHI + 1) was 0.52.

adjust for fixed variables, such as sex and race/ethnicity, because the models involve within-subject comparisons (changes of OSA status associated with changes in hypertension status). As illustrated in Figure 2, the odds of developing hypertension was significantly associated with higher REM AHI: the odds ratio for REM AHI greater than or equal to 15 relative to REM AHI less than 1 was 1.77 (95% confidence interval, 1.08–2.92). We also repeated the conditional analysis using a further subset of 276 subjects that were observed both without and with hypertension at different time points *and* had non-REM AHI less than or equal to 5 at those same time points. In this subgroup, the odds of developing hypertension was significantly associated with higher REM AHI: the odds ratio for REM AHI greater than or equal to 15 relative to REM AHI less than 1 was 1.98 (95% confidence interval, 1.01–3.88).

Discussion

Our analysis of the Wisconsin Sleep Cohort participants, a large sample of community-dwelling middle-aged adults, shows for the first time that OSA in REM sleep, independent of non-REM OSA, is significantly associated with prevalent hypertension after adjusting for confounders. Importantly, we found a graded relationship between increasing REM AHI severity categories and prevalent hypertension in the entire cohort and in the subsample of participants with non-REM AHI less than or equal to 5 who thus presented with a "more pure" form of REM-related OSA. In this subgroup of participants (in whom there was minimal to no OSA during non-REM sleep), the relationship between REM AHI and hypertension became more robust when we defined hypertension using ABPM recordings. Indeed, a twofold increase in REM AHI was associated with 24% higher odds of prevalent hypertension. Longitudinal analysis also revealed that REM AHI greater than or equal to 15 was independently associated with increased risk of developing hypertension. Our findings are novel because, to our knowledge, this is the first study to evaluate the association of REM-related OSA and cardiovascular morbidity in a large community-based sample selected without regard to the presence of OSA symptoms or other related morbidities.

REM sleep usually accounts for 20–25% of total sleep time. It remains unclear whether obstructive respiratory events during REM sleep have a higher cardiometabolic impact compared with events in non-REM sleep. Our findings support the notion that obstructive events in REM sleep, as opposed to non-REM sleep, are associated with prevalent and incident hypertension. Indeed, our results showed that higher REM AHI is significantly positively associated with hypertension, whereas non-REM AHI was not significantly associated with hypertension in any of our models. Currently, there are no prospective studies to establish whether this association is causal.

Multiple mechanistic pathways are likely to be involved in the link between REM OSA and hypertension. Compared with events in non-REM sleep, obstructive apneas and hypopneas during REM sleep last longer and are associated with significantly larger oxygen desaturation (33–35). When compared with non-REM sleep or quiet wakefulness, REM sleep is associated with increased sympathetic activation and reduced vagal tone in normal subjects and even more so in patients with OSA (25–27). REM sleep induces not only an increase in heart rate

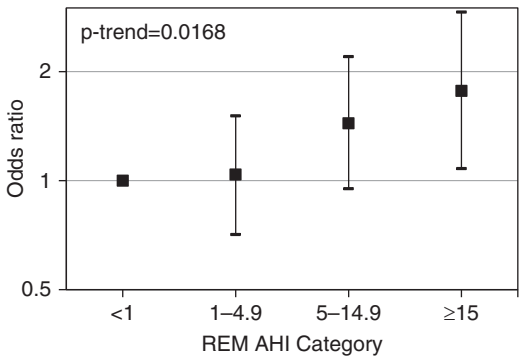

Figure 2. Adjusted odds ratio for estimating the risk of developing hypertension based on REM apnea–hypopnea index (AHI) severity categories. Conditional logistic regression model fitted to longitudinally explore the independent association between obstructive sleep apnea during REM sleep and development of hypertension. Estimates are adjusted for age, body mass index, waist-to-hip ratio, smoking, alcohol, and log non-REM AHI. The *P* value for $\log_2$(non-REM AHI + 1) was 0.28.

and blood pressure but also an increase in myocardial metabolic demand. Additional support for the hypothesis that obstructive events during REM sleep may be more deleterious comes from experimental studies with a canine model demonstrating reduced coronary blood flow during REM sleep in areas of stenosed coronary artery circulation (28, 29). Therefore, obstructive respiratory events in REM sleep, a state of sleep that is already under increased sympathetic dominance, could impose a greater cardiovascular risk compared with non-REM sleep.

Currently there is lack of consensus as to whether patients with disordered breathing events predominantly during REM sleep should be treated if their overall AHI does not meet the threshold for the clinical diagnosis of OSA ($\geq$5 events/h). Indeed, our analysis suggests that up to 70% of the sleep studies with REM AHI greater than or equal to 15 would have been clinically classified as no OSA (overall AHI $<$ 5) or mild OSA (overall AHI, 5–14.9) (*see* Table E3). This degree of disordered breathing during REM sleep is associated with increased risk of hypertension and therefore further research is needed to establish whether treating such patients can decrease the cardiovascular risk associated with untreated REM OSA.

Our findings may have important clinical implications for the duration of CPAP use that is needed to decrease the risk of hypertension and mitigate the adverse cardiovascular consequences of OSA. In clinical practice, 4 hours of nightly CPAP use for 70% of the nights is considered adequate adherence to therapy (45). 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 blood pressure 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 (46). 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 h per 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 blood pressure (47). Grimaldi and colleagues (41) 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. In contrast, 7 hours of CPAP therapy would cover most REM sleep. Therefore, the failure to treat REM OSA because of insufficient CPAP use may have clinical relevance in the context of mitigating its adverse cardiovascular consequences. Undoubtedly, further research is needed to establish the optimal duration of CPAP use needed to reverse the negative cardiovascular and metabolic consequences of OSA.

Our study has several limitations. The observational nature of the study precludes definitive causal inferences. However, our findings from longitudinal analyses strengthen our hypothesis that REM OSA is adversely associated with developing hypertension. Another limitation is that even including non-REM AHI as a covariate in our models, there may be residual confounding effects by OSA events not occurring during REM sleep. However, we performed additional analyses restricted to subjects without any significant non-REM OSA (non-REM AHI $\leq$ 5 events/h), while still statistically controlling for the small residual non-REM AHI variability in those subjects. REM AHI remained associated with the outcomes in the restricted samples, suggesting that confounding by non-REM OSA does not explain the observed REM OSA-hypertension associations. In our study hypopneas were classified using greater than or equal to 4% oxygen desaturation. Moreover, we do not have data on REM and non-REM microarousals for a substantial portion of the cohort. We therefore cannot ascertain whether the observed adverse effect of REM OSA on blood pressure would still be detected using hypopnea definitions incorporating greater than or equal to 3% oxygen desaturation or microarousals. Lastly, our findings may not be generalizable to African Americans or Hispanics because 96% of the subjects included in our cohort are non-Hispanic whites.

Notwithstanding the limitations, our study is unique in that it uses a large community-based sample, which enabled us to adjust for numerous important confounding covariates. Additionally, we used both cross-sectional and longitudinal analytic approaches to examine our hypotheses. Furthermore, we believe that our conservative inclusion criterion of at least 30 minutes of REM sleep reduces the possibility of exaggerating the effects of REM OSA in individuals with short REM duration.

It is estimated that at least 25 million American men and women suffer from undiagnosed mild to moderate OSA and as many as 20% of these individuals may have REM-related OSA (19, 21, 22, 38). This is a problem of major clinical significance and public health importance given that REM-related OSA occurs more commonly in women and younger individuals (19–22, 48), including children (49), and may determine a lifelong elevated cardiometabolic risk if undiagnosed and untreated.

In summary, the results of this study provide unique evidence that OSA during REM sleep, independent of OSA during non-REM sleep or even in the absence of any meaningful OSA during non-REM sleep, is independently associated with both incident and prevalent hypertension. We found a significant dose-response association suggesting that at higher REM AHI levels, the risk for hypertension is greater. This is an important finding because patients with REM-related OSA may be minimally symptomatic and frequently do not complain of excessive daytime sleepiness, which may lead to delay in diagnosis and therapy. Because REM sleep is dominant during the latter part of the sleep period, REM-related OSA may often remain untreated with 3–4 hours of nightly CPAP use. Additional mechanistic studies are needed to establish whether events during REM sleep have a larger impact on cardiometabolic risk compared with events in non-REM sleep. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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