Association of obstructive sleep apnoea with cardiovascular events in women and men with acute coronary syndrome

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In patients with acute coronary syndrome, >40% of female patients had obstructive sleep apnoea (OSA). OSA was associated with an increased risk of long-term cardiovascular events following an acute coronary syndrome, particularly among women. https://bit.ly/3TWKi8S

Cite this article as: Wang X, Fan J, Guo R, *et al*. Association of obstructive sleep apnoea with cardiovascular events in women and men with acute coronary syndrome. *Eur Respir J* 2023; 61: 2201110 [DOI: 10.1183/13993003.01110-2022].

Received: 30 May 2022
Accepted: 18 Aug 2022

Abstract

Background The impact of sex on the association of obstructive sleep apnoea (OSA) with recurrent cardiovascular events following acute coronary syndrome (ACS) remains uncertain. This study sought to examine the association between OSA and long-term cardiovascular outcomes in women and men with ACS.

Methods In this prospective cohort study, we recruited 2160 ACS patients undergoing portable sleep monitoring between June 2015 and January 2020. The primary end-point was major adverse cardiovascular and cerebrovascular event (MACCE), including cardiovascular death, myocardial infarction, stroke, ischaemia-driven revascularisation or hospitalisation for unstable angina or heart failure.

Results After exclusion of patients with failed sleep studies, central sleep apnoea, regular continuous positive airway pressure therapy and loss of follow-up, 1927 patients were enrolled. Among them, 298 (15.5%) were women and 1014 (52.6%) had OSA (apnoea–hypopnoea index $\geqslant$15 events·h^{-1}). The prevalence of OSA was 43.0% and 54.4% in women and men, respectively. In 4339 person-years (median 2.9 years, interquartile range 1.5–3.6 years), the cumulative incidence of MACCE was significantly higher in OSA *versus* non-OSA groups in the overall population (22.4% *versus* 17.7%; adjusted hazard ratio (HR) 1.29, 95% CI 1.04–1.59; p=0.018). OSA was associated with greater risk of MACCE in women (28.1% *versus* 18.8%; adjusted HR 1.68, 95% CI 1.02–2.78; p=0.042), but not in men (21.6% *versus* 17.5%; adjusted HR 1.22, 95% CI 0.96–1.54; p=0.10). No significant interaction was noted between sex and OSA for MACCE (interaction p=0.32). The incremental risk in women was attributable to higher rates of hospitalisation for unstable angina and ischaemia-driven revascularisation.

Conclusions In hospitalised ACS patients, OSA was associated with increased risk of subsequent events, particularly among women. Female patients with ACS should not be neglected for OSA screening and dedicated intervention studies focusing on women with ACS and comorbid OSA should be prioritised.

Introduction

Obstructive sleep apnoea (OSA) is a common disorder that affects 17% of women and 34% of men in the general population [1]. OSA is associated with oxidative stress, sympathetic activation, inflammatory responses and endothelial dysfunction that could induce or exacerbate cardiovascular comorbidities [2, 3], including acute coronary syndrome (ACS) [4]. OSA prevalence is as high as 36–63% in ACS patients across various ethnicities [5]. Existing data have suggested sex-based differences in the pathophysiology, symptoms, prevalence of comorbidities, cardiovascular consequences and treatment effects of OSA [6–8].

The sex of the patient also influences the severity of ACS in OSA patients [9]. However, whether sex-specific differences exist in the relationship between OSA and cardiovascular outcomes in ACS patients is less clear.

In the Atherosclerosis Risk in Communities (ARIC) cohort [8] the association between OSA and cardiovascular events seems to be more pronounced in women than men without prevalent cardiovascular disease, but this was not evident from the Sleep Heart Health Study (SHHS) [10–12], reflecting differences in sample representation. However, for patients with established ACS, no studies have directly evaluated the association of OSA with recurrent cardiovascular events in women due to underrepresentation of women in prior ACS cohorts. Indeed, we previously reported the prognostic value of OSA in a mid-term analysis [13], the population of which was part of the overall cohort. No sex-stratified analysis was performed due to the small number of patients in that previous study [13]. Therefore, we used final data from a large-scale, prospective cohort to elucidate the association of OSA with subsequent cardiovascular events in women and men with ACS.

Methods

Study design and participants

The OSA-ACS project (www.clinicaltrials.gov identifier NCT03362385) was a large-scale, prospective cohort study to assess the association of OSA with cardiovascular outcomes of hospitalised ACS patients in Beijing Anzhen Hospital, Capital Medical University (Beijing, China) between June 2015 and January 2020, with follow-up until December 2020. We recruited patients aged 18–85 years and admitted for ACS with an overnight sleep study. ACS was defined as the acute presentation of coronary disease, including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and unstable angina. We excluded patients with cardiogenic shock, cardiac arrest, malignancy with life expectancy <2 years and failed sleep study (patients without adequate and satisfactory signal recording). Patients with predominantly central sleep apnoea (⩾50% central events and central apnoea–hypopnoea index (AHI) ⩾10 events·h^{-1}) and those receiving regular continuous positive airway pressure (CPAP) therapy and lost to follow-up after discharge were also excluded from the analysis.

This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [14], and was conducted in accordance with the amended Declaration of Helsinki [15]. The protocol was approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University (2013025). All patients provided written informed consent.

Procedures

All patients underwent an overnight sleep study using a type III portable sleep monitoring device (ApneaLink Air; Resmed, Australia) after clinical stabilisation during hospitalisation (median 2 days (interquartile range (IQR) 1–3 days) after admission). Devices were applied to the patients by trained research staff independently at bedtime and were collected the next morning. Output from the portable diagnostic device was recorded by research staff blinded to the clinical characteristics of the patients, in a specialised sleep apnoea database. The following signals were recorded: nasal airflow, thoraco-abdominal movements, snoring episodes, heart rate and pulse oximetry. We scored the sleep studies according to the American Academy of Sleep Medicine criteria [16]. Apnoea was defined as an absence of airflow for ⩾10 s (obstructive if thoraco-abdominal movement was present, and central if thoraco-abdominal movement was absent). Hypopnoea was defined as an airflow reduction of 30% for ⩾10 s with a decrease in arterial oxygen saturation (S_{aO_2}) >4%. AHI was the number of apnoeas and hypopnoeas per hour of recording. OSA was defined as AHI ⩾15 events·h^{-1}. Patients with AHI <15 events·h^{-1} were considered as the non-OSA group [17, 18].

All patients received standard care during index ACS hospitalisation according to current guidelines [19, 20]. The baseline demographic, clinical and procedural information was recorded. The degree of self-reported sleepiness was analysed using the Epworth Sleepiness Scale (ESS) [21]. Patients with AHI ⩾15 events·h^{-1}, particularly those with excessive daytime sleepiness, were referred to a sleep centre for further evaluation.

End-points

All patients were followed-up for a minimum of 6 months and scheduled at 1 month, 3 months, 6 months and 12 months, and every 6 months thereafter (if applicable). Clinical events were collected *via* clinic visit, medical records or telephone calls by research staff who were blinded to the patients' sleep results.

The primary end-point was major adverse cardiovascular and cerebrovascular events (MACCE), defined as a composite of cardiovascular death, myocardial infarction, stroke, ischaemia-driven revascularisation or hospitalisation for unstable angina or heart failure. Secondary end-points included the individual components of the primary end-point, a composite of cardiovascular death, myocardial infarction or ischaemic stroke, a composite of cardiac event (cardiovascular death, myocardial infarction, ischaemia-driven revascularisation or hospitalisation for unstable angina or heart failure), all-cause death and repeat revascularisation. All end-points were defined according to the proposed definitions by the Standardized Data Collection for Cardiovascular Trials Initiative [22] (supplementary methods). All events were evaluated independently by adjudicators blinded to the results of the sleep study. The adjudicators also reviewed the source documents and established the necessity for hospital admission and/or revascularisation.

Statistical analyses

Assuming a 5% absolute increase [23, 24] in the event rate for ACS patients with OSA compared with those without OSA (from 15% to 20%), we estimated that 2014 patients would be required, accounting for a 10% drop-out rate (α=0.05 and power=80%) (supplementary methods). Baseline clinical and procedural characteristics were summarised by sex as well as sex and OSA/non-OSA groups, using mean±SD or median (interquartile range) for continuous variables and frequencies for categorical variables. We used the Shapiro–Wilk test of normality of continuous variables. Continuous variables with a normal distribution were compared by t-test and those with a non-normal distribution were compared by Mann–Whitney U-test. Categorical variables were compared using Chi-squared statistics or Fisher exact test, when appropriate. The cumulative incidences of the primary and secondary end-points according to OSA groups in the overall population and in female and male subgroups were shown as Kaplan–Meier curves and were compared by the log-rank test.

To assess the relationship between OSA (AHI $\geqslant$15 events·h^{-1}) and time to subsequent cardiovascular events in the overall population and by sex, we used unadjusted, partially adjusted and fully adjusted Cox proportional hazards models. Model covariates were selected based on clinical relevance or variables that showed a univariate relationship with outcome. These included 1) age and body mass index (BMI); 2) age, BMI, smoking (no (referent), past, current), hypertension, diabetes mellitus, hyperlipidaemia, prior myocardial infarction, prior stroke and clinical presentation (unstable angina (referent), acute myocardial infarction). In addition, we conducted sensitivity analyses by stratifying the patients into no (AHI <5 events·h^{-1}), mild (5$\leqslant$AHI<15 events·h^{-1}) and moderate/severe (AHI $\geqslant$15 events·h^{-1}) OSA groups, and using AHI (or logAHI+1) as a continuous variable. We repeated the analyses by using individual components of the primary outcome as well as other composite outcomes as the dependent variables. Multiplicative interaction terms were included in the fully adjusted models to evaluate if sex modified the associations between OSA and risk of cardiovascular events. Additionally, we evaluated the associations between nocturnal hypoxaemia and sleepiness indicators with MACCE by sex. Finally, we performed important subgroup analyses by covariate levels of interest. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final models. If a patient experienced more than one event, only the first event was included in the analysis. Hazard ratio (HR) with 95% confidence interval was calculated.

All analyses were conducted with SPSS 25.0 (IBM SPSS, Armonk, New York, NY, USA). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline clinical and procedural characteristics

2160 patients with ACS were recruited, of whom 2058 underwent a successful overnight sleep study. Patients with central sleep apnoea and loss of follow-up were excluded; this left 1969 patients with OSA and follow-up. Among them, only 42 (2.1%) of patients received regular CPAP therapy (>4 h·day^{-1} and >21 days per month) and the rate was similar between women and men (2.3% *versus* 2.1%, p=0.83). 1927 patients were included in the final analysis (figure 1). Mean±SD patient age was 56.4±10.5 years. Of these, 298 (15.5%) were women and 1014 (52.6%) had OSA. Women, compared with men, were older and less obese, with a higher prevalence of traditional risk factors including hypertension, diabetes and hyperlipidaemia, but were less likely to be current smokers. Women were less likely than men to have a diagnosis of myocardial infarction and have undergone revascularisation. The prevalence of OSA was lower in women than men (43.0% *versus* 54.4%, p<0.001) (supplementary table S1).

Baseline characteristics according to sex and OSA category are presented in tables 1 and 2. In both sexes, patients with OSA exhibited higher BMI and waist-to-hip ratio. Among women, patients with OSA were

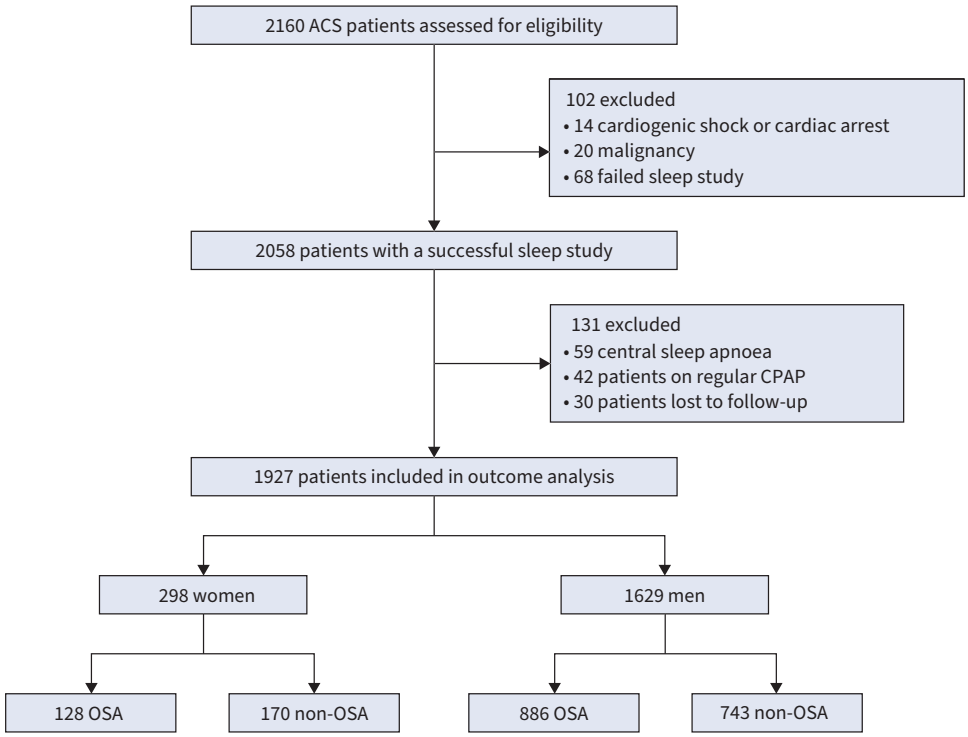


FIGURE 1 Study flowchart. ACS: acute coronary syndrome; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea.

older and had worse renal function. Among men, patients with OSA were more likely to have hypertension, prior percutaneous coronary intervention (PCI), worse renal function, worse left ventricular function and to receive antihypertensive drugs. Other information was generally well matched between OSA and non-OSA patients in both sexes.

Outcomes of OSA versus *non-OSA groups overall and by sex*

In 4339 person-years (median 2.9 years, IQR 1.5–3.6 years), the primary outcome of MACCE occurred in 389 (20.2%) patients. The cumulative incidence of MACCE was significantly higher in patients with OSA compared with those without OSA in the overall sample (22.4% *versus* 17.7%; adjusted HR 1.29, 95% CI 1.04–1.59; p=0.018) (figure 2a and table 3) after adjusting for anthropometric (age and BMI) as well as other potential confounders (risk factors and clinical presentation). We then conducted sensitivity analysis according to OSA severity and found that only moderate/severe OSA (HR 1.40, 95% CI 1.01–1.92; p=0.041) and not mild OSA (HR 1.05, 95% CI 0.78–1.48; p=0.77) was associated with increased risk of MACCE compared with the no-OSA group. In addition, we performed a linear regression analysis using AHI as a continuous variable, but did not find a significant association with MACCE (AHI: HR 1.00, 95% CI 1.00–1.01; p=0.26; logAHI+1: HR 1.28, 95% CI 0.99–1.66; p=0.06). Additionally, to evaluate for potential correlations between OSA (AHI value) and hypoxaemia indicators as well as sleepiness (ESS), we created unadjusted, partially adjusted or fully adjusted models where each hypoxaemia and sleepiness indicator was individually introduced as a covariate, and found that the association between OSA and MACCE remained robust; 95% confidence intervals did not cross the line of unity (figure 3). No significant differences were observed between OSA and non-OSA groups in individual cardiovascular events (table 3).

In sex-stratified analyses, OSA was associated with a higher incidence of MACCE in both women (log-rank p=0.029) and men (log-rank p=0.022). However, in multivariable Cox models, OSA was associated with greater risk of long-term MACCE in women (28.1% *versus* 18.8%; adjusted HR 1.68, 95% CI 1.02–2.78 p=0.042), but not in men (21.6% *versus* 17.5%; adjusted HR 1.22, 95% CI 0.96–1.54; p=0.10) (table 3, figure 2b and c). No significant interaction was noted between sex and OSA with respect

TABLE 1 Baseline clinical characteristics by sex and obstructive sleep apnoea (OSA) categories

	All	Women[#]			Men[¶]		
		OSA	Non-OSA	p-value[+]	OSA	Non-OSA	p-value[§]
Subjects	1927	128	170		886	743	
Demographics							
Age, years	56.4±10.5	65.8±6.5	62.6±9.1	0.001	55.2±10.4	54.8±10.1	0.40
BMI, kg·m^{-2}	27.1±3.6	27.6±3.8	26.0±3.8	0.001	28.1±3.5	26.0±3.3	<0.001
Waist-to-hip ratio	0.98 (0.95–1.02)	0.97 (0.93–1.01)	0.94 (0.99–0.91)	0.003	0.99 (0.96–1.03)	0.98 (0.94–1.01)	<0.001
Neck circumference, cm	41 (38–43)	37 (36–39)	36 (34–38)	0.001	41 (39–43)	39 (37–41)	<0.001
Systolic BP, mmHg	126 (117–138)	130 (120–141)	130 (120–144)	0.90	126 (117–138)	125 (116–136)	0.18
Diastolic BP, mmHg	76 (70–84)	71 (68–80)	74 (67–80)	0.59	79 (70–86)	75 (70–83)	<0.001
Medical history							
Diabetes	609 (31.6)	59 (46.1)	62 (36.5)	0.09	260 (29.3)	228 (30.7)	0.56
Hypertension	1247 (64.7)	106 (82.8)	134 (78.8)	0.39	585 (66.0)	422 (56.8)	<0.001
Hyperlipidaemia	637 (33.1)	58 (45.3)	64 (37.6)	0.18	285 (32.2)	230 (31.0)	0.60
Family history of premature CAD	104 (5.4)	5 (3.9)	12 (7.1)	0.25	46 (5.2)	41 (5.5)	0.77
Prior stroke	207 (10.7)	21 (16.4)	21 (12.4)	0.32	100 (11.3)	65 (8.7)	0.09
Prior myocardial infarction	316 (16.4)	12 (9.4)	13 (7.6)	0.59	165 (18.6)	126 (17.0)	0.38
Prior PCI	399 (20.7)	27 (21.1)	27 (15.9)	0.25	207 (23.4)	138 (18.6)	0.02
Prior CABG	29 (1.5)	4 (3.1)	2 (1.2)	0.41	14 (1.6)	9 (1.2)	0.53
Smoking				0.14			0.59
No	654 (33.9)	118 (92.2)	144 (84.7)		215 (24.3)	177 (23.8)	
Current	913 (47.4)	8 (6.3)	20 (11.8)		488 (55.1)	397 (53.4)	
Previous	360 (18.7)	2 (1.6)	6 (3.5)		183 (20.7)	169 (22.7)	
Drinking				0.44			0.04
No	1181 (61.3)	123 (96.1)	160 (94.1)		466 (52.6)	432 (58.1)	
Current	637 (33.1)	5 (3.9)	10 (5.9)		352 (39.7)	270 (36.3)	
Previous	109 (5.7)	0 (0.0)	0 (0.0)		68 (7.7)	41 (5.5)	
Baseline tests							
eGFR, mL·min^{-1}·1.73 m^{-2}	104.9 (89.4–121.2)	100.9 (80.0–116.3)	109.1 (88.2–128.9)	0.01	103.2 (88.6–119.9)	106.4 (90.9–122.3)	0.04
hs-CRP, mg·L^{-1}	2.0 (0.8–6.1)	2.6 (1.1–6.8)	1.5 (0.7–4.0)	0.007	2.5 (1.0–7.5)	1.4 (0.6–4.8)	<0.001
LVEF, %	61 (56–65)	63 (59–67)	63 (60–67)	0.60	60 (55–65)	62 (56–65)	0.02

Data are presented as n, mean±SD, median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; eGFR: glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; LVEF: left ventricular ejection fraction. [#]: n=298; [¶]: n=1629; [+]: comparison between OSA and non-OSA groups in women; [§]: comparison between OSA and non-OSA groups in men.

to MACCE (interaction p=0.32). In patients with OSA, the MACCE rate was nominally higher in women compared with men (28.1% *versus* 21.6%; HR 1.31, 95% CI 0.92–1.88; p=0.13). In patients without OSA, the MACCE rate was similar between sexes (18.8% *versus* 17.5%; HR 1.01, 95% CI 0.68–1.48; p=0.97). Additionally, nocturnal hypoxaemia and sleepiness were not associated with increased risk of MACCE in both sexes (supplementary table S2).

There was no significant difference in the incidence of cardiovascular death, myocardial infarction, ischaemic stroke and the composite of ischaemic events between OSA and non-OSA groups in both women and men (table 3 and supplementary figure S1). The increased risk of MACCE in women was primarily attributable to significantly higher rates of hospitalisation for unstable angina (23.4% *versus* 12.9%; adjusted HR 2.00, 95% CI 1.12–3.56; p=0.019) and ischaemia-driven revascularisation (13.3% *versus* 5.9%; adjusted HR 2.66, 95% CI 1.16–6.13; p=0.021) in OSA *versus* non-OSA groups (figure 4). In contrast, the rate of hospitalisation for unstable angina (14.1% *versus* 12.8%; adjusted HR 1.12, 95% CI 0.85–1.49; p=0.42) and ischaemia-driven revascularisation (8.7% *versus* 7.4%; adjusted HR 1.11, 95% CI 0.77–1.60; p=0.58) was similar in men with OSA compared with those without OSA (figure 4). There was no significant interaction between sex and OSA for those secondary end-points (interaction p≥0.07 for all) except repeat revascularisation (interaction p=0.015). The crude numbers of events are listed in supplementary table S3.

TABLE 2 Clinical presentations and management by sex and obstructive sleep apnoea (OSA) categories

	All	Women[#]			Men[¶]		
		OSA	Non-OSA	p-value[+]	OSA	Non-OSA	p-value[§]
Subjects	1927	128	170		886	743	
Diagnosis				0.07			0.12
STEMI	430 (22.3)	23 (18.0)	17 (10.0)		228 (25.7)	162 (21.8)	
NSTEMI	365 (18.9)	17 (13.3)	34 (20.0)		174 (19.6)	140 (18.8)	
Unstable angina	1132 (58.7)	88 (68.8)	119 (70.0)		484 (54.6)	441 (59.4)	
Procedures							
Coronary angiography	1877 (97.4)	125 (97.7)	163 (95.9)	0.52	865 (97.6)	724 (97.4)	0.81
Revascularisation	1335 (69.3)	83 (64.8)	93 (54.7)	0.08	642 (72.5)	517 (69.6)	0.20
PCI	1209 (62.7)	75 (58.6)	82 (48.2)	0.08	592 (66.8)	460 (61.9)	0.04
DES use	1051 (86.9)	64/75 (85.3)	74/82 (90.2)	0.35	517/592 (87.3)	396/460 (86.1)	0.55
Baseline TIMI 0 or 1	422 (34.9)	21/75 (28.0)	19/82 (23.2)	0.49	223/592 (37.7)	159/460 (34.6)	0.30
Final TIMI 3	1189 (98.3)	72/75 (96.0)	81/82 (98.8)	0.35	582/592 (98.3)	454/460 (98.7)	0.61
CABG	130 (6.7)	8 (6.3)	11 (6.5)	0.94	51 (5.8)	60 (8.1)	0.06
Sleep study							
AHI, events·h^{-1}	16.0 (8.0–30.0)	29.3 (20.2–39.5)	7.1 (2.8–10.2)	<0.001	29.1 (20.8–42.7)	7.7 (4.5–10.9)	<0.001
Number of apnoeas	19.0 (4.0–75.0)	35.5 (13.0–95.3)	3.0 (1.0–8.0)	<0.001	73.0 (30.0–152.0)	6.0 (2.0–15.0)	<0.001
Number of obstructive apnoeas	11.0 (2.0–44.0)	24.0 (7.0–67.3)	2.0 (0.0–5.0)	<0.001	41.0 (14.0–98.0)	3.0 (1.0–10.0)	<0.001
Number of central apnoeas	2.0 (0.0–11.0)	3.0 (1.0–11.3)	0.0 (0.0–1.0)	<0.001	9.0 (2.0–28.0)	1.0 (0.0–3.0)	<0.001
ODI, events·h^{-1}	16.2 (8.8–28.6)	27.7 (20.9–39.3)	9.0 (4.3–12.0)	<0.001	27.5 (20.1–39.8)	8.5 (5.0–11.8)	<0.001
Nadir S_{aO_2}, %	85 (81–88)	82 (78–85)	87 (84–89)	<0.001	83 (77–86)	88 (85–90)	<0.001
Mean S_{aO_2}, %	94 (93–95)	93 (92–94)	94 (93–95)	<0.001	93 (92–94)	95 (93–95)	<0.001
Time with S_{aO_2} <90%, %	2.3 (0.4–10.0)	7.9 (2.9–21.2)	1.0 (0.2–5.0)	<0.001	6.0 (2.0–15.0)	0.5 (0.0–2.2)	<0.001
Epworth Sleepiness Scale	7.0 (4.0–11.0)	7.0 (3.5–11.5)	6.0 (2.0–9.0)	0.06	8.0 (5.0–12.0)	6.0 (3.0–11.0)	<0.001
Medications on discharge							
Aspirin	1877 (97.4)	124 (96.9)	163 (95.9)	0.76	863 (97.4)	727 (97.8)	0.56
$P2Y_{12}$ inhibitors	1768 (91.7)	118 (92.2)	151 (88.8)	0.33	820 (92.6)	679 (91.4)	0.39
β-Blockers	1488 (77.2)	96 (75.0)	130 (76.5)	0.77	703 (79.3)	559 (75.2)	0.048
ACEIs/ARBs	1195 (62.0)	89 (69.5)	103 (60.6)	0.11	576 (65.0)	427 (57.5)	0.002
Statins	1897 (98.4)	124 (96.9)	167 (98.2)	0.47	873 (98.5)	733 (98.7)	0.84

Data are presented as n, median (interquartile range), n (%) or n/N (%), unless otherwise stated. STEMI: ST-segment-elevation myocardial infarction; NSTEMI: non-ST-segment-elevation myocardial infarction; PCI: percutaneous coronary intervention; DES: drug-eluting stent; TIMI: thrombolysis in myocardial infarction; CABG: coronary artery bypass grafting; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; S_{aO_2}: arterial oxygen saturation; ACEI: angiotensin-converting enzymes inhibitor; ARB: angiotensin receptor blocker. [#]: n=298; [¶]: n=1629; [+]: comparison between OSA and non-OSA groups in women; [§]: comparison between OSA and non-OSA groups in men.

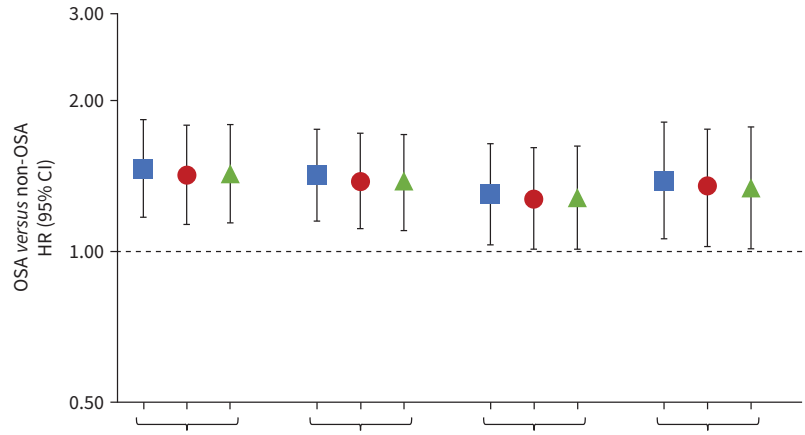
Subgroup analyses

We performed additional subgroup analyses according to age, hypertension, diabetes mellitus, hyperlipidaemia, prior coronary artery disease and clinical presentation. Although differences were found between some subgroups, the association of OSA with MACCE was not modified by these confounding factors (interaction p⩾0.12 for all) (supplementary table S4).

Discussion

In this large prospective ACS cohort, the presence of OSA was associated with a significantly higher risk of subsequent cardiovascular events after ACS onset at a median follow-up of nearly 3 years. Despite the higher prevalence of OSA in male patients, >40% of female patients also had OSA. In sex-stratified analyses, OSA was associated with an increased risk of MACCE in women but not in men, after adjustment for anthropometric and cardiovascular risk factors, although no significant sex-by-OSA interaction was noted. The incremental risk associated with OSA in women might be explained by ischaemia-driven unplanned rehospitalisation and/or revascularisation. To the best of our knowledge, this study is the first to explore sex differences in the relationship of OSA with cardiovascular outcomes in patients with established ACS.

Accumulating evidence has suggested that OSA is an independent predictor of adverse cardiovascular outcomes in the long run [23–26], but might be cardioprotective in the acute setting after ACS [27, 28]. In the Sleep and Stent study (68.5% ACS), patients with OSA had 1.57 times the risk of incurring an MACCE after PCI at 1.9 years' follow-up [23]. However, the recently published ISAACC study reported



Indicators of hypoxaemia and sleepiness	Nadir S_{aO_2} <median	Mean S_{aO_2} <median	TSA_{90} >median	ESS >10
None	1.46 (1.17–1.83)	1.42 (1.15–1.75)	1.30 (1.03–1.64)	1.38 (1.06–1.81)
Age and BMI	1.42 (1.13–1.78)	1.38 (1.11–1.72)	1.27 (1.01–1.61)	1.35 (1.02–1.79)
Age, BMI and others#	1.43 (1.14–1.79)	1.38 (1.15–1.71)	1.28 (1.01–1.62)	1.34 (1.01–1.77)

FIGURE 2 Obstructive sleep apnoea (OSA) and risk of major adverse cardiovascular and cerebrovascular event (MACCE) adjusted for hypoxaemia indicators and sleepiness. OSA was associated with a greater risk of MACCE after adjustment for hypoxaemia indicators (nadir arterial oxygen saturation (S_{aO_2}), mean S_{aO_2} and time with S_{aO_2} <90% (TSA_{90})) and sleepiness (Epworth Sleepiness Scale (ESS)) in each model. Statistical models were adjusted for an indicator of hypoxaemia and sleepiness only as well as other anthropometric and clinical variables. Hazard ratios (HR) shown on a logarithmic scale. BMI: body mass index. #: smoking (no (referent), past, current), hypertension, diabetes mellitus, hyperlipidaemia, prior myocardial infarction, prior stroke and clinical presentation (unstable angina (referent), acute myocardial infarction).

that OSA does not increase the risk of recurrent cardiovascular events after ACS at 3.4 years' follow-up [29]. In contrast, our study with a larger population showed a significantly and gradually greater risk of MACCE at a median follow-up of 2.9 years, which was consistent with the Sleep and Stent study [23]. The variability of results might be explained by differences in ethnic background and underlying risk factors in the ACS population, and also suggests potential heterogeneity of ACS phenotype. It is notable that the patients in the OSA-ACS project had more traditional risk factors and more severe daytime sleepiness than those in the ISAACC study [29] and were comparable with the Sleep and Stent study [23].

Although the association of OSA with subsequent cardiovascular events in ACS patients is well documented, data on the impact of sex on this association are limited and conflicting. The differences in study design, outcomes and follow-up duration might explain the distinct findings. The SHHS showed that OSA severity may be associated with mortality [10], incident coronary artery disease and heart failure [11] or stroke [12] in men, but not in women. The SHHS is a community-based cohort where only 24% of men and 11% of women had OSA (AHI $\geqslant$15 events·h^{-1}), while our study included a clinical cohort with a broad range of OSA severities. In contrast, the combined ARIC and SHHS cohort study showed that OSA was associated with incident cardiovascular events, death and left ventricular hypertrophy among women, but not men [8]. One explanation proposed by the authors was that the SHHS sample was younger and experienced lower overall events rates in comparison with the sample in ARIC [8]. Overall, prior historical cohorts primarily focused on subjects free of cardiovascular diseases. In the context of secondary prevention for ACS patients, no studies have assessed the sex-associated difference in the impact of OSA on long-term prognosis. Our study included consecutive ACS patients with >40% of patients with myocardial infarction, thus representing a high-risk subset compared with the primary prevention cohort. The results showed a higher risk of subsequent cardiovascular events among women but not men, in whom other comorbidities interacting with OSA may play a more important role [30]. It should be noted that there was no signal of interaction between sex and OSA for the combined or individual cardiovascular events, possibly due to the lack of power as a result of the small proportion of women in this cohort and

TABLE 3 Cox regression analyses evaluating the association between obstructive sleep apnoea (OSA) and risk of cardiovascular events in the overall population and by sex

	Unadjusted		Partially adjusted[#]		Fully adjusted[¶]	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
MACCE						
Overall	1.35 (1.10–1.65)	0.004	1.30 (1.05–1.60)	0.015	1.29 (1.04–1.59)	0.018
Women	1.69 (1.05–2.72)	0.031	1.66 (1.01–2.71)	0.046	1.68 (1.02–2.78)	0.042
Men	1.30 (1.04–1.62)	0.022	1.24 (0.98–1.57)	0.07	1.22 (0.96–1.54)	0.10
Cardiovascular death						
Overall	1.26 (0.63–2.51)	0.52	1.19 (0.58–2.44)	0.63	1.13 (0.55–2.31)	0.75
Women	2.81 (0.26–31.05)	0.40	4.18 (0.34–50.94)	0.26	3.73 (0.24–56.99)	0.35
Men	1.12 (0.55–2.31)	0.75	0.96 (0.45–2.03)	0.91	0.86 (0.40–1.85)	0.70
All-cause death						
Overall	0.93 (0.52, 1.66)	0.80	0.84 (0.46, 1.53)	0.57	0.81 (0.44, 1.48)	0.50
Women	1.11 (0.30–4.13)	0.88	1.09 (0.28–4.22)	0.91	1.33 (0.32–5.48)	0.70
Men	0.91 (0.48–1.73)	0.78	0.76 (0.39–1.48)	0.41	0.69 (0.35–1.36)	0.28
Myocardial infarction						
Overall	1.71 (0.96–3.03)	0.07	1.63 (0.89–2.99)	0.12	1.51 (0.82–1.77)	0.19
Women	2.29 (0.55–9.57)	0.26	1.97 (0.46–8.43)	0.36	2.59 (0.55–12.10)	0.23
Men	1.61 (0.86–3.02)	0.14	1.53 (0.78–3.00)	0.21	1.35 (0.69–2.64)	0.39
Stroke						
Overall	1.31 (0.71–2.40)	0.39	1.27 (0.67–2.37)	0.46	1.25 (0.66–1.34)	0.49
Women	0.57 (0.15–2.21)	0.42	0.54 (0.13–2.23)	0.40	0.35 (0.08–1.59)	0.18
Men	1.77 (0.86–3.64)	0.12	1.78 (0.84–3.77)	0.14	1.71 (0.80–3.63)	0.17
Ischaemic stroke						
Overall	1.41 (0.72–2.77)	0.32	1.38 (0.68–2.78)	0.37	1.36 (0.67–2.75)	0.39
Women	1.01 (0.23–4.51)	0.99	0.84 (0.17–4.07)	0.82	0.60 (0.11–3.18)	0.55
Men	1.58 (0.73–3.43)	0.25	1.67 (0.75–3.75)	0.21	1.59 (0.71–3.58)	0.26
Hospitalisation for unstable angina						
Overall	1.26 (0.99–1.60)	0.06	1.20 (0.94–1.55)	0.15	1.21 (0.94–1.55)	0.14
Women	2.08 (1.20–3.60)	0.009	1.93 (1.09–3.42)	0.024	2.00 (1.12–3.56)	0.019
Men	1.15 (0.88–1.50)	0.30	1.12 (0.85–1.49)	0.42	1.12 (0.85–1.49)	0.42
Hospitalisation for heart failure						
Overall	1.02 (0.43–2.40)	0.97	0.94 (0.39–2.28)	0.89	0.91 (0.38–2.22)	0.84
Women[+]						
Men	1.16 (0.47–2.89)	0.75	1.02 (0.39–2.64)	0.97	0.96 (0.37–2.51)	0.94
Ischaemia-driven revascularisation						
Overall	1.36 (0.99–1.86)	0.06	1.30 (0.93–1.81)	0.12	1.27 (0.91–1.77)	0.16
Women	2.43 (1.11–5.31)	0.026	2.58 (1.13–5.87)	0.024	2.66 (1.16–6.13)	0.021
Men	1.21 (0.86–1.71)	0.28	1.15 (0.80–1.66)	0.46	1.11 (0.77–1.60)	0.58
Composite for cardiovascular death, myocardial infarction, or ischaemic stroke						
Overall	1.61 (1.10–2.35)	0.014	1.53 (1.03–2.27)	0.036	1.47 (0.99–2.19)	0.06
Women	1.73 (0.68–4.37)	0.25	1.57 (0.60–4.12)	0.36	1.78 (0.67–4.75)	0.25
Men	1.59 (1.05–2.41)	0.03	1.49 (0.96–2.31)	0.08	1.36 (0.87–2.12)	0.17
Composite for cardiac events[§]						
Overall	1.33 (1.07–1.64)	0.009	1.27 (1.02–1.58)	0.034	1.26 (1.01–1.57)	0.042
Women	1.88 (1.13–3.12)	0.016	1.81 (1.07–3.06)	0.028	1.87 (1.10–3.19)	0.021
Men	1.25 (0.99–1.57)	0.06	1.18 (0.93–1.51)	0.18	1.16 (0.91–1.48)	0.24
All repeat revascularisation						
Overall	1.23 (0.94–1.60)	0.13	1.18 (0.90–1.56)	0.23	1.15 (0.87–1.51)	0.33
Women	2.75 (1.32–5.70)	0.007	3.02 (1.40–6.54)	0.005	3.06 (1.40–6.72)	0.005
Men	1.06 (0.80–1.41)	0.67	1.01 (0.75–1.36)	0.94	0.98 (0.72–1.32)	0.87

HR: hazard ratio; MACCE: major adverse cardiovascular and cerebrovascular event. [#]: adjusted for age and body mass index (BMI); [¶]: adjusted for age, BMI, smoking (no (referent), past, current), hypertension, diabetes mellitus, hyperlipidaemia, prior myocardial infarction, prior stroke and clinical presentation (unstable angina (referent), acute myocardial infarction); [+]: univariate and/or multivariate Cox regression was not done due to no or few number of events; [§]: includes cardiovascular death, myocardial infarction, ischaemia-driven revascularisation or hospitalisation for unstable angina or heart failure.

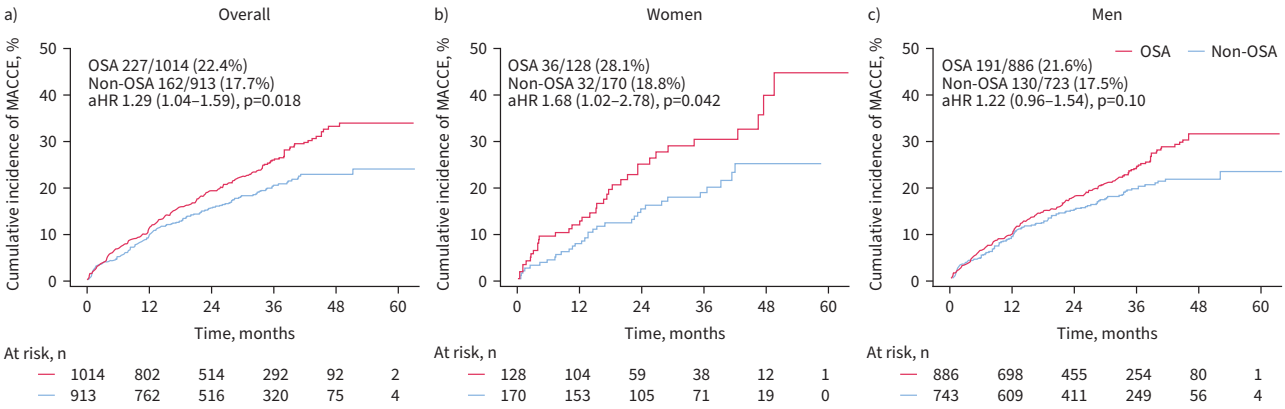


FIGURE 3 Obstructive sleep apnoea (OSA) and risk of major adverse cardiovascular and cerebrovascular event (MACCE) in a) the overall population and by sex: b) women; c) men. Kaplan–Meier estimates and fully adjusted hazard ratios (aHR; with 95% confidence intervals) for MACCE between OSA and non-OSA groups in the overall population and by sex. Data are presented as n/N (%).

small number of events in a relatively short follow-up duration. Thus, the suggestion of greater risk in women with OSA and clinical relevance should be regarded with caution until more evidence appears from female-dominated cohorts.

The potential associations of OSA with outcomes in women may be explained by specific characteristics of symptoms, pathophysiology and consequences of OSA. Women with OSA predominantly present nonspecific symptoms including insomnia, depression, fatigue and morning headache [31]. Women were more likely to have rapid eye movement-dominant OSA [7, 32, 33] with shorter respiratory events [34], which may be associated with higher sympathetic activity and nocturnal ischaemia, leading to higher cardiovascular risk. Women with OSA display greater endothelial dysfunction [35] and platelet activation [36], all implicated in the progression of atherosclerosis and ischaemic events. Furthermore, we found that the female patients were older than the males. This is true as men develop OSA earlier in life, whereas women generally develop OSA after menopause [37]. We can speculate that the longer lifetime exposure to OSA in men may provide some protection from OSA-related injury [8]. This is also true in the acute setting of ACS, since OSA-related intermittent hypoxia may lead to ischaemic pre-conditioning and promote the development of coronary collaterals [38, 39]. It is noteworthy that women had less previous myocardial infarction than men, leading to less cardioprotective effect from pre-existing ischaemia [40]. Finally, women also had ≈30% higher prevalence of all three traditional risk factors (hypertension, diabetes, hyperlipidaemia). Coexistence of these factors with OSA may generate synergistic effects to promote the development of new lesions and increase ischaemic events including hospitalisation for unstable angina and ischaemia-driven revascularisation in ACS patients [41, 42].

In patients with non-sleepy OSA and stable coronary artery disease, data from randomised controlled trials (SAVE [43] and Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea [44] studies) do not support a beneficial effect of CPAP on secondary cardiovascular protection. The ISAACC trial [29] also failed to show that CPAP treatment protected against cardiovascular events in ACS patients. The neutral results suggest the deleterious effects of OSA may be related to different clinical phenotypes [40]. In the SAVE study, high-risk clinical phenotypes (*e.g.* patients with cerebrovascular disease and diabetes) in relation to cardiovascular events responded better to CPAP treatment [45]. It should be noted that women represented <20% of the overall population in all three interventional trials [29, 43, 44], thereby limiting the sample to a potentially lower-risk group. In the present study, female patients with OSA had a significantly early and increased risk of recurrent events after ACS, therefore representing a high-risk subset perhaps more likely to respond to the intervention. For patients with ACS, it is important to screen for OSA, particularly in women. These findings should motivate dedicated studies to further explore the benefits of CPAP treatment in women with ACS.

Study limitations

First, although the sample was large, women represented only 15.5% of the overall population, which may be underpowered to detect sex-specific differences. However, women are usually less represented (14.8–

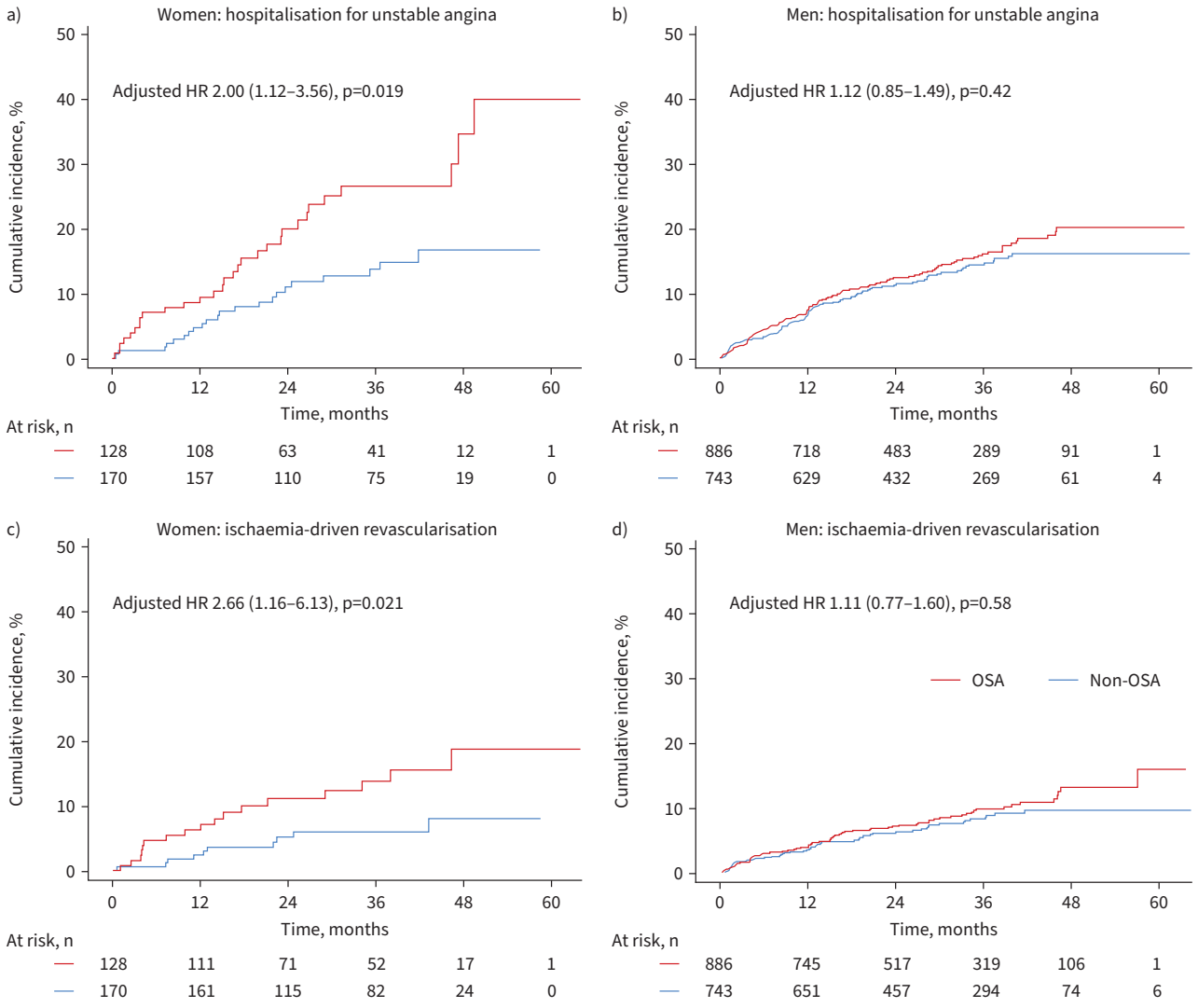


FIGURE 4 Cumulative incidence of hospitalisation for unstable angina and ischaemia-driven revascularisation by sex and obstructive sleep apnoea (OSA) categories. Kaplan–Meier estimates and fully adjusted hazard ratios (HR) for a, b) hospitalisation for unstable angina and c, d) ischaemia-driven revascularisation between OSA and non-OSA groups in a, c) women and b, d) men.

16.0%) in coronary artery disease cohort [23] or randomised studies [29, 44]. The exploratory results should be validated in female-dominated ACS cohorts. Second, the diagnosis of OSA based on portable sleep monitors may underestimate the severity of OSA. However, studies have shown that portable polygraphy can be used as an alternative to polysomnography for OSA diagnosis [46]. Third, although OSA severity may be overestimated during the acute setting of ACS [47], this is true for OSA assessment in the setting of any high-risk acute disease including heart failure. Fourth, portable sleep studies are probably less accurate than traditional attended polysomnography for detection of central sleep apnoea during the acute setting of ACS with potential exposure to sedating medications. However, we performed the sleep studies after clinical stabilisation at a median 2 days after admission, when the sedating medications (*e.g.* morphine) used in the urgent setting would have been metabolised. Fifth, the heterogeneity of OSA in terms of symptoms, pathophysiology and comorbidities should be considered. Future studies should integrate symptoms and sleep disturbances in each sex and link treatment selection with clinical phenotype. Finally, the overall sample was predominantly East-Asian and non-obese. The study results may thus not be readily generalisable to Western and obese populations.

Conclusions

In this prospective cohort with hospitalised ACS patients, OSA was associated with increased risk of subsequent cardiovascular events, particularly among women. Female patients should not be neglected for OSA screening during ACS hospitalisation and dedicated intervention studies focusing on women with ACS and comorbid OSA should be prioritised.

Acknowledgements: The authors thank Guanqi Zhao, Zexuan Li, Xin Huang, Siyi Li and Ge Wang (Center for Coronary Artery Disease, Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China) for study data collection, and Xiaoyan Yan and Pu Liu (Peking University Clinical Research Institute, Beijing, China) for statistical analysis assistance.

Data availability statement: All of the individual patient data collected during the study will be shared. The data will be made available within 12 months after publication. All available data can be obtained by contacting the corresponding author. It will be necessary to provide a detailed protocol for the proposed study, to provide the approval of an ethics committee, to supply a signed data access agreement, and to have discussion with the original authors for re-analysis.

Author contributions: Study concept and design: Xiao Wang, Jingyao Fan, Virend K. Somers and Shaoping Nie. Acquisition, analysis or interpretation of data: Xiao Wang, Jingyao Fan, Ruifeng Guo, Wen Hao, Virend K. Somers and Shaoping Nie. Drafting of the manuscript: Xiao Wang. Critical revision of the manuscript for important intellectual content: all authors. Obtained funding: Xiao Wang and Shaoping Nie. Administrative, technical or material support: Changsheng Ma and Xinliang Ma. Xiao Wang, Jingyao Fan and Shaoping Nie had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Conflict of interest: Changsheng Ma reports honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer Ingelheim (BI), Bayer and AstraZeneca for giving lectures. Shaoping Nie reports research grants (paid to institution) from Boston Scientific, Abbott, Jiangsu Hengrui Pharmaceuticals, China Resources Sanjiu Medical & Pharmaceuticals and East China Pharmaceuticals. Virend K. Somers has served as a consultant for Respicardia, Bayer, Lilly, Resmed and Jazz Pharmaceuticals, and serves on the scientific advisory board for Sleep Number. The rest of the authors have no relevant relationships to disclose.

Support statement: This study was funded by grants from Beijing Nova Program (Z201100006820087), Natural Science Foundation of Beijing, China (7222046), National Natural Science Foundation of China (81870322, 81900504), National Key R&D Program of China (2020YFC2004800), and Interdisciplinary Cooperation Project of Beijing Nova Program (Z211100002121165). Funding information for this article has been deposited with the Crossref Funder Registry.

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