Journal of the American Heart Association

ORIGINAL RESEARCH

Sleep Apnea is Associated With Accelerated Vascular Aging: Results From 2 European Community-Based Cohort Studies

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BACKGROUND: The mechanisms underlying the association between obstructive sleep apnea (OSA) and cardiovascular disease may include accelerated vascular aging. The aim was to compare the magnitude of vascular aging in patients with high versus low risk of OSA.

METHODS AND RESULTS: In 2 community-based studies, the PPS3 (Paris Prospective Study 3) and the Maastricht Study, high risk of OSA was determined with the Berlin questionnaire (a screening questionnaire for OSA). We assessed carotid artery properties (carotid intima-media thickness, Young's elastic modulus, carotid-femoral pulse wave velocity, carotid pulse wave velocity, carotid diameter using high precision ultrasound echography), and carotid-femoral pulse wave velocity (in the Maastricht Study only). Regression coefficients were estimated on pooled data using multivariate linear regression. A total of 8615 participants without prior cardiovascular disease were included (6840 from PPS3, 62% men, mean age 59.5±6.2 years, and 1775 from the Maastricht Study, 51% men, 58.9±8.1 years). Overall, high risk of OSA prevalence was 16.8% (n=1150) in PPS3 and 23.8% (n=423) in the Maastricht Study. A high risk of OSA was associated with greater carotid intima-media thickness (β=0.21; 0.17–0.26), Young's elastic modulus (β=0.21; 0.17–0.25), carotid-femoral pulse wave velocity (β=0.24; 0.14–0.34), carotid pulse wave velocity (β=0.31; 0.26–0.35), and carotid diameter (β=0.43; 0.38–0.48), after adjustment for age, sex, total cholesterol, smoking, education level, diabetes mellitus, heart rate, and study site. Consistent associations were observed after additional adjustments for mean blood pressure, body mass index, or antihypertensive medications.

CONCLUSIONS: These data lend support for accelerated vascular aging in individuals with high risk of OSA. This may, at least in part, underlie the association between OSA and cardiovascular disease.

Key Words: community-based study ■ sleep apnea ■ vascular aging

Obstructive sleep apnea (OSA) is highly prevalent and has been reported to be up to 49% in men and 23% in women above 40 years of age.[1] Besides being associated with an increased risk of mortality, OSA is a major risk factor for cardiovascular diseases (CVD), notably coronary artery disease, heart

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.021318

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Current evidence of a possible association between obstructive sleep apnea and accelerated vascular aging is limited and inconsistent.
- In 2 large European community-based studies, obstructive sleep apnea was associated with structural and functional biomarkers of accelerated vascular aging.

What Are the Clinical Implications?

- Accelerated vascular aging may underlie partly the well-established association between obstructive sleep apnea and cardiovascular disease.
- Vascular aging may be an additional target for preventing cardiovascular disease onset in patients with obstructive sleep apnea.

Nonstandard Abbreviations and Acronyms

PPS3	Paris Prospective Study 3

failure, and stroke.[2–6] However, the mechanisms underlying the association between OSA and CVD are incompletely understood.

It has been hypothesized that this increased cardiovascular risk in individuals with OSA may be mediated, or explained, by accelerated vascular aging.[7] Vascular aging is characterized by accumulation of functional and structural changes of vessels throughout life and is a major contributor to CVD.[8,9] Key manifestations of vascular aging include arterial stiffening, greater carotid intima-media thickness (IMT), and carotid diameter enlargement. Several OSA-related mechanisms, such as intermittent hypoxia, sympathetic activation, and low-grade inflammation, may contribute to accelerated vascular aging, beyond the effect of chronological age. Finding evidence for an association between OSA and accelerated vascular aging may stimulate strategies aimed at promoting optimal vascular health as a target to prevent CVD in individuals with OSA.[10,11]

Current evidence on a possible association between OSA and accelerated vascular aging is limited. Most previous studies were conducted in clinical samples[12–16] and, so far, the results of only 3 population-based studies have been reported, with conflicting conclusions.[17–19] In addition, although vascular aging has multiple manifestations, most studies investigated only 1 parameter of vascular aging in relation to OSA.[17,20]

The aim of this study was to investigate the association between OSA and a comprehensive set of manifestations of vascular aging, that is, local carotid stiffness, carotid IMT, carotid diameter, and carotid-femoral pulse wave velocity (cfPWV), in participants free of CVD, using data from 2 community-based cohort studies from 2 different European countries, the PPS3 (Paris Prospective Study 3) in France and the Maastricht Study in the Netherlands. In addition, to allow for international comparisons with existing community-based studies that evaluated the association between OSA and carotid plaques,[17–19] the association of OSA with presence of carotid plaques, a measure of carotid atherosclerosis, was explored.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design of Studies

The Paris Prospective Study 3

The PPS3 (Paris, France) is an ongoing prospective observational community-based cohort study on novel determinants of the main phenotypes of CVD.[21] Between 2008 and 2012, 10 157 men and women aged 50 to 75 years were recruited in a preventive medical center. The standard health check-up comprised a clinical examination including measurement of height, weight, and blood pressure, coupled with standard biological tests after an overnight fast. A self-administered questionnaire provided information related to sleep habits, lifestyle (tobacco and alcohol consumption, physical activity, diet), personal and family medical history, and current health status. The study was registered in the World Health Organization international clinical trial registry platform (NCT00741728). The Ethics Committee of the Cochin Hospital (Paris, France) approved the study protocol and all volunteers signed an informed consent form.

The Maastricht Study

The Maastricht Study is an observational prospective population-based cohort study. The rationale and design have been described previously.[22] In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, the municipal registries, and the regional Diabetes Patient Registry

via mailings. Recruitment was stratified according to known type 2 diabetes mellitus status. The present report includes data from 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. This study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Main Exposure: High Risk of Obstructive Sleep Apnea

The Berlin questionnaire, which has been designed for screening subjects at high risk of OSA (hrOSA),[23] was used to identify participants who are very likely to have OSA. The sensitivity and negative predictive value of the Berlin questionnaire to detect severe OSA (apnea-hypopnea index ≥30 per hour), as compared with gold-standard polysomnography, ranges from 76.9% to 93.4% and 71.4% to 96.3%, respectively.[24,25] The scoring of the Berlin questionnaire is given in Table S1. Briefly, this is a 10-item questionnaire distributed in 3 categories related to snoring, tiredness, and presence of comorbidities. Each category can be rated as positive or negative and a high risk of OSA is defined by 2 or 3 positive categories (see categories scoring system in the supplementary material).[23] Of note, in each cohort, 3 of the 10 items of the Berlin questionnaire were not available and were assigned 0 points (ie, not present).

Outcomes: Vascular Aging Variables

In both cohorts, trained vascular technicians unaware of the participants' clinical characteristics performed high-precision carotid ultrasound examinations. Measurements took place in a dark, quiet room and were performed in the supine position after a resting period of 10 minutes. Talking or sleeping was not allowed during the examination. In PPS3, measurements were performed on the right common carotid artery, 10 mm proximal from the carotid bulb bifurcation, using the ArtLab (Esaote) high-resolution echo-tracking technology. In the Maastricht Study, structural properties of the left carotid artery, at least 10 mm proximal to the carotid bulb, were determined with use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe, Maastricht, the Netherlands). Details have been published elsewhere for PPS3[21,26] and the Maastricht Study.[22]

Common Carotid Variables

In both cohorts, carotid IMT was calculated along a plaque-free segment of the common carotid artery during end-diastole. IMT was defined as the distance between the lumen-intima and media-adventitia interfaces of the far (posterior) wall. In both cohorts, the operator also determined carotid diameter on a plaque-free segment of the common carotid artery during end-diastole. Young's elastic modulus was calculated as 3×(1+LCSA/WCSA)/DC, where LCSA is diastolic lumen cross-sectional area, WCSA is wall cross-sectional area, and DC the carotid distensibility coefficient. DC was calculated according to the following equation: ΔLCSA/(LCSA×PP), where ΔLCSA is stroke change in lumen area, and PP is local pulse pressure estimated from the carotid distension waveform. Local carotid pulse wave velocity was estimated from the Bramwell and Hill equation:[27]

$$\frac{1}{\sqrt{\rho x DC}}$$

where ρ is blood viscosity (1060 kg/m^3).

Aortic Stiffness

Aortic stiffness was evaluated in the Maastricht Study only. cfPWV was measured, according to recent recommendations,[28] using applanation tonometry (SphygmoCor, Atcor Medical). Pressure waveforms were determined at the right common carotid and right common femoral arteries. The difference in the time of pulse arrival from the R-wave of the electrocardiogram between the 2 sites (transit time) was determined using the intersecting tangents algorithm. The pulse wave travel distance was calculated as 80% of the direct straight distance (measured with an infantometer) between the 2 arterial sites. The median of 3 consecutive cfPWV (defined as traveled distance divided by transit time) recordings in the analyses was used.

Carotid Plaques

Carotid plaques presence (yes/no) was available in PPS3 only. A carotid plaque was defined as a focal thickening encroaching into the carotid lumen of more than 1.5 mm (as measured from the intima-lumen interface to the media-adventitia interface) or at least 50% of the surrounding IMT.

Covariates

In both cohort studies, smoking was considered as a categorical variable: never, ex-smoker, and current smoker. Education level was considered as low (no education, primary education, or lower vocational education), medium (intermediate vocational education or higher secondary education), and high (higher professional education, university education). Total and low-density lipoprotein cholesterol and glucose

were measured after an overnight fast. Diabetes mellitus was defined as a fasting glucose level ≥7 mmol/L and/or use of glucose-lowering medication. In addition, in the Maastricht Study all participants underwent an oral glucose tolerance test, and diabetes mellitus was also defined as a 2-hour plasma glucose of ≥11.1 mmol/L. In PPS3, blood pressure and heart rate were recorded over 10 minutes in the supine position during the echotracking measurements. In the Maastricht Study, blood pressure and heart rate were measured after a minimum of 10 minutes of seated rest (Omron 705IT), and the average of at least 3 blood pressure readings was used. Prevalent CVD was defined as self-reported history of angina pectoris, myocardial infarction, or stroke in both studies. In the Maastricht Study, peripheral arterial disease was also considered as prevalent CVD. Further potential confounders were considered. In each study, the use of renin-angiotensin system blockers was assessed, as was the use of lipid-modifying medication. Medications were coded using the World Health Organization Anatomical Therapeutic Chemical classification. Further, the estimated glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation. Finally, in the Maastricht Study only, a 24-hour ambulatory blood pressure monitoring was performed.

Potential Mediating Factors

Markers of low-grade inflammation and autonomic dysfunction were determined in both studies. In PPS3, interleukin-6 was quantified using a MULTI-SPOT® 4 Spot Special Order Human triplex of customized kit (reference N45JA-1; Meso Scale Discovery, Rockville, MD), and hs-CRP (high-sensitivity C-reactive protein) using the V-plex Human CRP Kit (reference K151STD; Meso Scale Discovery). In the Maastricht Study, interleukin-6 and hs-CRP were measured in EDTA plasma samples with commercially available 4-plex sandwich immunoassay kits (Meso Scale Discovery), as described previously.[22] Heart rate variability was approximated using the variance of the RR interval, obtained during carotid echotracking in PPS3 and from a 24-hour electrocardiogram, recorded by use of a 12-lead Holter system (Fysiologic ECG Services, Amsterdam, the Netherlands) in the Maastricht Study, as described previously.[29]

Statistical Analysis

Descriptive statistics used percentages and mean± SD, and bivariate comparisons used chi-square test or Student's *t* test, where appropriate.

Analyses were conducted on pooled data and quantified the association between presence of hrOSA (main exposure) and vascular aging variables (main outcome measures), that is, Young's elastic modulus, local carotid PWV, carotid diameter, carotid IMT, and cfPWV. In main analysis, vascular aging variables were evaluated as continuous outcomes. We used multivariate linear regression modeling. In secondary analysis and to provide clinical insights, vascular aging variables were considered in study-specific quartiles and odds ratios (ORs) were estimated by multivariate multinomial logistic regression analysis using the first quartile as the reference category. In PPS3, the association between hrOSA and carotid plaques presence was estimated with multivariate logistic regression. All regression models were adjusted for age, sex, total cholesterol, smoking, education level, diabetes mellitus, heart rate, and study site (except for cfPWV being available in the Maastricht Study only and for carotid plaques being available in PPS3 only).

Several supplementary analyses were performed. Analyses were further adjusted for mean blood pressure, body mass index (BMI), and the use of antihypertensive medications. These were considered as sensitivity analyses because both hypertension and BMI are part of the definition of hrOSA, which increases the risk of overfitting of the model. To better control for blood pressure, analyses were also adjusted for 24-hour ambulatory blood pressure monitoring (Maastricht Study only). Analyses were then adjusted for other potential confounding factors such as the use of renin-angiotensin system blockers, lipid-modifying medications, estimated glomerular filtration rate, and low-density lipoprotein cholesterol. Analyses were also run separately in each cohort study. Instead of using study-specific quartiles, analysis was rerun considering common quartiles of vascular aging variables. To study the potential impact of missing data, analyses in each cohort were repeated after performing multiple imputations by chained equations.[30] For the 3 missing items of the Berlin questionnaire, we additionally imputed them as present (1 point for each item), instead of being absent as in the main analysis (0 points for each missing item). To investigate whether any association between OSA and vascular aging variables may be mediated by low-grade inflammation or autonomic dysfunction, we further adjusted for markers of low-grade inflammation (interleukin-6 and hs-CRP) and for autonomic dysfunction (variance of the RR interval).

Analyses were 2 sided and were performed using R software version 3.6.2.

RESULTS

Overall, 8583 participants in PPS3 and 3451 in the Maastricht Study were asked to fill in a sleep questionnaire. Participants with prevalent CVD were excluded (n=200 in PPS3 and n=666 in the Maastricht Study). Next, participants with missing data on vascular aging

variables, on the Berlin questionnaire and on any covariate were excluded, leaving an analytical sample of 8615 participants (6840 in PPS3 and 1775 in the Maastricht Study, Figure 1). The baseline characteristics of included and excluded participants are compared in Table S2. In general, excluded participants had a worse risk profile as compared with included participants, that is, they were more likely to have hrOSA and to have more adverse levels of accelerated vascular aging variables.

In PPS3, the study population comprised 62% men (n=4240) and the mean age was 59.5±6.2 years; in the Maastricht Study, there were 51% men (n=906) and the mean age was 58.9±8.1 years. In total, 16.8% (n=1150)

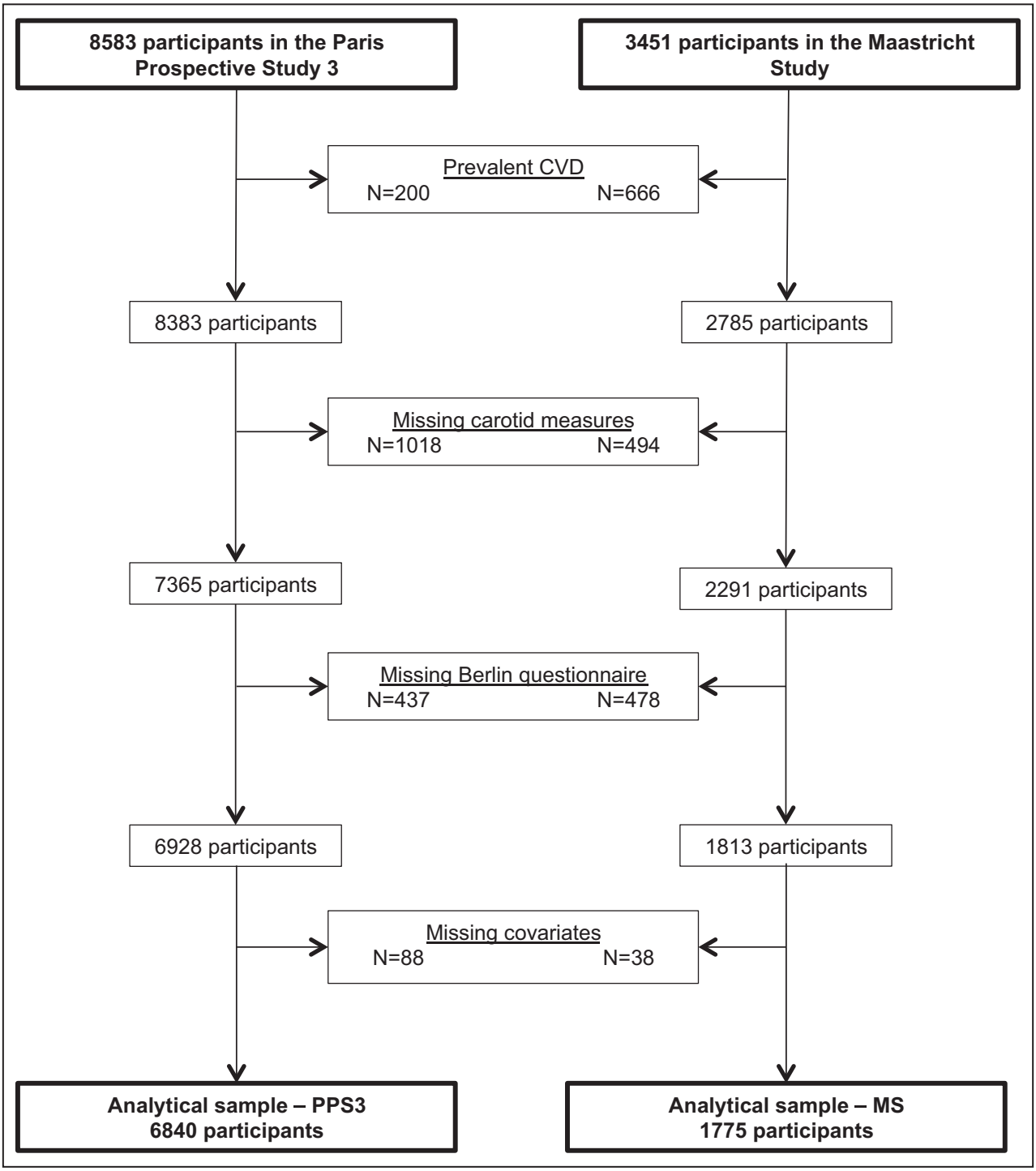

Figure 1. Studies' flow chart.
CVD indicates cardiovascular disease; MS, Maastricht Study; and PPS3, Paris Prospective Study 3.

participants had hrOSA in PPS3 and 23.8% (n=423) in the Maastricht Study. Participants' characteristics according to the presence of hrOSA are presented in Table 1. In each cohort, participants with hrOSA, as compared with those without hrOSA, were older, and more often male and current smokers, and more often had diabetes mellitus, a lower educational level, and a higher BMI. In addition, they had a higher Young's elastic modulus, carotid pulse wave velocity, carotid IMT, larger carotid diameter, and cfPWV. Participants with

Table 1. Participants' Characteristics According to the Likelihood of Obstructive Sleep Apnea in Each Cohort

	PPS3 n=6840		Maastricht Study n=1775	
	Low Risk of OSA n=5690 (83.2%)	High Risk of OSA n=1150 (16.8%)	Low Risk of OSA n=1352 (76.2%)	High Risk of OSA n=423 (23.8%)
Vascular aging variables				
Young's elastic modulus (kPa)	470.3±199	557.3±258	709.5±344	820.0±457
Carotid PWV (m/s)	6.7±1.3	7.3±1.4	8.3±1.6	8.9±1.8
Carotid-femoral PWV (m/s)	…	…	8.6±1.9	9.5±2.4
Carotid intima-media thickness (µm)	628.9±112	668.8±118	839.0±144	875.6±159
Carotid diameter (mm)	7.1±0.66	7.5±0.75	7.6±0.81	8.0±0.90
Carotid atherosclerosis: plaques presence	559 (9.8)	177 (15.4)	…	…
Cardiovascular measures				
Systolic blood pressure (mm Hg)	127.3+14.2	142.1±15.8	124.7±13.7	131.8±14.3
Diastolic blood pressure (mm Hg)	74.1±8.7	81.1±10.0	75.2±7.1	78.2±7.9
Pulse pressure (mm Hg)	44.2±9.8	50.5±11.4	49.6±9.5	53.6±10.2
Mean blood pressure (mm Hg)	91.8±9.7	101.4±10.7	93.2±11.0	101.5±10.3
Antihypertensive medications	493 (8.7)	376 (32.7)	256 (18.9)	244 (57.7)
Heart rate (bpm)	61.0±8.6	62.8±9.2	67.2±10.0	68.5±11.3
Heart rate variability (SD of RR interval)	54.7	53.9	55.1	51.7
General and metabolic characteristics				
Male sex	3381 (59.4)	859 (74.7)	624 (46.1)	282 (66.7)
Age, y	59.3±6.1	60.0±6.3	58.4±8.1	60.5±7.8
Smoking				
Never	3094 (54.4)	504 (43.8)	519 (38.4)	112 (26.5)
Ex-smoker	1832 (32.2)	469 (40.7)	668 (49.4)	249 (58.9)
Current	764 (13.4)	177 (15.4)	165 (12.2)	62 (14.7)
Education level				
Low	1549 (27.2)	367 (31.9)	348 (25.7)	146 (34.5)
Medium	1041 (18.3)	195 (17.0)	402 (29.7)	121 (28.6)
High	3100 (54.5)	588 (51.1)	602 (44.5)	156 (36.9)
Body mass index (kg/m^2)	24.4±3.2	27.4±3.9	25.5±3.6	29.6±4.7
Diabetes mellitus	165 (2.9)	76 (6.6)	218 (16.1)*	157 (37.1)*
Total cholesterol (mmol/L)	5.7±0.9	5.7±0.9	5.5±1.1	5.1±1.2
Low-density lipoprotein cholesterol (mmol/L)	3.7±0.8	3.7±0.8	3.3±1.0	3.2±1.1
Interleukin-6 (pg/mL)	0.73±1.14	0.82±0.72	0.83±2.6	1.12±4.8
High-sensitivity C-reactive protein (mg/L)	2.5±6.6	3.1±5.6	2.4±6.4	3.4±5.9
Estimated glomerular filtration rate (mL/min/1.73 m^2)	72.0±15.1	68.2±14.1	90.4±13.6	87.3±14.3

Values are mean±SD or number (%). Carotid-femoral PWV was evaluated in the Maastricht Study only, whereas carotid plaques presence was measured in the PPS3 only. Bpm indicates beats per minute; OSA, obstructive sleep apnea; PPS3, Paris Prospective Study 3; and PWV, pulse wave velocity.

*Type 2 diabetes mellitus was oversampled by design in the Maastricht Study.

hrOSA also more often had carotid plaques (15.4%) when compared with those without hrOSA (9.8%).

The presence of hrOSA was significantly associated with higher levels of all vascular aging variables, after adjustment for age, sex, smoking, education level, total cholesterol, diabetes mellitus, heart rate, and study site (Table 2). hrOSA presence was related to a graded increase in the likelihood of belonging to higher quartiles of vascular aging variables in multivariate analysis and to an increased odds of presenting with carotid plaques (Figure 2).

In sensitivity analyses, after additional adjustment for mean blood pressure or BMI or antihypertensive medications, associations of hrOSA with vascular aging variables were attenuated but remained significant. However, the association with cfPWV was no longer significant after adjustment for mean blood pressure (Table 2 and Table S3). Further adjustment for 24-hour ambulatory blood pressure monitoring provided results that were similar to those obtained after adjustment for mean blood pressure (Table S4). After adjustment for renin-angiotensin system blockers, low-density lipoprotein cholesterol level, lipid-modifying medications, and estimated glomerular filtration rate, regressions coefficients remained unchanged (Table S5). Separate analysis by cohort, including multiple imputation of missing data, yielded results that were in line with those obtained on pooled data analysis (Table S6). When considering common quartiles instead of study specific, results stayed unchanged. After imputing the 3 missing items of the Berlin questionnaire as being present, associations with carotid IMT and carotid diameter did not change, and effect estimates for associations with Young's elastic modulus, carotid pulse wave velocity, and cfPWV were of greater magnitude compared with the main analysis (Table S7). Lastly, further adjustment for markers of low-grade inflammation (interleukin-6 and hs-CRP) or autonomic dysfunction (RR interval), did not materially change the results (Table S8).

DISCUSSION

In 8615 participants free of previous CVD from the PPS3 (France) and the Maastricht Study (the Netherlands), 2 European community-based studies, hrOSA, as determined by the Berlin questionnaire, was consistently associated with a large set of markers indicating accelerated vascular aging and with presence of carotid plaques.

Meta-analyses of published data have reported significant associations between OSA, as determined by polysomnography and carotid IMT[31,32] and cfPWV.[33] However, the studies considered in these meta-analyses were of small sample size (n<100)[14,16,20,34] and focused on clinic-based patients–with generally more severe OSA phenotypes than in the general population setting.[13,15,34] In addition, most previous studies investigated 1 arterial variable, either carotid IMT or cfPWV.[13,14,16,35] To our best knowledge, only 3 population-based studies, the MESA (Multi-Ethnic Study of Atherosclerosis; n=1615),[18] the SHHS (Sleep Heart Health Study; n=985),[17] and the WSC (Wisconsin Sleep Cohort; n=790),[19] all conducted in US populations, have previously evaluated the association between OSA, as measured by polysomnography, and carotid IMT or carotid plaques. In MESA, a significant association with carotid plaques was found only in individuals younger than 68 years, and there was no association with carotid IMT.[18] In the SHHS, significant associations with carotid IMT and carotid plaques in crude analysis became nonsignificant after adjustment for several confounders, particularly BMI.[17] In the WSC, in which carotid IMT and presence of carotid plaques were determined 13.5 years on average after the first polysomnography, baseline OSA was associated with carotid IMT and carotid plaques in multivariable analysis.[19]

The current findings replicated the association between OSA and carotid plaques as found in previous studies, and extends these earlier works by

Table 2. Associations of High Risk of Obstructive Sleep Apnea (Exposure) With Vascular Aging Variables (Outcomes) in Pooled Data From the Paris Prospective Study 3 and the Maastricht Study

Outcomes	Model 1	Model 1+Mean Blood Pressure	Model 1+Body Mass Index	Model 1+Antihypertensive Medication
	Regression Coefficient (95% CI)			
Young's elastic modulus (kPa)	67.2 (53.6–80.8)	23.4 (9.5–37.3)	49.6 (35.4–63.8)	56.8 (42.8–70.9)
Carotid PWV (m/s)	0.47 (0.40–0.54)	0.18 (0.11–0.26)	0.34 (0.27–0.42)	0.42 (0.34–0.49)
Carotid diameter (mm)	0.26 (0.23–0.30)	0.18 (0.14–0.21)	0.17 (0.13–0.20)	0.22 (0.19–0.26)
Carotid intima-media thickness (μm)	30.0 (23.7–36.4)	21.6 (14.9–28.2)	20.1 (13.5–26.8)	28.3 (21.7–35.0)
Carotid-femoral PWV* (m/s)	0.48 (0.28–0.68)	0.20 (–0.004 to 0.40)	0.43 (0.22–0.65)	0.44 (0.25–0.65)

Regression coefficients (95% CI) are from multivariate linear regression analyses. Model 1 is adjusted for age, sex, smoking, education level, total cholesterol, diabetes mellitus, heart rate, and study site (except for the analysis of carotid-femoral PWV, which is available in the Maastricht Study only). PWV indicates pulse wave velocity.

*In the Maastricht Study only.

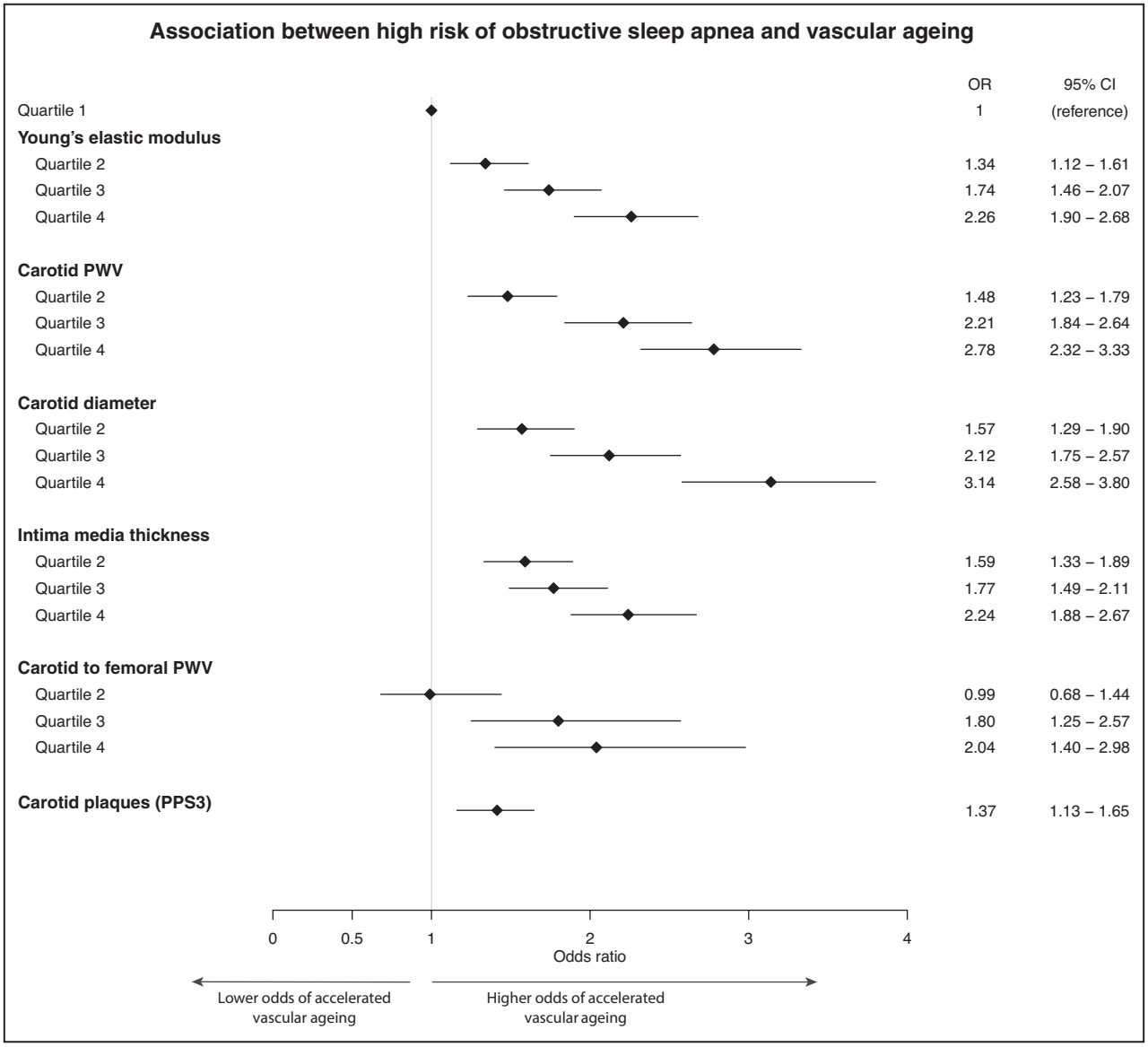

Figure 2. Association between high risk of obstructive sleep apnea (exposure) and vascular aging variables (outcomes). Odds ratios and 95% CIs were obtained by multinomial logistic regression using the first quartile of each study as the reference category. Regression models were adjusted for age, sex, smoking, education level, total cholesterol, diabetes mellitus, heart rate, and study site (except for carotid-femoral PWV, available in the Maastricht Study only and for carotid plaques, available in PPS3 only). Diamonds indicate OR and horizontal dark line indicate 95% CI. OR indicates odds ratio; PPS3, Paris Prospective Study 3; and PWV, pulse wave velocity.

several aspects. This is the largest study on OSA and vascular aging variables (n=8615 participants in total versus n=1615 or lower in previous studies), and we included multiple arterial variables encompassing several dimensions of vascular aging. The fact that hrOSA shows consistent associations with several markers of accelerated vascular aging in 2 independent cohort studies emphasizes the likelihood and robustness of the present findings. Hence, sleep apnea is likely to affect both structural (diameter, IMT) and functional (carotid pulse wave velocity, cfPWV, Young's elastic modulus) parameters. In addition, several potential confounders were considered, which is critical when studying associations between OSA and arterial variables, given that patients with OSA often present with multiple proatherogenic factors.[14,36] Of note, results were independent of mean blood pressure, except for cfPWV, 24-hour ambulatory blood pressure monitoring, antihypertensive medications including renin-angiotensin system blockers, and BMI. Also, this analysis conducted in 2 European community-based studies extends previous studies that were done in US populations only.

Several OSA-related mechanisms may be on the pathophysiological pathway between OSA and accelerated vascular aging.[37] Key characteristics of OSA, including intermittent hypoxia, recurrent arousals, and increased intrathoracic pressure, may contribute to accelerated vascular aging via different mechanisms, such as systemic inflammation, sympathetic activation, increased oxidative stress, and/or an increased wall stress on intrathoracic vessels.[38,39] However and although exploratory, associations did not change after adjustment for markers of low-grade inflammation and autonomic dysfunction in sensitivity analysis. Therefore, these mechanistic pathways need to be explored more in details in dedicated studies.

Implications

The observation that hrOSA is related to several markers of accelerated vascular aging, an important contributor to CVD,[8] suggests that accelerated vascular aging may, at least in part, underlie the well-established association between OSA and CVD. This hypothesis should be evaluated prospectively by quantifying the mediating effect of accelerated vascular aging on the association between presence of OSA and onset of CVD. The results also lend support to intervention studies evaluating to what extent accelerated vascular aging may be an additional target for preventing CVD onset in patients with OSA. Although not uniformly observed,[36,40,41] some observational studies[42,43] and small randomized controlled trials[44,45] have reported that vascular aging could be reversed with the use of continuous positive airway pressure therapy in patients with OSA. However, the impact of vascular aging reversal on CVD onset was not evaluated in these studies.

Limitations

We acknowledge the following limitations. First, OSA was not assessed by objective measures, such as polysomnography, but by questionnaire. However, good performance of the Berlin questionnaire as a screening tool for detecting severe OSA in the general population setting has been previously demonstrated.[24,25] Furthermore, the Berlin questionnaire is easily usable in daily clinical practice. Second, analysis of the association with the severity of OSA was not possible. Third, although 3 items of the questionnaire were not available, the way we assigned these items (ie, either absent or present) did not affect the conclusions on the association between OSA and vascular aging parameters. Fourth, the cross-sectional nature of the analysis precludes any causality assumption; however, regardless of causal considerations our data show that OSA is accompanied by markers of accelerated vascular aging. It also precludes to assess the directionality of the association between OSA presence and vascular aging. Fifth, vascular aging variables were assessed at a single point, precluding exploring the association between OSA and change in vascular aging. Future studies should investigate whether the changes in carotid artery phenotypes that occur with OSA are chronologically premature in their onset (accelerated), relative to controls (non-OSA) using longitudinal designs. Sixth, the 2 studies mainly include European participants from White race so that the generalizability of our findings to other populations may not hold true.

CONCLUSIONS

In conclusion, in 2 large European cohort studies, hrOSA was consistently associated with several markers of accelerated vascular aging. These results suggest that accelerated vascular aging may be, at least in part, on the path of the well-established association between OSA and CVD.

ARTICLE INFORMATION

Received March 9, 2021; accepted May 27, 2021.

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Sources of Funding

The PPS3 was supported by grants from The National Research Agency (ANR), the Research Foundation for Hypertension (RFHTA), the Research Institute in Public Health (IRESP), and the Region Ile de France (Domaine d'Intérêt Majeur). The Maastricht Study was supported by the European Regional Development Fund via OP-Zuid, the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 31O.041), Stichting De Weijerhorst (Maastricht, The Netherlands), the Pearl String Initiative Diabetes (Amsterdam, The Netherlands), the Cardiovascular Center (CVC, Maastricht, the Netherlands), CARIM School for Cardiovascular Diseases (Maastricht, The Netherlands), CAPHRI Care and Public Health Research Institute (Maastricht, The Netherlands), NUTRIM School for Nutrition and Translational Research in Metabolism (Maastricht, the Netherlands), Stichting Annadal (Maastricht, The Netherlands), Health Foundation Limburg (Maastricht, The Netherlands), and by unrestricted grants from Janssen-Cilag B.V. (Tilburg, The Netherlands), Novo Nordisk Farma B.V. (Alphen aan den Rijn, the Netherlands), and Sanofi-Aventis Netherlands B.V. (Gouda, the Netherlands).

Disclosures

None.

Supplementary Material

Table S1–S8

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SUPPLEMENTAL MATERIAL

Table S1. Berlin questionnaire and its adaptation in PPS3 and the Maastricht Study.

Questions	Answers	Rating	Rating in MS	Rating in PPS3
Category 1				
Do you snore?	a. Yes b. No	1 point if 'Yes'	1 point if 'Yes'	1 point if 'Yes'
Your snoring is:	a. Slightly louder than breathing b. As loud as talking c. Louder than talking d. Very loud	1 point if 'c' or 'd'	1 point if 'Yes' to the question: 'Is your snoring very loud?'	Not available*
How often do you snore?	a. Almost every day b. 3-4 times per week c. 1-2 times per week d. 1-2 times per month e. Rarely or never	1 point if 'a' or 'b'	Not available*	1 point if 'a' or 'b'
Has your snoring ever bothered other people?	a. Yes b. No	1 point if 'a'	Not available*	Not available*
Has anyone noticed that you stop breathing during your sleep?	a. Almost every day b. 3-4 times per week c. 1-2 times per week d. 1-2 times per month e. Rarely or never	2 points if 'a' or 'b'	2 points if 'Yes' to the question: 'Do you have breathing pauses during your sleep?'	2 points if 'a' or 'b'
Category 2				
How often do you feel tired or fatigued after your sleep?	a. Almost every day b. 3-4 times per week c. 1-2 times per week d. 1-2 times per month e. Rarely or never	1 point if 'a' or 'b'	Not available*	Not available*
During your waking time, do you feel tired, fatigued or not up to par?	a. Almost every day b. 3-4 times per week c. 1-2 times per week d. 1-2 times per month e. Rarely or never	1 point if 'a' or 'b'	1 point if 'Yes' to the question: 'Do you feel tired during daytime?'	1 point if 'a' or 'b'

Have you ever nodded off or fallen asleep while driving a vehicle?	a. Yes b. No	1 point if 'a'	1 point if 'a'	1 point if 'a'
Category 3	Body mass index	1 point if >30kg/m^2	1 point if >30kg/m^2	1 point if >30kg/m^2
	Hypertension	1 point if hypertension	1 point if hypertension	1 point if hypertension

Note: Category 1 and 2 are positive if the total score is 2 points or more for each category. Category 3 is positive if the total score is 1 point or more. The Berlin questionnaire is positive (*i.e.* high risk of obstructive sleep apnea) if 2 or 3 categories are positive.
*0 point assigned in main analysis and 1 point assigned in sensitivity analysis.
Abbreviations: PPS3: Paris Prospective Study 3; MS: the Maastricht Study.

Table S2. Comparison of included and excluded participants in each study.

	Paris (PPS3)		Maastricht Study	
	Included N=6840	Excluded N=1743	Included N=1775	Excluded N=1676
Vascular ageing variables				
Young's elastic modulus (kPa)	484.9 ± 212.7	550 ± 269.0	735.8 ± 376.7	778.2 + 373.0
Carotid PWV (m/s)	6.8 ± 1.3	7.3 ± 1.6	8.4 ± 1.7	8.7 ± 1.7
Carotid-femoral PWV (m/s)*	-	-	8.78 ± 2.03	9.39 ±2.30
Carotid intima-media thickness (µm)	660.9 ± 120.1	635.6 ± 114.6	847.8 ± 148.4	877.7 ± 169.1
Carotid diameter (mm)	7.13 ± 0.70	7.30 ± 0.79	7.74 ± 0.84	7.95 ± 0.89
Carotid atherosclerosis: plaques presence**	736 (10.8)	259 (15.0)	-	-
High risk of OSA	1150 (16.8)	264 (22.3)	423 (23.8)	313 (36.9)
Blood pressure measures				
Systolic blood pressure (mmHg)	129.8 ± 15.5	134.8 ± 17.8	126.4 ± 14.2	129.2 ± 14.8
Diastolic blood pressure (mmHg)	75.3 ± 9.3	76.9 ± 10.1	75.9 ± 7.5	75.8 ± 7.6
Pulse pressure (mmHg)	45.2 ± 10.3	48.8 ± 12.0	50.5 ± 9.8	53.4 ± 11.0
Mean blood pressure (mmHg)	93.5 ± 10.5	96.2 ± 11.6	95.2 ± 11.4	96.5 ± 11.4
Antihypertensive medications	869 (12.7)	447 (25.9)	500 (28.2)	866 (52.8)
Heart rate (bpm)	61.3 ± 8.7	62.3 ± 9.6	65.7 ± 10.4	68.7 ± 11.7
General & metabolic characteristics				
Male sex	4240 (62.0)	966 (55.9)	906 (51.0)	855 (52.0)
Age (years)	59.5 ± 6.2	61.3 ± 6.6	58.9 ± 8.1	60.7 ± 8.3
Smoking				
Never	3598 (52.6)	851 (49.7)	631 (35.5)	525 (33.2)
Ex-smoker	2301 (33.6)	615 (35.9)	917 (51.7)	817 (51.7)
Current	941 (13.8)	247 (14.4)	227 (12.8)	239 (15.1)

Education level				
Low	1916 (28.0)	537 (32.6)	494 (27.8)	631 (40.3)
Medium	1236 (18.1)	286 (17.4)	523 (29.5)	423 (27.0)
High	3688 (53.9)	824 (50.0)	758 (42.7)	513 (32.7)
BMI (kg/m^2)	24.9 ± 3.5	25.7 ± 4.2	26.5 ± 4.2	27.7 ± 4.8
Diabetes	241 (3.5)	87 (5.1)	375 (21.1)	590 (36.8)
Total cholesterol (mmol/L)	5.7 ± 0.9	5.7 ± 1.0	5.4 ± 1.1	5.0 ± 1.2

Note: values are mean ± SD or number (%).
*Available in the Maastricht study only; ** available in PPS3 only
Abbreviations: PPS3: Paris Prospective Study 3; PWV: pulse wave velocity; OSA: obstructive sleep apnea; BMI: body mass index; bpm: beats per minute.

Table S3. Association between high risk of obstructive sleep apnea (exposure) and quartiles of vascular ageing variables (outcomes) in pooled data from the Paris Prospective Study 3 and the Maastricht Study.

	OR (95% CI)		
Outcome	Model 1	Model 1 + mean blood pressure	Model 1 + body mass index
Young's elastic modulus			
Quartile 1	1 (ref)	1 (ref)	1 (ref)
Quartile 2	1.34 (1.12 – 1.61)	1.10 (0.92 – 1.33)	1.18 (0.98 – 1.42)
Quartile 3	1.74 (1.46 – 2.07)	1.22 (1.01 – 1.46)	1.45 (1.21 – 1.74)
Quartile 4	2.26 (1.90 – 2.68)	1.33 (1.11 – 1.60)	1.71 (1.43 – 2.05)
Carotid PWV			
Quartile 1	1 (ref)	1 (ref)	1 (ref)
Quartile 2	1.48 (1.23 – 1.79)	1.15 (0.95 – 1.40)	1.30 (1.07 – 1.57)
Quartile 3	2.21 (1.84 – 2.64)	1.47 (1.22 – 1.78)	1.77 (1.47 – 2.14)
Quartile 4	2.78 (2.32 – 3.33)	1.51 (1.24 – 1.83)	2.01 (1.67 – 2.43)
Carotid diameter			
Quartile 1	1 (ref)	1 (ref)	1 (ref)
Quartile 2	1.57 (1.29 – 1.90)	1.36 (1.11 – 1.66)	1.29 (1.05 – 1.58)
Quartile 3	2.12 (1.75 – 2.57)	1.68 (1.37 – 2.05)	1.54 (1.26 – 1.88)
Quartile 4	3.14 (2.58 – 3.80)	2.12 (1.73 – 2.60)	1.97 (1.61 – 2.41)
Carotid intima-media thickness			
Quartile 1	1 (ref)	1 (ref)	1 (ref)
Quartile 2	1.59 (1.33 – 1.89)	1.46 (1.21 – 1.75)	1.44 (1.20 – 1.73)
Quartile 3	1.77 (1.49 – 2.11)	1.54 (1.28 – 1.85)	1.49 (1.24 – 1.80)
Quartile 4	2.24 (1.88 – 2.67)	1.83 (1.52 – 2.20)	1.73 (1.44 – 2.07)
Carotid-femoral PWV*			
Quartile 1	1 (ref)	1 (ref)	1 (ref)
Quartile 2	0.99 (0.68 – 1.44)	0.75 (0.51 – 1.12)	0.85 (0.57 – 1.28)
Quartile 3	1.80 (1.25 – 2.57)	1.18 (0.81 – 1.72)	1.49 (1.01 – 2.20)
Quartile 4	2.04 (1.40 – 2.98)	1.18 (0.79 – 1.76)	1.66 (1.11 – 2.48)

Note: odds ratios and 95% confidence intervals were obtained by multinomial logistic regression using the first quartile of each study as the reference category. Model 1 is adjusted for age, sex, smoking, education level, total cholesterol, diabetes, heart rate and study site (except for carotid-femoral PWV, available in Maastricht only)
Abbreviations: OR: odd ratio; CI: confidence interval; PWV: pulse wave velocity.
* in Maastricht Study only.

Table S4. Associations of high risk of obstructive sleep apnea (exposure) with vascular ageing variables (outcomes) after adjustment for 24-hour ambulatory blood pressure monitoring (the Maastricht Study only).

	Maastricht study Regression coefficient (95% CI)		
Outcome	Model 1 N=1775	Model 1 + mean blood pressure N=1775	Model 1 + 24h ABPM N=1575
Young's elastic modulus (kPa)	60.4 (21.1 – 99.7)	25.1 (-1.5 – 65.2)	26.4 (-1.3 – 66.0)
Carotid PWV (m/s)	0.37 (0.21 – 0.54)	0.18 (0.01 – 0.34)	0.23 (0.06 – 0.40)
Carotid diameter (mm)	0.16 (0.08 – 0.24)	0.11 (0.02 – 0.19)	0.10 (0.01 – 0.18)
Carotid IMT (μm)	17.9 (2.0 – 33.7)	12.2 (-4.2 – 28.5)	16.3 (-0.85 – 33.4)
Carotid-femoral PWV (m/s)	0.48 (0.28 – 0.68)	0.20 (-0.01 – 0.40)	0.28 (0.07 – 0.49)

Note: regression coefficients (95% CI) are from multivariate linear regression analyses. Model 1 is adjusted for age, sex, smoking, education level, total cholesterol, diabetes and heart rate.

Table S5. Associations of high risk of obstructive sleep apnea (exposure) with vascular ageing variables (outcomes) after adjustment for further potential confounders.

	Model 1	Model 1 + RAS blockers	Model 1 + lipid-modifying medications	Model 1 + eGFR	Model 1 + LDL cholesterol*
Outcomes	**Unstandardized regression coefficient (95% CI)**				
Young's elastic modulus (kPa)	67.2 (53.6 – 80.8)	62.3 (48.4 – 79.2)	65.3 (51.0 – 79.6)	66.6 (53.0 – 80.2)	67.9 (54.3 – 81.5)
Carotid PWV (m/s)	0.47 (0.40 – 0.54)	0.45 (0.38 – 0.52)	0.45 (0.38 – 0.53)	0.46 (0.39 – 0.53)	0.47 (0.40 – 0.54)
Carotid diameter (mm)	0.26 (0.23 – 0.30)	0.24 (0.20 – 0.27)	0.26 (0.22 – 0.30)	0.26 (0.23 – 0.30)	0.26 (0.23 – 0.30)
Carotid IMT (μm)	30.0 (23.7 – 36.4)	29.4 (22.8 – 35.9)	28.8 (22.2 – 35.5)	30.0 (23.6 – 36.4)	30.0 (23.6 – 36.4)

Note: regression coefficients (95% CI) are from multivariate linear regression analyses. Model 1 is adjusted for age, sex, smoking, education level, total cholesterol, diabetes, heart rate, and study site (except for the analysis of carotid-femoral PWV which is available in Maastricht study only).

* not adjusted for total cholesterol

Table S6. Multivariate associations of high risk of obstructive sleep apnea (exposure) with vascular ageing variables (outcomes) in each study, before and after multiple imputations.

Outcome	PPS3 Regression coefficient (95% CI)		Maastricht study Regression coefficient (95% CI)	
	Non imputed data N=6840	After multiple imputations* N=8583	Non imputed data N=1775	After multiple imputations* N=3451
Young's elastic modulus (kPa)	71.0 (57.8 – 84.1)	68.3 (54.4 – 82.2)	60.4 (21.1 – 99.7)	43.2 (10.2 – 76.1)
Carotid PWV (m/s)	0.51 (0.43 – 0.59)	0.44 (0.37 – 0.51)	0.37 (0.21 – 0.54)	0.25 (0.11 – 0.39)
Carotid diameter (mm)	0.29 (0.25 – 0.33)	0.29 (0.25 – 0.32)	0.16 (0.08 – 0.24)	0.10 (0.02 – 0.18)
Carotid IMT (µm)	33.7 (26.8 – 40.5)	32.5 (26.2 – 38.8)	17.9 (2.0 – 33.7)	9.2 (-7.3 – 25.7)
Carotid-femoral PWV (m/s)	-	-	0.48 (0.28 – 0.68)	0.36 (0.16 – 0.56)

Note: regression coefficients derived from multivariate linear regression. Models are adjusted for age, sex, smoking, education level, total cholesterol, diabetes and heart rate. Carotid-femoral PWV was measured in the Maastricht study.

Abbreviations: PPS3: Paris Prospective Study 3; OR: odd ratio; CI: confidence interval; ref: reference category; IMT: intima media thickness; PWV: pulse wave velocity.

*Multiple imputations were performed by chained equation.

Table S7. **Associations of high risk of obstructive sleep apnea (exposure) with vascular ageing variables (outcomes) after assigning missing item of the Berlin questionnaire as present in pooled data from the Paris Prospective study 3 and the Maastricht Study.**

	Regression coefficient (95% CI)	
Outcomes	Imputing missing items as absent (0 point)	Imputing missing items as present (1 point)
Young's elastic modulus (kPa)	67.2 (53.6 – 80.8)	73.6 (62.8 – 84.4)
Carotid PWV (m/s)	0.47 (0.40 – 0.54)	0.52 (0.46 – 0.58)
Carotid diameter (mm)	0.26 (0.23 – 0.30)	0.20 (0.18 – 0.23)
Carotid IMT (µm)	30.0 (23.7 – 36.4)	22.9 (17.5 – 28.0)
Carotid-femoral PWV* (m/s)	0.48 (0.28 – 0.68)	0.50 (0.32 – 0.69)

Note: regression coefficients (95% CI) are from multivariate linear regression analyses. Model 1 is adjusted for age, sex, smoking, education level, total cholesterol, diabetes, heart rate, and study site (except for the analysis of carotid-femoral PWV which is available in Maastricht study only).
Abbreviations: CI: confidence interval; IMT: intima media thickness; PWV: pulse wave velocity.
* in Maastricht Study only.

Table S8. **Mediating effect of markers of low-grade inflammation and sympathetic activation in the associations of high risk of obstructive sleep apnea (exposure) and vascular ageing variables (outcomes) in pooled data from the Paris Prospective study 3 and the Maastricht Study.**

	Regression coefficient (95% CI)			
Outcome	Model 1	Model 1 + hs-CRP	Model 1 + IL-6	Model 1 + R-R interval variance
Young's elastic modulus (kPa)	67.2 (53.6 – 80.8)	67.3 (53.7 – 80.9)	67.8 (54.2 – 81.4)	65.7 (52.0 – 79.5)
Carotid PWV (m/s)	0.47 (0.40 – 0.54)	0.47 (0.40 – 0.54)	0.47 (0.40 – 0.54)	0.47 (0.40 – 0.54)
Carotid diameter (mm)	0.26 (0.23 – 0.30)	0.26 (0.22 – 0.29)	0.26 (0.23 – 0.30)	0.27 (0.23 – 0.30)
Carotid IMT (µm)	30.0 (23.7 – 36.4)	30.1 (23.7 – 36.5)	30.3 (24.0 – 36.8)	31.2 (24.7 – 37.7)
Carotid-femoral PWV* (m/s)	0.48 (0.28 – 0.68)	0.48 (0.28 – 0.68)	0.48 (0.28 – 0.68)	0.39 (0.15 – 0.62)

Note: regression coefficients (95% CI) are from multivariate linear regression analyses. Model 1 is adjusted for age, sex, smoking, education level, total cholesterol, diabetes, heart rate, and study site (except for the analysis of carotid-femoral PWV which is available in Maastricht study only).

Abbreviations: CI: confidence interval; IMT: intima media thickness; PWV: pulse wave velocity; hs-CRP: high-sensitive C reactive protein; IL-6: interleukin-6

* in Maastricht Study only.