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Characteristics of hypertension and arterial stiffness in obstructive sleep apnea: A Scandinavian experience from a prospective study of 6408 normotensive and hypertensive patients

Sahrai Saeed MD, PhD, FESC[1] | Andrea Romarheim MD[1] | Giuseppe Mancia MD, PhD[2] | Ingvild West Saxvig MD, PhD[3,4] | Shashi Gulati MD[5] | Sverre Lehmann MD, PhD[6,7] | Bjørn Bjorvatn MD, PhD[3,4,7]

[1] Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

[2] Milano and Policlinico di Monza, University of Milano-Bicocca, Monza, Italy

[3] Center for Sleep Medicine, Haukeland University Hospital, Bergen, Norway

[4] Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, Norway

[5] Department of Otolaryngology/Head & Neck Surgery, Haukeland University Hospital, Bergen, Norway

[6] Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

[7] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Correspondence
Sahrai Saeed, Department of Heart Disease, Haukeland University Hospital, Bergen, Norway.
Email: sahrai.saeed@helse-bergen.no

Abstract

The impact of obstructive sleep apnea (OSA) on arterial stiffness is less studied. We aimed to investigate the prevalence and covariates of increased pulse pressure (PP), a surrogate marker of arterial stiffness, in the entire study population as well as in separate analyses in normotensive and hypertensive patients. Further, we also explored the impact of smoking on brachial BP in hypertensive patients. Between 2012 and 2019, a total of 6408 participants with suspected OSA underwent a standard out-of-center respiratory polygraphy. OSA was defined by an apnea-hypopnea index (AHI) ≥15/h regardless of symptoms. PP ≥60 mmHg was used as a surrogate marker of increased arterial stiffness. Mean age was 49.3±13.7 years, 69.4% were male, and 34.5% had OSA. The prevalence of hypertension was 70.8% in OSA and 46.7% in No-OSA (AHI < 15/h) controls ($P < .0001$). Hypertension was controlled (clinic BP < 140/90 mmHg) in 45.5% and uncontrolled in 54.5% ($P < .001$). Mean PP was 50±12 mmHg in smokers and 52±12 mmHg in non-smokers ($P = .001$). Increased PP was found in 24.2% of the entire study population and was higher in patients with OSA compared to No-OSA group (27.5% vs 22.4%, $P < .0001$). In an unadjusted logistic regression model, OSA was associated with a 1.3-fold higher risk of having increased PP (95% CI 1.16-1.48, $P < .001$). In a multivariable-adjusted model, higher age, male sex, and history of hypertension, but not OSA (OR 0.89; 95% CI 0.77-1.02, $P = .104$) were associated with increased PP. In this large study of nearly 6500 participants who were referred with suspected OSA, one-third were diagnosed with OSA and a quarter had increased arterial stiffness by elevated brachial PP. Hypertension but not OSA per se was associated with increased arterial stiffness. Hypertension was highly prevalent and poorly controlled.

KEYWORDS
apnea-hypopnea index, arterial stiffness, blood pressure, hypertension, obstructive sleep apnea, pulse pressure

1 | INTRODUCTION

Obstructive sleep apnea (OSA), ie, a condition characterized by recurrent collapse of upper airways during sleep associated with intermittent episodes of apnea/hypopnea and nocturnal hypoxemia, is a cardiovascular (CV) risk factor,[1] which can markedly increase total CV risk.[2] Studies performed in the past 10–20 years have identified several OSA-related factors that can account for this marked increase. First, although detectable in lean and normotensive patients,[3] OSA is highly prevalent in patients with obesity and hypertension in whom it is often the cause of resistance to treatment.[4–5] Second, OSA patients are characterized by a non-dipping blood pressure (BP) pattern and nocturnal hypertension,[6] sympathetic activation, and an increased BP variability.[3,6] Finally, compared with No-OSA controls, OSA patients exhibit not only a greater prevalence of cardiometabolic abnormalities, but also a more frequent association with subclinical cardiac damage, ie, greater left ventricular (LV) mass and an abnormal LV geometry.[7] However, the impact of OSA on extra-cardiac organ damage has been less well clarified, this being the case also for an independent CV risk factor such as increased arterial stiffness,[7] which has been shown to have an inconsistent association with OSA in studies in which arterial stiffness was measured by a gold standard approach such as pulse wave velocity (PWV).[8–11]

In the present study, we addressed the relationship between OSA and arterial stiffness in more than six thousand consecutive patients in whom OSA was investigated by a competent center for sleep disorders and arterial stiffness was measured by pulse pressure (PP), ie, a simple and widely available hemodynamic variable, which reflects age-dependent large artery stiffness in middle age and older people.[7] PP has been shown to have an adverse prognostic significance,[12–14] and is indicated by the European guidelines as a surrogate marker of arterial stiffening and high CV risk when its value is ≥60 mmHg.[4] Hence, our primary aims were to (1) investigate the prevalence and covariates of increased PP in the entire study population as well as in separate analyses in normotensive and hypertensive patients; (2) assess in all subgroups the prevalence and characteristic of OSA. Given the complex association between smoking and BP,[15] the impact of smoking on brachial BP in hypertensive patients was explored as a secondary aim.

2 | METHODS

2.1 | Study design and population

The study population included 6590 consecutive patients with suspected OSA who were referred to the Center for Sleep Medicine at Haukeland University Hospital, Bergen between February 2012 and February 2019. Among these, 182 patients (2.8%) had incomplete respiratory polygraphic sleep studies, leaving 6408 patients eligible for inclusion in the present study. Another 230 patients (3.5%) had missing brachial BP measurements and/or lack of information on previous history of hypertension, and were excluded from the hypertension sub-analyses. The diagnosis of OSA was based upon a standard out-of-center respiratory polygraphy using a commercially available type 3 portable monitor (Embletta or NOX T3, Resmed Norway AS) as described in details elsewhere.[16–17] According to the 2007 American Academy of Sleep Medicine Manual,[18] apneas were defined as a reduction of 90% or more of baseline nasal airflow with a duration of at least 10 seconds, and hypopneas as a nasal flow reduction of 30–90% of baseline, lasting at least 10 seconds accompanied by an oxygen desaturation of ≥4%. In line with the American Academy of Sleep Medicine recommendation, moderate or severe OSA was defined by an apnea-hypopnea index (AHI) ≥15/h irrespective of symptoms,[18] and this definition was used to characterize patients with OSA in the present study.

A written informed consent was obtained from all patients enrolled in the study. The study was approved by The Regional Committee for Medical and Health Research Ethics, Health Region West (REK vest) (REK vest 2014/1060).

2.2 | Assessment of cardiovascular risk factors

The patients filled out a standard questionnaire prior to the respiratory sleep study, which was subsequently checked and revised by a nurse or doctor during the consultation. The patients were asked about their smoking (number of cigarettes per day) and drinking habits (daily consumption, 3–5 days per week, 1–2 days per week, rarely or never). More than 2 days per week alcohol use was defined as excessive alcohol consumption. The self-reported questionnaire included information on medical comorbidities such as previous myocardial infarction, angina pectoris, stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), asthma as well as current medications for the same conditions, the details of which were further clarified during the consultation. During the consultation, the patients' weight (kg) and height (m) were measured and body mass index (BMI) was calculated by weight in kg divided by squared height in meters. Obesity was defined as BMI ≥30 kg/m^2.

BP was measured by a nurse or a doctor after a 10-minute rest in the sitting position, using an automatic device (OMRON or Scan-Med) with appropriate cuff size for the individual patient. In case of strongly deviating values, BP was measured manually. Hypertension was defined as previously known hypertension, current use of antihypertensive medications, or elevated clinic BP (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) values. Hypertension control in treated patients

was defined as clinic BP < 140/90 mmHg. Increased PP (difference between systolic and diastolic values ≥60 mmHg) was used as a surrogate marker of increased arterial stiffness.[4]

2.3 | Statistical analyses

SPSS version 26.0 (IBM corporation, Armonk, New York, USA) was used for the data analyses. Descriptive analyses were performed to assess the prevalence of common CV risk factors and morbidities, overall and according to the OSA status. Comparison between participants with No-OSA (AHI < 15/h) and OSA (AHI ≥15/h) was performed by Student's *t*-test and chi-square, as appropriate. The predictors of increased PP (≥60 mmHg) were identified in univariate and multivariate logistic regression analyses and reported as odds ratio (OR) and 95% confidence intervals (CI). Multivariate models were adjusted for age, gender, smoking and alcohol habits, BMI, diabetes, history of hypertension, and antihypertensive treatment based upon either significant association in univariate analyses, or clinical or epidemiological relevance (age, gender, diabetes). Bivariate associations were identified by Pearson's correlation coefficients. A *P*-value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population characteristics

The characteristics of the whole cohort (n = 6408) and according to the OSA categories are presented in **Table 1**. Mean age was 49.3±13.7 years, and 69.4% were male. The prevalence of increased PP was 24.2% in the entire study population and was higher in OSA than No-OSA participants (Figure 1A). Mean age was 47.9±13.0 years in individuals with normal PP and 54.5±14.6 years with increased PP ($P < .0001$). Participants with increased PP were more likely to have hypertension, diabetes and obesity compared with those with normal PP (Figure 2A-C). Increased PP was more common in participants > 50 years than < 50 years (Figure 2D). OSA (AHI ≥15/h) was found in 34.5% (n = 2211) of the total study population. There was a modest direct correlation between AHI and age (Pearson $R = 0.25$, $P < .001$). Participants with OSA were older, more likely to be male and have higher BMI, clinic BP and higher burden of medical comorbidities compared to No-OSA controls (all $P < .0001$). The prevalence of hypertension was 71% in participants with OSA versus 47% in No-OSA controls. The proportion of elevated clinic BP progressively increased with OSA severity level, while the proportion of participants with increased PP was higher in the group of patients with AHI 5–14.9/h compared to those with AHI < 5/h, and was equally high in patients with AHI 15–29.9/h and AHI ≥30/h (Figure 3). Mean PP was 52±12 mmHg in OSA and 51±12 mmHg No-OSA groups ($P < .0001$), and 50±12 mmHg in smokers and 52±12 mmHg in non-smokers ($P = .001$). The prevalence of OSA (AHI ≥15/h) was 33.5% in participants with normal PP and 39.8% in increased PP ($P < .0001$).

The univariate predictors of increased PP in the entire study population are presented in **Table 2**. In an unadjusted logistic regression model, OSA was associated with a 1.3-fold higher risk of having increased PP. However, in a multivariable-adjusted model, higher age, male sex, and history of hypertension were associated with higher risk of increased PP, while OSA (AHI ≥15/h) did not retain its association with increased PP, independent of smoking and alcohol habits, BMI and diabetes (Table 2). In the same multivariate model, when the cut-off of OSA was changed from AHI ≥15/h to AHI ≥5/h, the results remained mainly unchanged, and OSA was still not associated with an increased PP (OR 0.93; 95% CI 0.80-1.09, $P = .378$).

3.2 | Overall hypertensive participants

The characteristics of hypertensive participants (n = 3526) according to OSA categories are presented in **Table 3**. The overall prevalence of hypertension was 55%. Hypertensive OSA participants were older, predominantly males and had higher BMI and higher prevalence of diabetes compared to their No-OSA counterparts. Clinic BP and PP were equally high in both groups (Table 3). Increased PP was found in 35.2% (n = 533) of the OSA and 37.1% (n = 695) of the No-OSA groups ($P = .252$). Mean age (54.4 ± 12.9 vs 51.3 ± 11.0 years, $P < .0001$) and BMI (31.1 ± 6.1 vs 30.5 ± 6.0 kg/m^2, $P = .014$) were significantly higher in hypertensive non-smokers than hypertensive current smokers. In a univariate logistic regression analysis in hypertensive patients, OSA was not associated with increased PP (OR 0.92; 95% CI 0.80-1.06, $P = .252$). In a multivariate logistic regression model, older age was associated with higher odds and antihypertensive treatment with lower odds of increased PP (Table 4). In the same multivariable-adjusted model, smoking was associated with lower risk of increased PP (Table 4).

3.3 | Treated hypertensive participants

The characteristics of treated hypertensive participants (n = 1899) are presented in Table 3. Participants with treated hypertension and OSA were older, more likely to be male and had higher BMI, and higher prevalence of diabetes compared with No-OSA counterparts. Clinic systolic BP and PP were comparable in both groups, although there was a trend for slightly higher diastolic BP in OSA group (Table 3). Increased PP as categorical variable was equally represented in both groups: 34.3% (n = 309) in OSA and 33.9% (n = 292) in No-OSA groups ($P = .852$), and was high both in treated and untreated hypertensive and low in normotensive participants, without any significant difference according to the presence or absence of OSA (Figure 1B). Hypertension was controlled (clinic BP < 140/90 mmHg) in 45.5% and uncontrolled in 54.5% ($P < .001$). The prevalence of uncontrolled hypertension was 53.4% in OSA patients and 50.3% in No-OSA controls ($P = .202$). The presence of OSA was not associated with increased PP (Table 4). In a multivariate logistic regression model, higher age was identified as the only independent covariate of increased PP (Table 4).

TABLE 1 Baseline characteristics of the entire study population and according to the OSA categories

		OSA (AHI ≥15/h)		
	Study population	No	Yes	*P*
Patients, no. (%)	6408 (100)	4197 (65.5)	2211 (34.5)	NA
Age (year)	49.3 ± 13.7	46.6 ± 13.7	54.7 ± 11.9	<.0001
Male sex (%)	69.4	64.2	79.4	<.0001
Weight (kg)	93 ± 20	89 ± 19	99 ± 20	<.0001
Height (m)	1.76 ± 0.09	1.76 ± 0.09	1.77 ± 0.09	<.0001
BMI (kg/m^2)	29.8 ± 6.0	28.9 ± 6.0	31.6 ± 5.9	<.0001
Obesity (BMI ≥30 kg/m^2) (%)	42.4	35.7	55.3	<.0001
Current smokers (%)	21.0	21.8	20.0	.106
Excessive alcohol consumption* (%)	7.4	6.4	9.4	<.0001
Systolic BP (mmHg)	133 ± 15	131 ± 15	136 ± 16	<.0001
Diastolic BP (mmHg)	82 ± 10	80 ± 10	84 ± 11	<.0001
Elevated clinic BP (%)	39.0	33.7	49.1	<.0001
Pulse Pressure (mmHg)	52 ± 12	51 ± 12	52 ± 12	<.0001
Pulse pressure ≥60 mmHg (%)	24.2	22.4	27.5	<.0001
Hypertension (%)	55.0	46.7	70.8	<.0001
Myocardial infarction (%)	5.6	3.9	8.7	<.0001
Angina pectoris (%)	3.5	2.8	4.7	<.0001
Previous stroke (%)	2.6	2.2	3.4	.004
Diabetes (%)	9.7	7.9	12.9	<.0001
COPD (%)	4.4	4.2	4.6	.469
Asthma (%)	16.8	18.2	14.4	<.0001
AHI (events per hour)	15.6 ± 17.7	5.7 ± 4.1	34.2 ± 18.8	<.0001
ODI (per hour)	13.7 ± 16.8	5.0 ± 4.5	30.0 ± 19.2	<.0001
Mean SaO_2 (%)	93 ± 2	94 ± 2	92 ± 3	<.0001

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; ODI, oxygen desaturation index.
*More than 2 days per week.

TABLE 2 Predictors of increased pulse pressure in univariate and multivariate logistic regression analyses in the entire study population

	Univariate		Multivariate	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (per year increase)	1.04 (1.03-1.04)	<.0001	1.03 (1.03-1.04)	<.0001
Male gender	1.22 (1.07-1.39)	.003	1.39 (1.20-1.61)	<.0001
Current smoking	0.82 (0.71-0.96)	.012	0.94 (0.80-1.10)	.428
Excessive alcohol consumption*	1.40 (1.14-1.72)	.002	1.09 (0.87-1.37)	.440
Higher BMI (kg/m^2)	1.01 (1.00-1.02)	.007	1.01 (1.00-1.02)	.060
Diabetes	1.66 (1.38-1.99)	<.0001	1.10 (0.90-1.35)	.347
History of hypertension	2.26 (2.00-2.54)	<.0001	1.56 (1.36-1.80)	<.0001
OSA (AHI ≥15/h)	1.32 (1.16-1.48)	<.001	0.89 (0.77-1.02)	.104
COPD	1.58 (1.21-2.07)	.001	…	…
Asthma	1.04 (0.88-1.21)	.671	…	…

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.
*More than 2 days per week.

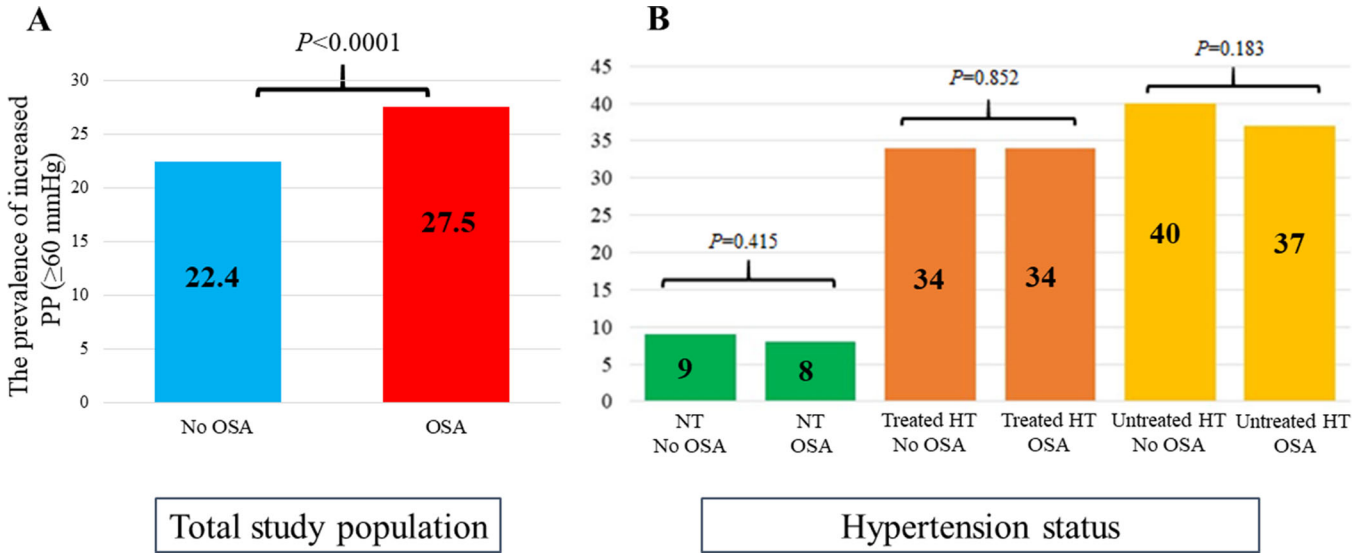

FIGURE 1 The prevalence of increased pulse pressure (PP) in total study population (A), and normotension (NT) and hypertension (HT) subgroups according to the present or absence of obstructive sleep apnea (OSA) (B)

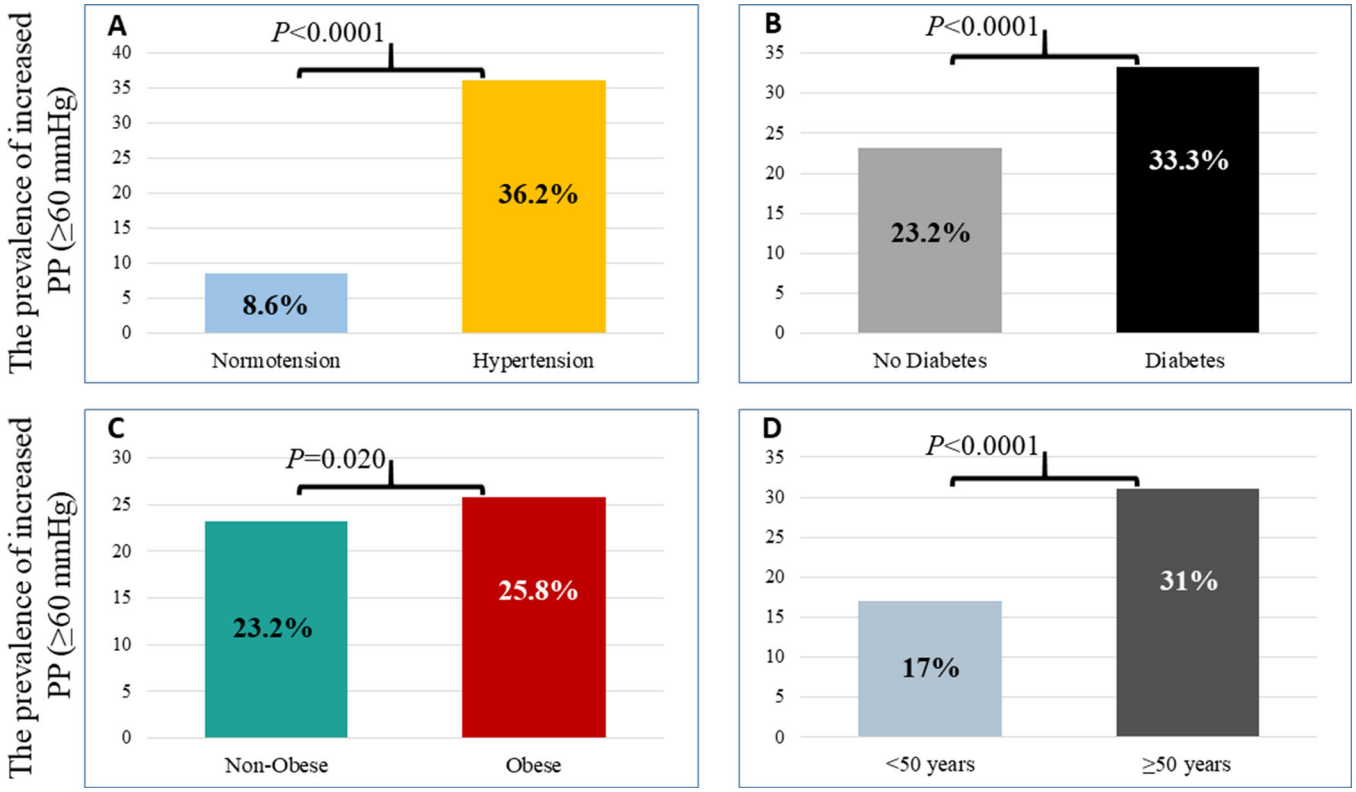

FIGURE 2 The prevalence of increased pulse pressure (PP) according to the presence or absence of hypertension (A), diabetes (B), obesity (C), and age categories (D)

3.4 | Normotensive participants

Normotensive OSA patients were older, more frequently males, and had higher body weight, height, BMI, and clinic BP compared with normotensive No-OSA patients (Table 3). PP in continuous scale was comparable in both groups, and an increased PP (> 60 mmHg) was found in 7.8% (n = 46) of normotensive OSA and in 8.9% (n = 180) of normotensive No-OSA controls (*P* = .415) (Figure 1B). Higher systolic BP was identified as the only significant predictor of increased PP independent of age, male sex,

TABLE 3 Baseline characteristics of overall hypertensive, treated hypertensive, and normotensive participants according to the OSA categories (AHI < 15/h vs AHI ≥15/h)

	Overall hypertensive patients (no. = 3526)			Treated hypertensive patients (no. = 1899)			Normotensive patients (no. = 2882)		
	No-OSA	OSA	*P*	No-OSA	OSA	*P*	No-OSA	OSA	*P*
Age (year)	51.4 ± 13.1	56.6 ± 11.4	<.0001	56.5 ± 11.5	59.3 ± 10	<.0001	42.3 ± 12.8	50.0 ± 12.0	<.0001
Male sex (%)	66	80	<.0001	62	79	<.0001	63	78	<.0001
Weight (kg)	93 ± 19	101 ± 21	<.0001	93 ± 19	100 ± 20	<.0001	86 ± 18	96 ± 19	<.0001
Height (m)	1.76 ± 0.10	1.77 ± 0.09	<.0001	1.75 ± 0.10	1.76 ± 0.09	<.0001	1.76 ± 0.09	1.77 ± 0.09	<.0001
BMI (kg/m^2)	30.2 ± 6.0	32.1 ± 6.0	<.0001	30.4 ± 6.6	32.2 ± 5.8	<.0001	27.8 ± 5.7	30.4 ± 5.6	<.0001
Obesity (BMI ≥30 kg/m^2) (%)	45	60	<.0001	47	62	<.0001	28	45	<.0001
Current smokers (%)	21	19	.089	19	18	.217	23	24	.621
Excessive alcohol consumption* (%)	7.6	10.1	.009	9	10	.408	5	8	.019
History of hypertension (%)	65	73	<.001	100	100	NA	0	0	NA
Systolic BP (mmHg)	141 ± 15	141 ± 15	.886	137 ± 15	138 ± 16	.226	123 ± 10	125 ± 9	<.0001
Diastolic BP (mmHg)	85 ± 10	86 ± 11	.049	82 ± 10	84 ± 11	.010	75 ± 8	78 ± 7	<.0001
Elevated clinic BP (%)	70	68	.230	50.3	53.4	.202	…	…	…
Pulse Pressure (mmHg)	55 ± 13	54 ± 13	.149	55 ± 13	54 ± 13	.507	47 ± 9	47 ± 8	.205
Pulse pressure ≥60 mmHg (%)	37	35	.252	34	34	.852	9	8	.415
Diabetes (%)	12	16	<.0001	18	22	.021	4	5	.538
COPD (%)	6.2	5.5	.372	8	6	.253	2	2	.980
Asthma (%)	19	15	.005	20	15	.013	18	13	.004
AHI (events per hour)	6.7 ± 4.1	35.3 ± 19.3	<.0001	7.3 ± 4.1	35.1 ± 18.0	<.0001	4.9 ± 3.8	31.5 ± 16.8	<.0001
ODI (per hour)	6.1 ± 4.6	31.4 ± 19.9	<.0001	6.8 ± 4.4	31.1 ± 18.4	<.0001	4.1 ± 4.2	26.6 ± 16.7	<.0001
Mean SaO_2 (%)	93 ± 2	91 ± 3	<.0001	93 ± 2	91 ± 3	<.0001	94 ± 2	92 ± 2	<.0001

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; ODI, oxygen desaturation index.
*More than 2 days per week.

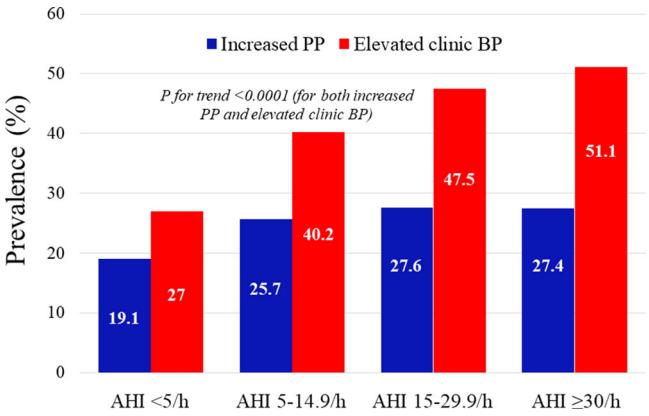

FIGURE 3 The prevalence of increased pulse pressure (PP) and elevated clinic blood pressure (BP) in patients with No-OSA and OSA categories according to the severity of apnea-hypopnea index (AHI/h)

smoking habits, excessive alcohol consumption, diabetes, and BMI (Table 4).

4 | DISCUSSION

To our knowledge, this is one of the largest studies on the relationship between OSA and arterial stiffness in normotensive and hypertensive patients, the latter with and without antihypertensive treatment, as well as with or without adequate BP control. The main results are the following: The prevalence of OSA defined as AHI ≥15/h was 34.5% in the total study population. Participants with OSA were older, and more likely to be male and have higher BMI, clinic BP and medical comorbidities compared to No-OSA controls (AHI < 15/h). Increased PP was found in 24% of the total cohort and was significantly higher in OSA than No-OSA participants (28% vs 22%). Participants with increased PP were older and had higher CV disease burden than those with

TABLE 4 Predictors of increased pulse pressure in univariate and multivariate logistic regression analyses in overall hypertensive, treated hypertensive, and normotensive participants

	Overall hypertensive patients (no. = 3526)		Treated hypertensive patients(no. = 1899)		Normotensive patients(no. = 2882)	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Multivariate models						
Age (per year increase)	1.03 (1.03-1.04)	<.0001	1.05 (1.04-1.07)	<.0001	0.99 (0.98-1.01)	.250
Male sex	1.15 (0.97-1.36)	.106	1.05 (0.83-1.33)	.662	1.15 (0.81-1.64)	.431
Current smoking	0.80 (0.66-0.97)	.020	0.80 (0.60-1.06)	.121	1.41 (1.00-2.00)	.050
Excessive alcohol consumption*	1.03 (0.80-1.33)	.834	0.84 (0.59-1.19)	.322	1.29 (0.74-2.24)	.378
Systolic BP (per mmHg increase)	…	…	…	…	1.18 (1.15-1.21)	<.0001
Body mass index (per kg/m^2)	0.99 (0.98-1.01)	.223	1.00 (0.98-1.02)	.771	0.97 (0.94-1.00)	.043
Diabetes	1.16 (0.93-1.44)	.195	1.26 (0.97-1.63)	.084	1.73 (0.88-3.38)	.110
Antihypertensive treatment	0.59 (0.50-0.69)	<.0001	…	…	…	…
OSA (AHI > 15/h)	…	…	…	…	…	…
Univariate models						
OSA (AHI > 15/h)	0.92 (0.80-1.06)	.252	1.02 (0.84-1.24)	.852	0.87 (0.62-1.22)	.415
COPD	1.27 (0.95-1.71)	.108	1.44 (0.99-2.10)	.059	0.88 (0.35-2.22)	.792
Asthma	1.11 (0.92-1.34)	.282	1.23 (0.95-1.60)	.118	0.77 (0.52-1.15)	.194

Abbreviations: AHI, apnea-hypopnea index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.
*More than 2 days per week.

normal PP. Hypertension and obesity were the most common modifiable CV risk factors and highly prevalent in OSA. In an adjusted model, hypertension but not OSA was associated with increased arterial stiffness. Poor BP control was equally represented both in OSA and No-OSA participants. Current smoking was associated with a lower risk of increased PP independently of age, sex, and other confounders.

4.1 | OSA and arterial stiffness

Increased PP is a marker of large artery stiffening and is associated with structural damage of the arterial wall due to increased pulsatile load, which is presumably the reason why large artery stiffening has been found to independently increase the risk of CV morbidity and mortality.[4] Studies exploring the impact of OSA on arterial stiffness assessed by PWV have come to contradictory conclusions. Some have documented an association between OSA and higher PWV,[8–11] while others have failed to confirm this association.[19–21] In addition to these inconsistencies, PWV has limited availability and is mostly used in the research field. Hence, it was highly desirable to explore the association of OSA with an alternative marker of large artery stiffening (increased PP) in our large study of 6408 patients with suspicion of OSA. Indeed, European hypertension guidelines define increased PP (≥60 mmHg) as a surrogate marker of asymptomatic target organ damage,[4] with a documented prognostic value in middle-aged and older people.[12–14] In our study, an increased PP (≥60 mmHg) was found in a quarter of the patients and the prevalence was significantly higher in OSA compared with No-OSA patients. Patients with increased PP were more likely to be hypertensive, diabetic and obese, and have higher prevalence of OSA (AHI > 15/h) compared with those with normal PP. In a univariate logistic regression analysis, OSA was associated with increased PP, but when the model was adjusted for age, sex, and other relevant confounders, OSA was no longer associated with increased PP neither in the overall population nor hypertensive or normotensive subgroups. Our results are in line with some previous studies which also could not document an association between OSA and arterial stiffness assessed by PWV.[19–21] In a meta-analysis of nine studies including 893 patients referred for suspicion of OSA, Joyeux-Faure and associates showed that increased arterial stiffness in patients with OSA was mainly driven by conventional CV risk factors rather than apnea parameters.[19] In their multivariate model, PWV was independently associated with age, systolic BP, and diabetes (all $P < .01$), but not with the severe OSA. Similarly, in the MESA (The Multi-Ethnic Study of Atherosclerosis) study of 708 participants, moderate to severe OSA (vs No-OSA controls) was not associated with aortic PWV.[20] However, in contrast to our results and those mentioned above,[19–21] a number of studies in the past have documented an association between OSA and increased arterial stiffness as reflected by higher PWV.[8–11,22] Most of these studies[8–9,11] had some methodological issues such as small sample sizes, inclusion of eastern populations who were non-obese by BMI[10–11] but had higher waist circumference, differences in OSA severity, as well as assessment of arterial stiffness by different methodologies. Our study suggests that it is not OSA per se but the consequences of OSA; ie, hypertension, as well as other CV risk factors such obesity, age, and male sex, which are the major determinants of increased arterial stiffness. However, an alternative explanation, although less likely, for the lack of association

between OSA and arterial stiffness/increased PP in our study may be the fact that polygraphy and brachial BP measurement were performed in the same setting and explored in a cross-sectional fashion. It is known that following the OSA screening and diagnosis, it may take months or years until the development of incident hypertension,[23] and resultant targert arterial damage. It has been shown that patients diagnosed with OSA at an older age have longer time duration since the prior hypertension diagnosis and less time to a subsequent hypertension diagnosis.[23]

4.2 | OSA and hypertension

OSA is a common cause of secondary hypertension,[4] and increases the risk of CV complications such as coronary artery disease, heart failure, arrhythmias (atrial fibrillation), and stroke. The proposed mechanisms by which OSA leads to hypertension is believed to be apneas/hypopneas causing repetitive hypoxemia, nocturnal BP elevation and fluctuation and increased sympathetic activity, endothelial damage/dysfunction, oxidative stress, and hypertension target arterial damage; ie, increased arterial stiffness.[7–24] Recent studies have shown that nonmuscle myosin light chain kinase (nmMLCK) may be a key mechanism in intermittent hypoxia-induced vascular oxidative stress and inflammation, both leading to functional and structural remodeling.[25] Furthermore, in hypertension, the presence of abdominal obesity or excessive fat deposition in the neck area, causes airway obstruction during sleep, and on molecular level leads to overproduction of adipokines, chronic low-grade inflammation, and increased arterial stiffness.

Normally, OSA is a precursor to hypertension. However, since both conditions share mostly the same risk factors, the co-occurrence of both conditions is common.[26] The overall prevalence of hypertension in our study was 55% and was clearly higher in OSA compared with non-OSA participants (71% vs 47%), and was poorly controlled (54.5% of all treated hypertensive participants, 53.4% of OSA, and 50.3% of non-OSA participants, $P = .202$). In the literature, there are few large-scale studies on hypertension control in OSA patients. An and associates assessed the time from OSA to hypertension diagnosis in a large retrospective study of electronic records over a period of 10-years.[23] Hypertension was diagnosed years prior to OSA, and with a longer separation in females. However, no BP measurements or hypertension control data were reported. Our results are largely in line with the results recently reported by the Jackson Heart Sleep Study, a longitudinal study of black adults in the US, aged 21 to 95 years.[27] The authors showed that the prevalence of uncontrolled hypertension was 48% (49% in AHI < 15/h and 46% in AHI ≥15/h) and resistant hypertension 14% (12% in AHI < 15/h and 20% in AHI ≥15/h). Hypertension was controlled in 37% of the entire study population.[27] Their threshold for hypertension control was clinic BP < 130/80 mmHg versus < 140/90 mmHg in our study, which may explain the slightly lower prevalence BP control in their study compared with ours. However, their sample was seven-fold smaller than ours, involved only blacks, and did not include any marker of arterial stiffness assessment. In a study of 95 hypertensive patients, OSA was independently associated with higher PWV and non-dipping BP pattern both in men and women.[22] Of note, at 18-month follow-up, patients with OSA had similar reductions in 24-hour BP and arterial stiffness to patients without OSA.[28]

In line with previous reports,[29] hypertension and obesity were the most common modifiable CV risk factors in OSA patients in our study. Hence, in addition to adequately treating OSA, every effort should be made to control any residual hypertension and BP variability caused by OSA,[30] as well as mitigate the CV risk in obesity by weight loss, dietary control, regular exercise, which all are known to increase insulin sensitivity. Finally, it has been shown that in patients with moderate to severe OSA, CPAP not only improved central systolic BP, but also significantly reduced arterial stiffness derived from aortic PWV.[31] However, this effect was observed only in CPAP adherent patients.

4.3 | Smoking and hypertension

In hypertensive patients, current smoking was associated with a lower odds of increased arterial stiffness. Mean PP was lower in hypertensive smokers than non-smokers (53 vs 55 mmHg, $P = .002$), yielding a 21% prevalence of increased PP in smokers and 25% in non-smokers ($P = .012$). Cigarette smoking is a known risk factor for CV disease, causes arterial stiffening and adversely affects wave reflection. Its cessation is one of the most effective lifestyle measures to prevent future CV events. However, the association between smoking and BP per se is complex. In acute situations, smoking increases the heart rate and BP through the stimulation of the sympathetic nervous system,[15,32–33] whereas its long-term effect on BP is a matter of debate. It is apparently paradoxical that a number of large epidemiological studies in the past, consistent with our findings, have documented lower BP level in current smokers than nonsmokers.[34] Recently, Li and associates showed in a study of 1248 men that the adjusted BP and PP were lower in current smokers versus nonsmokers and former smokers.[35] In their fully adjusted logistic regression model, former smokers had increased odds ratio and current smokers lower odds ratio of hypertension compared with never smokers (OR 0.83 95% CI 0.61-1.12). Epidemiologically, smoking is associated with lower BMI,[36] and it is possible that the lower BP observed in smokers is related to the lower body weight caused by smoking. We also showed that BMI was significantly lower in hypertensive current smokers than hypertensive non-smokers. However, the association between current smoking and lower odds of increased arterial stiffness was independent of BMI, age, sex, and other important confounders. More studies are needed to explore the mechanisms for the association between smoking and PP as a surrogate marker of arterial stiffness.

4.4 | Strength and limitations

One major strength of our study was the large sample size in which all patients were referred with suspicion of OSA. This allowed us to conduct multiple sub-analyses both in overall study population, and

hypertensive and normotensive participants. Second, BP was measured following a standardized methodology as recommended by guidelines.

The limitations were that the duration of antihypertensive treatment was not known. Arterial stiffness was not measured by the gold standard method; ie, PWV, which in practical terms may not be feasible to perform in such a large study due to its limited availability, and currently its utilization in the research area. However, our results are in line with those studies of OSA patients which used PWV as a marker of increased arterial stiffness.[19–21] The information on smoking status was ascertained through self-reported questionnaires and categorized in current smokers and non-smokers. Hence, there is a small possibility that some currently non-smokers may have former smoking history. Finally, we cannot exclude the risk of unidentified sources of confounding.

5 | CONCLUSION

In this large study of nearly 6500 participants with suspected OSA, one third were diagnosed with OSA (here defined as AHI ≥15/h) and a quarter had increased arterial stiffness by increased brachial PP (≥60 mmHg). When adjusted for age, sex, and other well-known prognosticators and confounders, it was hypertension but not OSA, which was associated with increased arterial stiffness; ie, hypertension acting as an intermediate stage in the disease continuum between OSA and increased arterial stiffness. Hypertension and obesity were the most common modifiable CV risk factors and highly prevalent in participants diagnosed with OSA. Hypertension was equally poorly controlled both in OSA and No-OSA participants. In hypertensive patients, current smoking was associated with a lower risk of having increased PP when adjusted for age, sex, and other relevant confounders.

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CONFLICT OF INTEREST

There are no conflicts of interest for any authors.

AUTHOR CONTRIBUTIONS

Sahrai Saeed, Giuseppe Mancia, Sverre Lehmann, and Bjørn Bjorvatn contributed to study conception, design, and interpretation. Sahrai Saeed and Giuseppe Mancia drafted the paper. Ingvild West Saxvig, Shashi Gulati, Sverre Lehmann, and Bjørn Bjorvatn contributed to data acquisition and critically revised the paper. Andrea Romarheim performed literature search and revised the paper. All authors approved the final version before submission.

ORCID

Sahrai Saeed MD, PhD, FESC https://orcid.org/0000-0003-4041-5019

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