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ORIGINAL ARTICLE

# Obstructive sleep apnea during rapid eye movement sleep is associated with early signs of atherosclerosis in women

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## Abstract

**Study Objectives:** Although obstructive sleep apnea (OSA) is associated with overall cardiovascular disease and mortality, the association with atherosclerotic cardiovascular disease is less clear, especially in women. Recently, it has been suggested that OSA during rapid eye movement (REM) sleep, associated with long apneas and deep desaturations, could have severe cardiometabolic consequences. The aim of this study was to investigate whether OSA during REM sleep is associated with early signs of atherosclerosis in a population-based sample of women.

**Methods:** In the community-based "Sleep and Health in Women" (SHE) cohort study, 400 women underwent polysomnography, anthropometric measurements, blood sampling, blood pressure measurement, and answered questionnaires. Ten years later, 201 of the original participants, free of known atherosclerotic disease at baseline and without continuous positive airway pressure treatment for OSA, underwent a high-frequency ultrasound of the common carotid artery to assess the individual thickness of the layers of the artery wall.

**Results:** Severe OSA during REM sleep (REM apnea–hypopnea index [AHI] ≥ 30) was associated with a thicker intima. This association was still significant after adjustment for age, body mass index, alcohol, and smoking, as well as for further adjustment for systolic blood pressure, low-density lipoprotein, C-reactive protein, and diabetes (β-coefficient, 0.008; *p*-value, 0.022). The association between a REM AHI of ≥30 and intima thickness was also seen in women with no or mild OSA and normal non-REM AHI.

**Conclusions:** In this study of a community-based sample of women, severe OSA during REM sleep was independently associated with early signs of atherosclerosis.

## Statement of Significance

Individuals with obstructive sleep apnea run an increased risk of cardiovascular disease, but the relationship between obstructive sleep apnea and atherosclerotic diseases is still unclear, especially in women. Sleep apnea and respiration deteriorate during rapid eye movement (REM)-sleep and sleep apnea during REM sleep might have severe adverse effects. In this study of a community-based sample of women, severe sleep apnea during REM sleep was associated with early signs of atherosclerosis, defined as increased intima thickness, at 10 years of follow-up. The association was also seen in women with low overall apnea–hypopnea index, normally not considered for treatment of sleep apnea. This suggests that occurrence of frequent obstructive apneas during REM sleep has to be taken into consideration when diagnosing and treating sleep apnea.

**Key words:** obstructive sleep apnea; cardiovascular morbidity; rapid eye movement–related sleep apnea; carotid artery intima thickness; atherosclerosis

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## Introduction

Obstructive sleep apnea (OSA) has been increasingly recognized as a risk factor for cardiovascular disease. OSA exposes the cardiovascular system to stress by intermittent hypoxia, activation of the sympathetic nervous system [1], and repeated episodes of negative intrathoracic pressure swings [2], and it is associated with an increased risk of hypertension [3], arrhythmias [4], and heart failure [5, 6]. In randomized controlled trials, the treatment of OSA with continuous positive airway pressure (CPAP) therapy has not been shown to reduce the risk of future cardiovascular events [7]. One possible explanation for this lack of effect could be that OSA during rapid eye movement (REM) sleep, occurring in the early morning hours, is often left untreated. OSA during REM sleep is associated with longer apneas and deeper desaturations [8], and it has been suggested that OSA during REM sleep could have more severe cardiometabolic consequences than OSA during non-REM sleep. In a recent study, severe OSA during REM sleep, in participants with prevalent cardiovascular disease, was associated with an increased risk of the composite endpoint of myocardial infarction, coronary artery revascularization, congestive heart failure, and stroke [9]. OSA during REM sleep has also been associated with incident hypertension [10], diastolic dysfunction [11], and insulin resistance [12], but it remains unclear whether OSA during REM sleep could promote atherosclerosis.

Several small clinic-based studies have reported an association between severe OSA based on a whole night and early signs of atherosclerosis defined as an increase in carotid intima-media thickness (IMT) [13], but, in epidemiological studies, the results are conflicting [14, 15]. IMT is a predictor of future cardiovascular morbidity [16], but, as a marker of early atherosclerosis, one limitation is its inability to distinguish intimal thickening, an early morphologic sign in the atherosclerotic process [17, 18], from changes in media thickness. Media thickness can increase due to smooth muscle hypertrophy caused by genetic factors, hypertension, and age-related sclerosis [19], or decrease in association with intimal thickening and plaque formation [20]. Studies using high-frequency ultrasound, which enables separate measurements of the intimal and medial layers, suggest that the thickness of the intima and the intima/media ratio detects early atherosclerosis more effectively than the combined thickness of the intima and media [21–23].

The aim of this study was to investigate whether OSA during REM sleep is associated with early signs of atherosclerosis, defined as increased intima thickness, in a population-based sample of women using high-frequency ultrasound to measure the individual layers of the common carotid artery wall.

## Methods

### Population

The "Sleep and Health in Women" (SHE) cohort study began in 2000 with a postal questionnaire sent to 10 000 randomly selected women aged ≥20 years from the population registry in the City of Uppsala in Sweden. Of the total study population aged 70 years and younger, a random sample of 170 women from the entire study population and a random sample of 230 snorers participated in the second phase of the study conducted between 2002 and 2004 [24]. Phase II of the study included a whole-night polysomnography, questionnaires, anthropometric measurements, blood sampling, blood pressure measurement, an electrocardiogram, and an oral glucose tolerance test (OGTT).

Ten years later, all the participants in phase II of the baseline study were invited to a follow-up study, which included a high-frequency ultrasound of the common carotid artery. Women who, at baseline in 2002–2004, had suffered a stroke, a myocardial infarction or angina pectoris, or had undergone a coronary artery bypass operation or a coronary angioplasty were excluded. We also excluded women with less than 30 min of REM sleep as well as women with CPAP treatment for OSA. A flow chart of the study sample is shown in Figure 1.

### Ethical approval

The written informed consent of all the participants was obtained and the Ethics Committee at Uppsala University, Uppsala, Sweden, approved the study protocol (approval numbers 01-238 and 2009/379).

### Baseline measurements

Whole-night ambulatory polysomnography (EMBLA, Flaga Inc., Iceland) included continuous 16-channel recordings of two electroencephalography leads (C3-A2, C4-A1), two electrooculography leads, three electromyography leads (submental, left and right anterior tibialis muscles), two airflow leads (oronasal thermistor and nasal flow pressure sensor), two respiratory effort leads from piezoelectric belts (thoracic and abdominal), two electrocardiography leads, one pharyngeal sound lead (from a piezovibration sensor), one oximeter lead, and one body position lead.

Sleep was scored manually in 30 s epochs [25]. An obstructive apnea was defined as the complete cessation of nasal and oral airflow lasting 10 s or more with continuing abdominal and thoracic movements [26]. Central apneas were scored at the cessation of both oro-nasal thermistor and nasal pressure for 10 s without respiratory movements, in combination with an oxygen desaturation of ≥3%. A hypopnea was defined as a ≥50% reduction in both oro-nasal thermistor and nasal pressure for at least 10 s compared with baseline in combination with a desaturation of ≥3% or an arousal. The apnea–hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas per hour of sleep. The oxygen desaturation index (ODI) was defined as the mean number of desaturations of ≥3% per hour of sleep. The REM AHI was calculated as the number of apneas and hypopneas during REM sleep divided by the hours spent in REM sleep. Commonly used clinical thresholds were used to divide AHI into categories: mild OSA (AHI, 5–<15), moderate OSA (AHI, 15–<30), and severe OSA (AHI, >30) [26]. The same cutoffs were used to divide the REM AHI into categories.

The women answered a questionnaire including medical history, lifestyle factors, and current medication. Alcohol consumption was divided into three categories: 0 g of alcohol/week, 1–<84 g/week, or ≥84 g/week. Smoking was categorized as never, former, and current smoking. Based on their answers about current medication, participants with antihypertensive medication (angiotensin II receptor antagonists, β-blockers, diuretics, angiotensin-converting enzyme inhibitors, calcium-channel blockers, and α-blockers) were identified. Fasting blood samples

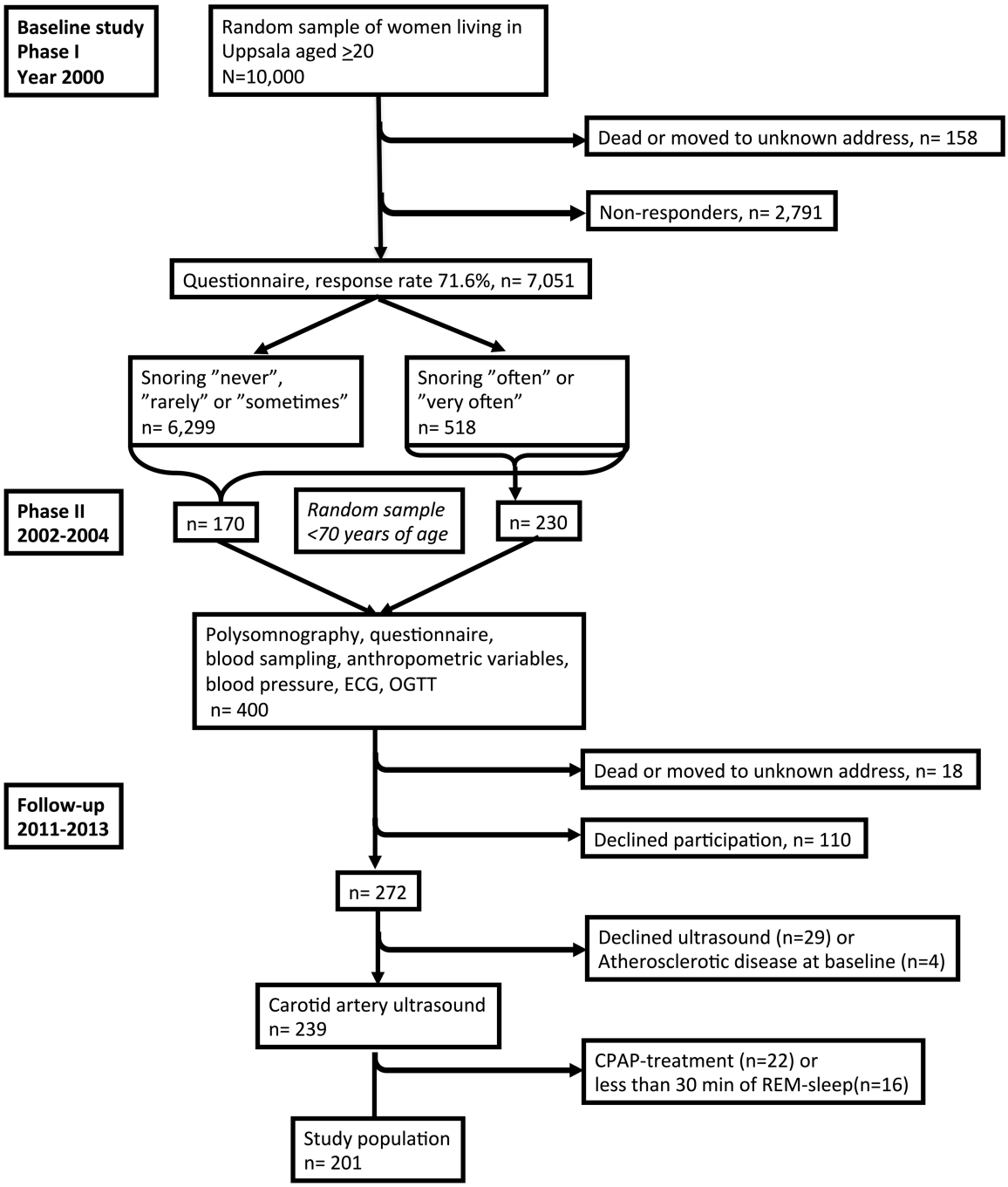


**Figure 1.** Flow chart describing the study sample. Women who, at baseline in 2002–2004, had suffered a stroke, a myocardial infarction, or angina pectoris, or had undergone a coronary artery bypass operation or a coronary angioplasty were excluded as well as women with CPAP treatment or less than 30 min of REM sleep. ECG = electrocardiogram; OGTT= oral glucose tolerance test.

were analyzed for glucose, C-reactive protein (CRP), low-density lipoprotein (LDL), and hemoglobin A1c (HbA1c). Follicle-stimulating hormone (FSH) was analyzed to assess menopausal status [27]. The participant's height and weight were measured and the body mass index (BMI) was calculated. Blood pressure was measured in the right arm after 15 min of rest in the supine position. Women without known diabetes mellitus and a fasting plasma glucose level of <7 mmol/L underwent an OGTT [28]. Based on the information from the questionnaire and OGTT, the women were then categorized as having diabetes, impaired glucose tolerance, impaired fasting glucose, or no impairment of glucose metabolism [29].

### Outcome—common carotid artery ultrasound at follow-up

The participants were examined with high-resolution ultrasound (Collagenoson Minhorst Company, Meudt, Germany) of the left common carotid artery using a broad-banded probe with 22 MHz center frequency. Details of the method have previously

been described [21]. The examination was performed after 15 min of rest with the participant sitting in an upright position looking straight ahead. The transducer was applied at the point of maximum pulsation of the common carotid artery in front of the sternocleidomastoid muscle, and the pulsating three-layer near wall was identified. Point estimates of the artery wall, not adjusted to the cardiac cycle, were obtained and means of 10 technically acceptable measurements were calculated and used in the analysis. The intima and media were measured separately. Measurements of the intima were made using the brightest echoes from leading edge to far edge, and the thickness of the media layer was measured as the distance between the two brightest echoes. The intima and media were measured in millimeters, and the IMT was calculated as the thickness of the intima plus the media and the intima-media (I/M) ratio was calculated as the thickness of the intima divided by the thickness of the media. The coefficient of variation (CV) for the common carotid artery intima and media thicknesses was 3.9 and 3.4 per cent, respectively [21]. The investigator performing the ultrasounds was blinded to the polysomnographic results.

### Statistical methods

Statistical analyses were performed using Stata 13.0 (Stata Corporation, College Station, TX). Associations between REM AHI and carotid artery wall variables (intima thickness, media thickness, IMT, and I/M) were analyzed using linear regression. The associations were analyzed first in an age-adjusted model, second in a model adjusting for confounding by age, BMI, alcohol, and smoking (Model 1), and finally in a mechanistic model considering possible intermediate mechanisms also including systolic blood pressure, LDL, CRP, and diabetes (Model 2). The calculations were performed first on the whole study population, second in the subset of women with no or mild OSA (AHI < 15), and finally, to further isolate the effect of OSA during REM sleep, only women with non-REM AHI < 5 were included. Additional analyses of OSA based on a whole night (AHI and ODI) and hypoxia measurements were also conducted. The validity of the regression models was examined with regression diagnostics such as residuals plots. Age was used as a categorical variable, dividing the participants into four groups: <40, 40–49, 50–59, and ≥60 years.

## Results

The final study population comprised 201 women (Figure 1). At baseline, 13 women (6.5%) had severe OSA (AHI ≥ 30) and 58 women (28.9%) had severe OSA during REM sleep. The mean REM duration was 77.1 ± 25.1 min, corresponding to 19.6 per cent of total sleep time. Sixteen women had less than 30 min of REM sleep. The majority (76.9%) of the women with severe OSA also had severe OSA during REM sleep, whereas only 10 (17.2%) of the 58 women with severe OSA during REM sleep had an AHI of ≥30. An AHI of <15 was seen in 14 (24.1%) of the women with severe OSA during REM sleep. Baseline characteristics and polysomnographic data are given in Tables 1 and 2. Women with severe OSA during REM sleep differed from women with an REM AHI of <30. They were older, had a higher BMI, higher blood pressure, and a more frequent diagnosis of hypertension. In addition, they had slightly higher LDL levels and more frequently impaired glucose tolerance, whereas there was no difference in smoking habits and alcohol consumption. At follow-up, a total of 22 women reported that they had treatment with CPAP. The median CPAP-treatment time for these women was 102 months (IQR 29–120 months).

**Table 1.** Baseline characteristics of the participants

| | All | AHI < 30 | AHI ≥ 30 | REM AHI < 30 | REM AHI ≥ 30 |
|---|---|---|---|---|---|
| No. of participants | 201 | 188 | 13 | 143 | 58 |
| Age, yr | 49.8 (10.4) | 49.2 (10.3) | 57.8 (8.6) | 47.3 (10.5) | 55.7 (7.5) |
| Body mass index, kg/m$^2$ | 26.1 (4.1) | 25.9 (4.0) | 29.4 (4.1) | 25.3 (3.4) | 28.1 (4.8) |
| Δ-BMI | 0.7 (2.5) | 0.7 (2.5) | 0.6 (1.8) | 0.7 (2.6) | 0.7 (2.3) |
| Smoking status, *n* (%) | | | | | |
| Never | 90 (45.5) | 87 (46.5) | 3 (27.3) | 67 (47.2) | 23 (41.1) |
| Former | 66 (33.3) | 61 (32.6) | 5 (45.5) | 44 (30.1) | 22 (39.3) |
| Current | 42 (21.1) | 39 (20.9) | 3(27.3) | 31 (21.8) | 11 (19.6) |
| Alcohol, g/week | 49.7 (21.3–84.0) | 51.3 (21.3–84.0) | 46.0 (23.3–92.4) | 42.6 (20.5–83.3) | 56.8 (28.4–90.0) |
| Postmenopausal, *n* (%) | 100 (49.8) | 90 (47.9) | 10 (76.9) | 60 (42.0) | 40 (69.0) |
| Hypertension, *n* (%) | 25 (12.8) | 22 (11.9) | 3 (27.3) | 13 (9.2) | 12 (21.8) |
| Antihypertensive medication, *n* (%) | 21(10.5) | 18 (9.6) | 3 (23.1) | 11 (7.7) | 10 (17.2) |
| Diabetes, self-reported, *n* (%) | 3 (1.5) | 3 (1.6) | 0 (0.0) | 2 (1.4) | 1 (1.8) |
| Systolic blood pressure, mm Hg | 123.3 (18.7) | 122.9 (18.8) | 129.6 (16.4) | 120.6 (16.7) | 130.1 (21.8) |
| Epworth Sleepiness Scale, points | 8.8 (4.0) | 8.9 (3.9) | 7.6 (4.5) | 8.9 (4.0) | 8.8 (3.9) |
| Oral glucose tolerance test, *n* (%) | | | | | |
| Normal | 169 (84.1) | 161 (85.6) | 8 (61.5) | 129 (90.2) | 40 (69.0) |
| Impaired fasting glucose | 6 (3.0) | 4 (2.13) | 2 (15.4) | 3 (2.1) | 3 (5.2) |
| Impaired glucose tolerance | 18 (9.0) | 15 (8.0) | 3 (23.1) | 5 (3.5) | 13 (22.4) |
| Diabetes | 8 (4.0) | 8 (4.3) | 0 (0.0) | 6 (4.2) | 2 (3.5) |
| LDL, mmol/L | 3.4 (0.9) | 3.3 (0.8) | 3.8 (0.9) | 3.3 (0.9) | 3.6 (0.8) |
| HbA1c, % | 4.6 (0.5) | 4.6 (0.5) | 4.6 (0.3) | 4.6 (0.6) | 4.6 (0.4) |
| CRP, mg/L | 1.2 (0.5–2.8) | 1.2 (0.5–2.4) | 2.6 (0.7–3.0) | 1.0 (0.5–2.3) | 1.6 (0.6–3.1) |

Data are presented as the means (SD) for normally distributed data, as the median (IQR) for not normally distributed data or as *n* (%).
Δ-BMI = Change in body mass index from baseline to follow-up; LDL = low-density lipoprotein; HbA1c = hemoglobin A1c.

Severe OSA during REM sleep (REM AHI ≥ 30) was associated with a thicker intima of 0.092 vs. 0.082 mm among women with an REM AHI of <5 ($p$ = 0.013) but not with media or IMT. This association remained after adjustment for age, BMI, alcohol, and smoking (Model 1) and also after further adjustment for systolic blood pressure, LDL, CRP, and diabetes (Model 2) (Table 3). Additional adjustment for postmenopausal status or antihypertensive medication did not change the results (data not shown).

Restricting the analysis to participants with an overall AHI of <15 reduced the study population to 139 women. In these analyses, severe OSA during REM sleep was still associated with a thicker intima after adjustment for confounders (Table 4). To isolate the effect of OSA during REM sleep from OSA during non-REM sleep, the analyses were repeated in the subset of women with non-REM AHI of <5. This reduced the study population further to 99 women. After adjustment for confounders, severe OSA during REM sleep was still associated with a thicker intima (Table 5). The prevalence of central apneas was low in the whole study sample, but in eight women central events represented more than 25 per cent of the total number of respiratory events during REM sleep. Excluding these women did not change the results.

Additional analyses of hypoxia measurements revealed no independent associations between mean saturation during REM sleep, overall mean saturation, the percentage of total sleep time with a saturation of <90 per cent or lowest saturation, and intima or IMT. The mean apnea length was associated with intima thickness and this association remained after adjustment for confounders (β-coefficient, 0.0007; $p$ = 0.016 in Model 2). Severe OSA, defined as an AHI of ≥30 or an ODI of ≥30, was not associated with age-adjusted intima thickness, nor with media thickness, IMT or I/M ratio (data not shown). Analyses including

**Table 2.** Polysomnographic data

| | All | AHI < 30 | AHI ≥ 30 | REM AHI < 30 | REM AHI ≥ 30 |
|---|---|---|---|---|---|
| No. of participants | 201 | 188 | 13 | 154 | 79 |
| TST, min | 392.9 (58.4) | 392.9 (57.9) | 392.2 (68.4) | 398.3 (57.9) | 379.6 (58.0) |
| AHI, events/hr | 7.6 (3.3–16.2) | 6.9 (3.0–15.2) | 37.6 (35.6–45.9) | 5.1 (2.2–9.0) | 18.1 (15.0–26.2) |
| ODI, events/hr | 4.5 (2.0–10.0) | 4.0 (2.0–9.0) | 33.0 (27.0–45.0) | 3.0 (1.0–5.0) | 12.5 (7.0–22.0) |
| NonREM AHI, events/hr | 5.0 (1.7–12.6) | 4.8 (1.5–10.9) | 40.9 (32.2–44.8) | 3.0 (1.1–6.7) | 12.6 (7.6–22.1) |
| REM AHI, events/hr | 17.6 (6.0–34.4) | 15.9 (5.4–30.1) | 50.6 (34.6–58.3) | 10.0 (2.8–20.0) | 42.3 (36.5–52.3) |
| Mean saturation, % | 95.5 (1.6) | 95.5 (1.6) | 94.8 (1.1) | 95.6 (1.6) | 95.0 (1.4) |
| Mean saturation REM sleep, % | 95.9 (94.6–96.8) | 96.0 (94.7–96.8) | 94.6 (92.8–95.6) | 96.1 (95.1–97.0) | 95.4 (93.6–96.2) |
| Lowest saturation, % | 88.5 (5.2) | 88.9 (4.9) | 83.0 (6.1) | 89.7 (4.7) | 85.5 (5.0) |
| Mean apnea length, s | 19.4 (4.4) | 19.2 (4.3) | 21.2 (5.9) | 18.5 (4.0) | 21.1 (4.9) |
| % of TST with saturation < 90% | 0.1 (0.0–0.7) | 0.1 (0.0–0.5) | 1.3 (0.4–3.6) | 0.1 (0.0–0.2) | 0.4 (0.1–1.8) |
| % of TST with REM sleep | 19.6 (5.1) | 19.7 (5.1) | 17.6 (5.7) | 19.9 (5.0) | 18.7 (5.5) |

Data are presented as the means (SD) for normally distributed data, as the median (IQR) for not normally distributed data or as $n$ (%).
TST = total sleep time; ODI = oxygen-desaturation index.

**Table 3.** Associations between sleep apnea during REM sleep and intima thickness (mm) in the whole study population ($n$ = 201)

| | Age adjusted | | | Adjusted model 1 | | | Adjusted model 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| REM AHI | β-coefficient | (95% CI) | $P$ | β-coefficient | (95% CI) | $P$ | β-coefficient | (95% CI) | $P$ |
| 5–14.9 | 0.006 | (−0.001–0.012) | 0.096 | 0.006 | (−0.001–0.013) | 0.081 | 0.004 | (−0.003–0.011) | 0.239 |
| 15–29.9 | 0.005 | (−0.001–0.011) | 0.117 | 0.006 | (−0.001–0.012) | 0.097 | 0.005 | (−0.002–0.012) | 0.158 |
| ≥30 | 0.007 | (0.0004–0.014) | 0.038 | 0.009 | (0.002–0.016) | 0.013 | 0.008 | (0.001–0.016) | 0.022 |
| $p$-Value for model (F-test) | | | 0.013 | | | 0.045 | | | 0.041 |

Results of linear regression analysis. Model 1 adjusted for age, BMI, alcohol, and smoking. Model 2 adjusted for age, BMI, alcohol, smoking, systolic blood pressure, LDL, CRP, and diabetes.

**Table 4.** Associations between sleep apnea during REM sleep and intima thickness (mm) in participants with AHI < 15 ($n$ = 139)

| | Age adjusted | | | Adjusted model 1 | | | Adjusted model 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| REM AHI | β-coefficient | (95% CI) | $P$ | β-coefficient | (95% CI) | $P$ | β-coefficient | (95% CI) | $P$ |
| 5–14.9 | 0.004 | (−0.003–0.010) | 0.239 | 0.004 | (−0.003–0.010) | 0.277 | 0.002 | (−0.005–0.009) | 0.653 |
| 15–29.9 | 0.005 | (−0.002–0.011) | 0.134 | 0.006 | (−0.001–0.013) | 0.078 | 0.007 | (0.000–0.014) | 0.066 |
| ≥30 | 0.013 | (0.004–0.022) | 0.005 | 0.015 | (0.005–0.024) | 0.002 | 0.017 | (0.006–0.027) | 0.002 |
| $p$-Value for model (F-test) | | | 0.023 | | | 0.048 | | | 0.077 |

Results of linear regression analysis. Model 1 adjusted for age, BMI, alcohol, and smoking. Model 2 adjusted for age, BMI, alcohol, smoking, systolic blood pressure, LDL, CRP, and diabetes.

**Table 5.** Associations between sleep apnea during REM sleep and intima thickness (mm) in participants with AHI < 15 and non-REM AHI < 5 ($n$ = 99)

| | Age adjusted | | | Adjusted model 1 | | | Adjusted model 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| REM AHI | β-coefficient | (95% CI) | *P* | β-coefficient | (95% CI) | *P* | β-coefficient | (95% CI) | *P* |
| 5–14.9 | 0.008 | (0.000–0.016) | 0.048 | 0.010 | (0.001–0.018) | 0.027 | 0.008 | (–0.004–0.011) | 0.094 |
| 15–29.9 | 0.008 | (0.000–0.015) | 0.039 | 0.011 | (0.003–0.019) | 0.007 | 0.012 | (–0.003–0.011) | 0.010 |
| ≥30 | 0.022 | (0.010–0.034) | <0.001 | 0.025 | (0.013–0.038) | <0.001 | 0.029 | (0.001–0.015) | <0.001 |
| *p*-Value for model (*F*-test) | | | 0.008 | | | 0.014 | | | 0.064 |

Results of linear regression analysis. Model 1 adjusted for age, BMI, alcohol, and smoking. Model 2 adjusted for age, BMI, alcohol, smoking, systolic blood pressure, LDL, CRP, and diabetes

women with CPAP treatment increased the group with severe OSA to 23 women but showed similar results.

## Discussion

In this study of a community-based sample of women, severe OSA during REM sleep was associated with a thicker intima at 10 years of follow-up. The association between severe OSA during REM sleep and intima thickness remained after adjustment for confounders and was also seen when restricting the analysis to women with no or mild OSA with an overall AHI of <15 and in women with normal non-REM AHI. These are novel findings indicating that OSA during REM sleep is independently associated with early atherosclerosis, defined as increased arterial intima thickness, in women.

This is the first study to report an association between OSA during REM sleep and signs of atherosclerosis. The results are in accordance with recently published data from the Sleep Heart Health Study where severe OSA during REM sleep, in participants with prevalent cardiovascular disease, was associated with an increased risk of the composite endpoint of myocardial infarction, coronary artery revascularization, congestive heart failure, and stroke [9]. In the Wisconsin Sleep Cohort, OSA during REM sleep was associated with incident nondipping nocturnal blood pressure [30] and prevalent and incident hypertension, whereas non-REM sleep apnea was not [10]. Appleton and coworkers also reported an association between severe OSA during REM sleep and hypertension in a community-based sample of men and the association remained when the study population was restricted to men with an overall AHI of <10 [31]. OSA during REM sleep has also been associated with diastolic dysfunction [11] and insulin resistance [12] and in a recently published study OSA during REM sleep was associated with increased peripheral arterial stiffness, another marker of vascular aging [32].

There are several possible ways OSA during REM sleep can contribute to the development and progression of atherosclerosis. OSA is associated with increased levels of inflammatory markers [33]. This is believed to be mainly an effect of intermittent hypoxia. Hypoxic ventilatory drive is reduced in REM sleep [34] and the respiratory effort in response to upper airway obstruction is lower [35]. OSA during REM sleep is therefore associated with longer apneas with deeper desaturations [8]. Intermittent hypoxia has also been reported to induce hyperlipidemia in animal models [36]. It can be hypothesized that the longer apneas during REM sleep with deeper desaturations cause a stronger inflammatory response and possibly also dyslipidemia and endothelial dysfunction and contribute over time to the development of atherosclerosis. This hypothesis is supported by recent data showing higher risk ratios for cardiovascular mortality with an AHI severity classification, based on the duration of apneas and the area of the desaturations, than for conventional AHI [37]. In secondary analyses, we found that a longer mean length of apneas was associated with a thicker intima. No clear association was seen with the percentage of total sleep time with an oxygen saturation of <90%, but we did not have access to information on saturation by sleep stages. OSA also causes sympathetic over-activity that remains while awake [1] and may contribute to the development of hypertension and affect glucose metabolism, well-known risk factors for atherosclerosis. REM sleep is associated with high sympathetic activity [1] and the effect of the already high sympathetic activity further augmented by obstructive events has been suggested as an explanation of the stronger association between OSA during REM sleep and hypertension [10] and insulin resistance [12].

The strengths of this study include the large community-based sample of women, long-term follow-up, and reliable polysomnography data with information on AHI in different sleep stages and the refined technique with high-resolution ultrasound with separate measurement of the carotid intima and media wall layers. There are, however, also several limitations. Even though we had detailed information about relevant covariates from questionnaires, anthropometric measurements, blood sampling, blood pressure measurement, and OGTT, residual confounding could be a problem. Another limitation is that because we only had carotid ultrasound at follow-up, we could not assess atherosclerotic progression and definite conclusions on causality cannot be made. We did, however, exclude those with known atherosclerotic disease at baseline to minimize the risk of reverse causation. Since a high proportion of individuals with moderate-to-severe OSA were CPAP-treated, we do not have power to properly address the impact of overall AHI on atherosclerosis and this might explain the lack of correlation between AHI and intima thickness. Furthermore, it is still unclear whether the association between severe OSA during REM sleep and early signs of atherosclerosis is explained by sleep stage-dependent mechanisms, or whether the association is due to individual severe obstructive events during REM sleep.

In this population-based sample of women, without known cardiovascular disease, severe OSA during REM sleep was associated with a 12 per cent increase in intima thickness compared with women with a REM AHI < 5. The clinical relevance of such an increase is not known, but as comparison women

in the PIVUS study with cardiovascular disease had a 31 per cent increase in intima thickness compared with women of the same age without cardiovascular disease [21]. Our results might suggest that the avoidance of OSA during REM sleep might reduce the risk of cardiovascular disease. CPAP adherence is often defined as CPAP use for at least 4 hr a night on 70 per cent of nights [38]. This leaves much of REM OSA untreated, since the amount of REM sleep increases throughout the night, with its highest concentration in the hours before morning awakening [39]. Randomized, controlled trials have failed to show any cardioprotective effect of CPAP treatment for 3–4 hr a night [7, 40, 41]. It is plausible that the recommendations on CPAP usage need to be modified to cover REM sleep as well, in order to obtain a better cardioprotective effect. This is supported by the results of observational studies and secondary analyses in randomized, controlled trials showing an association between the number of hours of CPAP use and a reduction in the incidence of cardiovascular disease [40–42]. However, the effect of the CPAP treatment of REM OSA on cardiometabolic outcomes must be studied first.

In conclusion, in a community-based sample of women, severe OSA during REM-sleep was independently associated with early signs of atherosclerosis with a thicker carotid intima 10 years later. The association between severe OSA during REM sleep and intima thickness was also seen when restricting the analysis to women with no or mild OSA, a group that is often left without treatment. This implies that the occurrence of frequent obstructive apneas during REM sleep might have to be taken into consideration when diagnosing sleep-disordered breathing and that CPAP usage longer than the often-recommended 4 hr a night might be needed to cover REM OSA as well, in order to obtain a cardioprotective effect, although this needs to be further evaluated.

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## Notes

*Conflict of interest statement*. None declared.

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