Received: 25 February 2022 | Revised: 9 June 2022 | Accepted: 13 June 2022

DOI: 10.1111/jsr.13681

RESEARCH ARTICLE

Self-reported symptoms of sleep-disordered breathing and risk of cardiovascular diseases: Observational and Mendelian randomization findings

Olga E. Titova[1] | Shuai Yuan[2] | John A. Baron[1,3,4] | Eva Lindberg[5] | Karl Michaëlsson[1] | Susanna C. Larsson[1,2]

[1]Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

[2]Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[3]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

[4]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina, USA

[5]Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

Correspondence
Olga E. Titova and Susanna C. Larsson, Unit of Medical Epidemiology, Department of Surgical Sciences, The EpiHub, Uppsala University, Dag Hammarskjölds väg 14 B, 75185 Uppsala.
Email: olga.titova@surgsci.uu.se; susanna.larsson@surgsci.uu.se

Funding information
Hjärt-Lungfonden, Grant/Award Number: 20190247; Swedish Research Council, Grant/Award Numbers: 2016-01042, 2019-00977; Swedish Research Council for Health, Working Life and Welfare, Grant/Award Numbers: 2018-00123, 2017-06100, 2017-00644, 2015-03257; Swedish Heart-Lung Foundation, Grant/Award Number: 20190247; Börjeson, Emil and Ragna Foundation

Summary

Sleep-disordered breathing may increase the risk of cardiovascular diseases, but observational findings are inconclusive. We investigated whether sleep-disordered breathing-related symptoms are associated with risk of several cardiovascular diseases using data from a cohort study and by performing Mendelian randomization analyses. The cohort study included 43,624 adults (56–94 years old) who completed questionnaires regarding symptoms of snoring and cessation of breathing, lifestyle habits and health characteristics. Participants were followed up for incident cardiovascular diseases and death over 8 years through linkage to the Swedish National Patient and Death Registers. The Mendelian randomization analyses were conducted using single-nucleotide polymorphisms robustly associated with sleep apnea in a recent genome-wide association study and summary-level data for major cardiovascular diseases from large-scale consortia. In the cohort study, an increased risk of atrial fibrillation was observed in participants who reported both snoring and cessation of breathing (hazard ratio [95% confidence interval] = 1.16 [1.03–1.30]) compared with those without sleep-disordered breathing symptoms. There was no association between sleep-disordered breathing symptoms and risk of myocardial infarction, heart failure, aortic valve stenosis or abdominal aortic aneurysm in multivariable analyses. Mendelian randomization analyses showed no association of genetic liability to sleep apnea with myocardial infarction, heart failure or atrial fibrillation, but revealed a suggestive association with coronary artery disease (odds ratio [95% confidence interval] = 1.24 [1.02–1.52]).

KEYWORDS
cardiovascular disease, cohort, Mendelian randomization, single-nucleotide polymorphisms, sleep apnea, sleep-disordered breathing

1 | INTRODUCTION

Cardiovascular diseases (CVDs) are the major cause of premature death worldwide, despite advances in CVD prevention and treatment, and a considerable decline in mortality. In addition to the traditional risk factors for CVDs, sleep-disordered breathing (SDB) may also contribute to development of CVDs. This is alarming, as the prevalence of SDB in the general population has been increasing, and it is estimated to vary from 10% to 40%, with a higher prevalence among men and the elderly (Kitakata et al., 2018; Lyons et al., 2020).

Obstructive sleep apnea (OSA), the most common type of SDB, is characterized by repeated episodes of either partial or full nocturnal cessation of breathing. The diagnosis of OSA is usually based on in-laboratory nocturnal polysomnography, the presence of cardiovascular comorbidities, and symptoms such as loud snoring, sleep-related breathing problems and daytime sleepiness (Semelka et al., 2016). Obesity is a common risk factor for both SDB and CVDs. SDB is associated with intermittent hypoxia, sleep fragmentation, systemic inflammation, oxidative stress, metabolic dysregulation (Ryan, 2018) and a decrease in the nocturnal dipping of blood pressure (Cuspidi et al., 2019), all of which may contribute to the initiation and progression of CVDs. Despite increasing prevalence and evidence of adverse health effects, OSA remains largely undiagnosed. This can be at least in part related to a lack of awareness of this condition and lack of access to sleep clinics to perform a laboratory-based investigation (e.g. using a gold-standard methodology, polysomnography; Osman et al., 2018). The apnea–hypopnea index (AHI) indicates the number of apneas and hypopneas events per hour of sleep, and has been the most commonly used measure of OSA severity (Oldenburg et al., 2021). Recent evidence suggests the nocturnal hypoxaemic burden parameter, defined as the time of oxygen saturation below 90%, as a better predictor of survival in patients with SDB and CVD (Oldenburg et al., 2016; Oldenburg et al., 2021). A number of questionnaire-based screening instruments used in primary care settings, preoperative screenings and research have been developed to better identify people at risk for OSA (Gottlieb & Punjabi, 2020). A meta-analysis including cross-sectional and case–control studies confirmed that OSA is prevalent in patients with CVDs (Wu et al., 2018). However, large cohort studies are needed to investigate whether SDB may increase risk of specific CVDs independently of obesity in participants with no history of CVD at baseline.

Given the heterogeneity of CVDs, there may well be differences in the contribution of SDB to the pathophysiology of different CVD events. Previous cohort studies on the association between SDB and subsequent CVD outcomes has mainly focused on ischaemic stroke and coronary heart disease (CHD), whereas data on myocardial infarction (MI) specifically and other CVDs such as heart failure (HF; Gottlieb et al., 2010; Ljunggren et al., 2016), atrial fibrillation (AF; Lin et al., 2015; Tung et al., 2017), aortic valve stenosis (AVS) and abdominal aortic aneurysm (AAA) are limited or non-existent. Conventional observational studies are susceptible to reverse causality and confounding, which may bias results. Mendelian randomization (MR) is an epidemiological approach that can be used to address causal hypothesis and provide less biased evidence on associations between modifiable risk factors and health outcomes, utilizing genetic variants that are strongly associated with a modifiable risk factor (Davies et al., 2018).

The aim of this study was to investigate the associations of self-reported SDB-related symptoms with specific CVDs, including MI, HF, AF, AVS and AAA in a cohort of 43,624 middle-aged and elderly men and women. We also used the MR approach to investigate the associations of genetic liability to sleep apnea with coronary artery disease (CAD), MI, HF and AF.

2 | MATERIALS AND METHODS

2.1 | Study population

The data from the National Research Infrastructure SIMPLER (Swedish Infrastructure for Medical Population-based Life-course Environmental Research) was used in the primary analysis. In 2008/2009, all participants completed structured questionnaires that included information on lifestyle and other risk factors for chronic diseases. We excluded individuals who died prior to 1 July 2009, and those who had missing information on SDB-related symptoms (Figure S1), leaving 43,624 participants (19,339 women and 24,285 men) with a mean baseline age of 70 years (56–94 years) for analysis. In the main analysis of each CVD outcome, we excluded participants with a diagnosis of the corresponding specific CVD before start of a follow-up (e.g. those with HF before baseline were excluded from the analysis of HF), as ascertained through linkage to the Swedish National Patient Register. The number of prevalent CVD cases excluded in each analysis is shown in Figure S1. The cohort study was conducted following the Helsinki declaration, and the participants provided written informed consent. The current data analysis was approved by the Swedish Ethical Review Authority.

2.2 | Exposure assessment

In 2008/2009, participants completed questionnaires that solicited information about snoring, cessation of breathing, educational attainment, alcohol consumption, smoking status, weight, height, physical activity, cohabitation status, and history of diabetes, hypertension and hypercholesterolaemia. Participants indicated how often they experienced sleep apnea or cessation of breathing as well as disturbing snoring during the past 3 months with the following categories: never; seldom; often; mostly; and always. Participants who reported that they experienced sleep apnea/cessation of breathing or snoring often, mostly or always were defined as having SDB symptoms.

2.3 | Case ascertainment and follow-up

Cases of CVDs and death were ascertained through linkage with the Swedish National Patient Register (covering both in- and out-patients)

and the Cause of Death Register using the unique personal identity number assigned to each Swedish resident and classified according to the International Classification of Diseases (ICD) 10th Revision codes. The endpoints in the present cohort study were acute MI (I21), HF (I50 and I11.0), AF (I48), AVS (I35.0 and I35.2) and AAA (I71.3 and I71.4). Participants were followed up from 1 July 2009 to the date of diagnosis of CVD, death from any cause, or 31 December 2017, whichever occurred first.

2.4 | Two-sample MR analysis

Summary-level data for the associations of sleep apnea-associated single-nucleotide polymorphisms (SNPs) with CVD outcomes were acquired from a meta-analysis of genome-wide associations studies (GWASs) for AF (60,620 cases and 970,216 non-cases; Nielsen et al., 2018), a meta-analysis of the CARDIoGRAMplusC4D consortium and the UK Biobank study for CAD (122,733 cases and 424,528 non-cases; van der Harst & Verweij, 2018), the CARDIoGRAMplusC4D consortium for MI (43,676 cases and 128,199 non-cases; Nikpay et al., 2015) and the HERMES consortium for HF (47,309 cases and 930,014 non-cases; S. Shah et al., 2020). CAD was defined as MI and other ischaemic heart diseases (ICD 10 codes I21–I25), replacement, transluminal balloon angioplasty, and other therapeutic transluminal operations on coronary artery and percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery, as well as self-reported CAD (van der Harst & Verweij, 2018). MR analyses for AAA and AVS were omitted because no large genetic data were available for these outcomes. Information of the definition of each CVD outcome was available in corresponding GWASs. Studies included in the GWASs had been approved by a relevant institutional review board, and participants had provided informed consent. The present MR analysis has been approved by the Swedish Ethical Review Authority.

2.5 | Instrumental variable selection

Thirty-nine SNPs associated with sleep apnea at the level of genome-wide significance ($p < 5 \times 10^{-8}$) were identified from a meta-analysis of five cohorts and a previous GWAS including a total of 510,484 participants of European ancestry (Campos et al., 2020). Sleep apnea cases in the included cohorts were defined based on self-reported diagnostic items, a self-reported diagnosis, or a general practitioner diagnosis based on ICD-10 codes (Campos et al., 2020). These SNPs were replicated in 23andMe, and this GWAS analysis was adjusted for body mass index (BMI), sex, age, genetic principal components and genotype platform (Campos et al., 2020). The TwoSampleMR package was used to assess linkage disequilibrium across 39 SNPs. We used 35 independent SNPs ($r^2 < 0.01$ and clump distance > 10 kb in European populations) as instrument variables for sleep apnea. The summary-level effect sizes (beta and standard error) of sleep apnea-associated SNPs were estimated based on the population from 23andMe. Details of the SNPs used as instrumental variables are available in Table S1.

2.6 | Statistical analysis

In the analysis based on SIMPLER cohort data, Cox proportional hazards regression models were used to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) with age as the time scale and sex (as a stratification variable) in the basic model. In a first multivariable model, we additionally adjusted for BMI (weight divided by the square of height; < 22.5 kg m^{-2}, 22.5–24.9 kg m^{-2}, 25.0–29.9 kg m^{-2}, or ≥ 30 kg m^{-2}). In a second multivariable model, we further adjusted for education (less than high school, high school, or university), smoking status (never, former, current smokers), alcohol intake (never drinkers, past or current drinkers of < 1 drink per week, 1–< 7 drinks per week, 7–< 15 drinks per week, 15–21 drinks per week, > 21 drinks per week), walking/bicycling (never/seldom, < 20 min per day, 20–40 min per day, > 40 min per day), exercise (almost never, < 1 hr per week, 1 hr per week, 2–3 hr per week, 4–5 hr per week, ≥ 5 hr per week), and history of diabetes (no/yes), hypertension (no/yes) and hypercholesterolaemia (no/yes). In sensitivity analyses, we additionally adjusted for cohabitation status (cohabiting versus not cohabiting). In the primary analysis, we treated SDB-related symptoms as a dichotomous variable (no SDB symptoms versus at least one SDB symptom that occurred often, mostly or always). In secondary analyses, the number of SDB symptoms was considered as an exposure variable: no SDB symptoms, snoring or sleep apnea/cessation of breathing, or both snoring and sleep apnea/cessation of breathing.

Proportional hazard assumptions were assessed by Schoenfeld's test. No interaction between SDB-related symptoms and age was observed in a basic model with regards to CVD outcomes (p for interaction >0.05). Because the association between SDB-related symptoms and CVD outcomes did not differ by sex (all p for interaction >0.2), all analyses were conducted for men and women combined. The proportion of missing data on the potential confounders used in the main analysis was less than 3%, except for smoking status that had less than 7% of missing values. A separate missing value category was created for each variable with missing values. Potential confounders were selected using directed acyclic graphs (Textor & Hardt, 2011) based on our a priori knowledge of the relationships among potential confounders, intermediate variables, exposure and outcome variables, and on existing information regarding factors associated with CVD and SDB (Al Lawati et al., 2009; Stewart et al., 2017). All statistical tests were two-sided, and p values below 0.05 were considered statistically significant. All statistical analyses were performed using Stata version 15.1 (StataCorp).

In the MR analyses, ratio estimates were calculated for each SNP as the beta coefficient for the SNP-CVD association divided by the beta coefficient for the SNP-sleep apnea trait association. These estimates were then combined across SNPs in a random-effects inverse-variance weighted (IVW) meta-analysis. This method provides high precision but does not correct for pleiotropic bias in the analysis if present (Burgess et al., 2017). The weighted median approach and

TABLE 1 Baseline characteristics of the study population according to the presence of SDB symptoms

Characteristics	Presence of SDB symptoms[a]	
	No	Yes
Number of participants	33,154	10,470
Age at baseline, years, mean (SD)	70.3 (8.1)	67.7 (7.2)
Men, %	50.9	70.7
Education > 12 years, %	21.7	21.4
Cigarette smoking, %		
Former smokers	34.9	43.9
Current smokers	8.1	10.1
Alcohol intake ≥ 15 drinks per week, %	3.0	5.2
Walking/bicycling > 40 min per day, %	34.9	29.5
Exercise ≥ 2 hr per week, %	15.5	14.2
BMI, kg m^{-2}, %		
25.0–29.9	40.1	47.4
≥ 30.0	11.1	19.2
Hypertension, %	40.8	44.3
Hypercholesterolaemia, %	24.1	29.8
Diabetes, %	8.9	10.3
Cohabiting, %	68.2	78.9

BMI, body mass index; SD, standard deviation; SDB, sleep-disordered breathing.
[a]Participants reported that at least one SDB symptom (cessation of breathing or disturbing snoring) occurred often, mostly or always.

MR-Egger regression were used as complementary analyses to examine the robustness of the results and correct for pleiotropy (Bowden et al., 2015). The weighted median approach generates consistent estimates if at least 50% of the weight in the analysis comes from valid instrumental variables (Burgess et al., 2017). The MR-Egger method can detect and adjust for directional pleiotropy but suffers from low power (Burgess et al., 2017). Additionally, the MR Pleiotropy Residual Sum and Outlier method, MR-PRESSO (Verbanck et al., 2018) was used to evaluate potential outlier SNPs. We also performed the leave-one-out analysis and made the scatter plot to visually examine possible outliers. Odds ratios (ORs) with their 95% CIs are calculated to per genetically predicted one-unit increase in log odds of sleep apnea. The MR analyses were performed using the mrrobust package in Stata (StataCorp LP; Spiller et al., 2019) and the TwoSampleMR and MR-PRESSO packages in R (R Foundation for Statistical Computing; Yavorska & Burgess, 2017).

3 | RESULTS

3.1 | Cohort study

The cohort consisted of 24,285 men and 19,339 women. Among them, 3437 participants (8%) reported cessation of breathing and 9972 (23%) indicated disturbing snoring. About 30% of the men and 16% of the women indicated having snoring or cessation of breathing; 9% of men and 4% of women reported that they experienced both snoring and cessation of breathing. Baseline characteristics of study participants according to SDB-related symptoms are shown in Table 1. Compared with those without SDB-related symptoms, individuals who indicated SDB symptoms were somewhat younger, were more likely to be men, had higher alcohol intake, were more likely to

TABLE 2 HRs (95% CIs) of CVDs according to the presence of SDB in the entire study population, follow-up 2009–2017

Outcome and model (total number)	At least one SDB symptom[a]	
	No	Yes
MI ($N = 41,105$)		
Total number of cases	1386	435
Basic model[b]	1.00 (reference)	1.02 (0.91–1.14)
Multivariable model 1[c]	1.00 (reference)	0.99 (0.88–1.11)
Multivariable model 2[d]	1.00 (reference)	0.97 (0.86–1.08)
HF ($N = 42,720$)		
Total number of cases	1784	485
Basic model[b]	1.00 (reference)	1.10 (0.99–1.22)
Multivariable model[c]	1.00 (reference)	1.02 (0.92–1.13)
Multivariable model 2[d]	1.00 (reference)	0.97 (0.88–1.08)
AF (total $N = 40,304$)		
Total number of cases	3402	1081
Basic model[b]	1.00 (reference)	**1.14 (1.06–1.22)**
Multivariable model[c]	1.00 (reference)	**1.07 (1.00–1.15)**
Multivariable model 2[d]	1.00 (reference)	1.05 (0.98–1.13)
AVS ($N = 43,317$)		
Total number of cases	338	114
Basic model[b]	1.00 (reference)	1.19 (0.95–1.47)
Multivariable model[c]	1.00 (reference)	1.13 (0.90–1.40)
Multivariable model 2[d]	1.00 (reference)	1.11 (0.89–1.38)
AAA ($N = 43,283$)		
Total number of cases	393	177
Basic model[b]	1.00 (reference)	1.15 (0.96–1.38)
Multivariable model[c]	1.00 (reference)	1.12 (0.93–1.34)
Multivariable model 2[d]	1.00 (reference)	1.00 (0.83–1.20)

Note: Bold values indicate $p < 0.05$.
AAA, abdominal aortic aneurysm; AF, atrial fibrillation; AVS, aortic valve stenosis; HF, heart failure; MI, myocardial infarction; SDB, sleep-disordered breathing.
[a]Participants reported that at least one SDB symptom (cessation of breathing or disturbing snoring) occurred often, mostly or always.
[b]Basic model included age (underlying time scale) and sex (as a stratification variable).
[c]The Cox proportional hazards regression model included age (underlying time scale), sex (as a stratification variable) and BMI.
[d]The Cox proportional hazards regression model included age (underlying time scale), sex (as a stratification variable), BMI, education, smoking status, alcohol consumption, walking/bicycling, exercise, and history of hypertension, hypercholesterolaemia and diabetes.

TABLE 3 HRs (95% CIs) of CVDs according to the number of SDB symptoms

Outcome and model (total number)	Number of SDB symptoms[a]		
	No	Snoring or cessation of breathing	Both snoring and cessation of breathing
MI ($N = 41,105$)			
Total number of cases	1386	310	125
Basic model[b]	1.00 (reference)	1.01 (0.89–1.14)	1.05 (0.87–1.26)
Multivariable model[c]	1.00 (reference)	0.98 (0.87–1.11)	1.00 (0.83–1.21)
Multivariable model 2[d]	1.00 (reference)	0.97 (0.85–1.10)	0.96 (0.80–1.16)
HF ($N = 42,720$)			
Total number of cases	1784	337	148
Basic model[b]	1.00 (reference)	1.04 (0.92–1.17)	**1.29 (1.09–1.53)**
Multivariable model[c]	1.00 (reference)	0.97 (0.86–1.10)	1.15 (0.97–1.36)
Multivariable model 2[d]	1.00 (reference)	0.94 (0.83–1.06)	1.07 (0.90–1.27)
AF (total $N = 40,304$)			
Total number of cases	3402	749	332
Basic model[b]	1.00 (reference)	1.07 (0.99–1.16)	**1.31 (1.17–1.47)**
Multivariable model[c]	1.00 (reference)	1.03 (0.95–1.11)	**1.21 (1.08–1.36)**
Multivariable model 2[d]	1.00 (reference)	1.01 (0.93–1.09)	**1.16 (1.03–1.30)**
AVS ($N = 43,317$)			
Total number of cases	338	83	31
Basic model[b]	1.00 (reference)	1.19 (0.94–1.52)	1.16 (0.80–1.69)
Multivariable model[c]	1.00 (reference)	1.15 (0.90–1.46)	1.07 (0.74–1.56)
Multivariable model 2[d]	1.00 (reference)	1.13 (0.89–1.45)	1.04 (0.72–1.52)
AAA ($N = 43,283$)			
Total number of cases	393	122	55
Basic model[b]	1.00 (reference)	1.13 (0.92–1.38)	1.21 (0.91–1.61)
Multivariable model[c]	1.00 (reference)	1.10 (0.90–1.35)	1.15 (0.86–1.54)
Multivariable model 2[d]	1.00 (reference)	1.00 (0.82–1.24)	0.99 (0.74–1.32)

Note: Bold values indicate $p < 0.05$.

AAA, abdominal aortic aneurysm; AF, atrial fibrillation; AVS, aortic valve stenosis; HF, heart failure; MI, myocardial infarction; SDB, sleep-disordered breathing.

[a]Cessation of breathing and disturbing snoring were reported to occur often, mostly or always.

[b]Basic model included age (underlying time scale) and sex (as a stratification variable).

[c]The Cox proportional hazards regression model included age (underlying time scale), sex (as a stratification variable) and BMI.

[d]The Cox proportional hazards regression model included age (underlying time scale), sex (as a stratification variable), BMI, education, smoking status, alcohol consumption, walking/bicycling, exercise, and history of hypertension, hypercholesterolaemia and diabetes.

be former or current cigarette smokers, were less physically active, had higher BMI, were more likely to report not living alone, and have a history of hypertension, hypercholesterolaemia and diabetes.

The number of incident CVD events during follow-up is shown in Tables 2 and 3. In the multivariable model, having at least one SDB symptom was associated with a higher risk of AF in the model controlled for age, sex and BMI (Table 2). In the subsequent analysis, having both snoring and cessation of breathing was linked to 16% higher risk of AF in the fully adjusted model (Table 3). In addition, an increased risk of HF was found in the basic model in participants who reported snoring and cessation of breathing (Table 3). However, there was no association between SDB-related symptoms and MI, HF, AVS or AAA in fully adjusted models (Tables 2 and 3). Sensitivity analysis, additionally adjusted for cohabitation status, produced similar results with no change in the HR or a slight change in the second decimal point (data not shown).

3.2 | Two-sample MR analysis

There was a suggestive association between genetic liability to sleep apnea and higher odds of CAD (OR, 1.24; 95% CI, 1.02–1.52; $p = 0.032$) in the main analysis, but the association did not persist in the weighted median and MR-Egger models (Figure 1; Table S2). We did not detect any association of genetic liability to sleep apnea with MI alone, AF or HF (Figure 1; Table S2), although the direction of association in the IVW analyses was the same. The lack of association

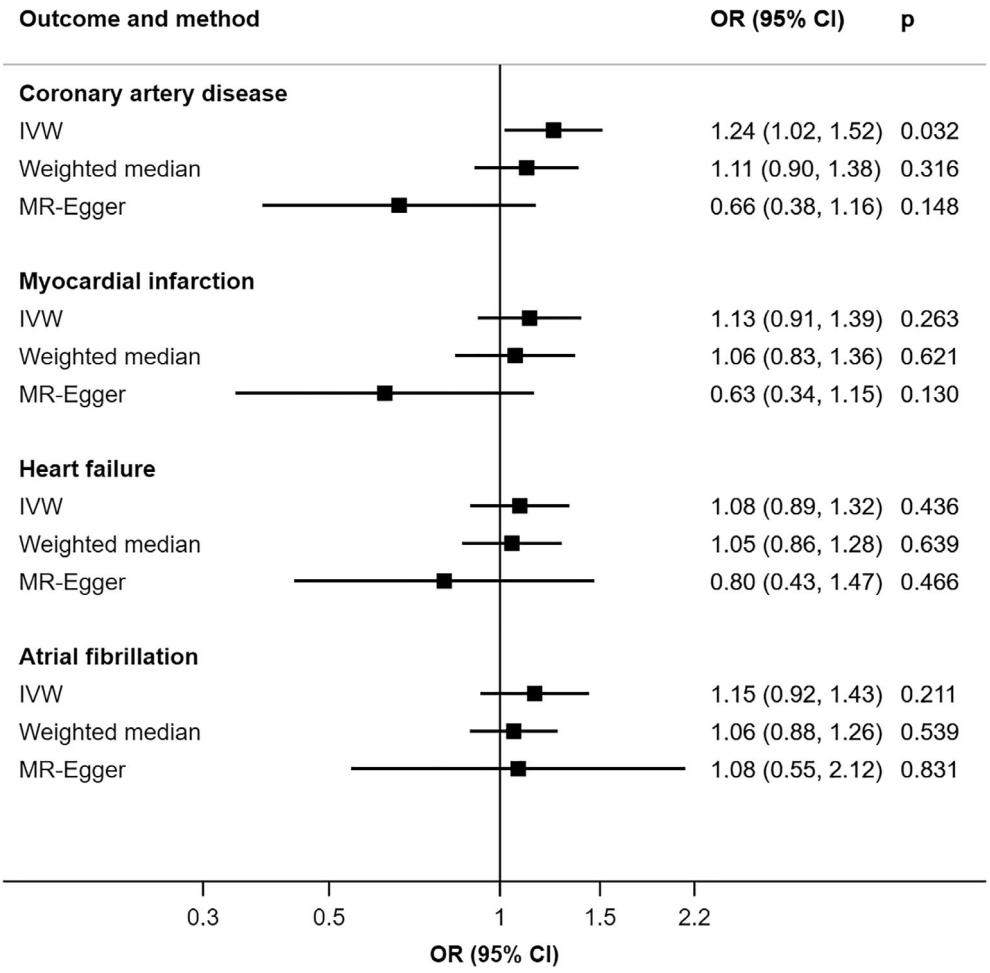

FIGURE 1 Associations of genetically predicted sleep apnea with several cardiovascular diseases (CVDs). ORs are per one unit increase in log odds of sleep apnea. IVW indicates inverse-variance weighted method; OR, odds ratio

remained in sensitivity analyses. Potential pleiotropy was detected in the analyses of CAD and MI (the MR-Egger intercepts were significantly deviated from zero; Table S2). Two possible outliers were suspected in the scatter plot for the analysis of CAD (Figure S2a). However, the MR-PRESSO analysis did not identify any outlying SNPs for analyses of CAD and MI (Table S2), and the association remained in the leave-one-out analysis for CAD (Figure S2b). Two outliers in the analysis of sleep apnea and HF as well as five outliers in the analysis of sleep apnea and AF were identified. Exclusion of these SNPs did not change the results substantially (Table S2).

4 | DISCUSSION

A traditional cohort study design and MR approach were used in the present study to investigate the association of SDB-related symptoms and risk of several CVDs. In the cohort study, an increased risk of AF was observed in participants who reported both snoring and cessation of breathing. No evidence of an association of SDB symptoms with risk of MI, HF, AVS or AAA was found. The MR study did not reveal any significant association of genetic liability to sleep apnea with AF, MI or HF, but showed suggestive evidence of a link between genetic liability to sleep apnea and higher odds of CAD.

Most of the current evidence of the association between SDB and cardiovascular events is based on cross-sectional or hospital-based studies that often included patients with multiple comorbidities and history of CVD, and the interpretation of the results might be limited by clinic referral bias. Our findings of a positive association between self-reported SDB variables and risk of AF are consistent with previous research based on reports of sleep apnea (Lin et al., 2015). In this cohort study of 4395 middle-aged and elderly (8.5-years follow-up, 212 AF cases), self-reported physician-diagnosed sleep apnea, but not habitual snoring, was associated with an increased risk of AF (Lin et al., 2015). In another study of 2912 individuals without SDB at baseline, objectively measured central sleep apnea but not OSA was linked to two- to threefold increased odds of developing AF (Tung et al., 2017).

Cohort studies of the associations of SDB with HF and MI (generally not differentiated from CHD) are relatively scarce and results are inconclusive. In a study of 4422 middle-aged and older men and women, free of HF and CHD at baseline, OSA was associated with a 13% increased risk of incident HF in men but not in women. In addition, OSA was linked to an increased risk of incident CHD (defined as MI, revascularization procedure, or CHD death) in men younger than 70 years of age (HRs [95% CIs] = 1.10 [1.00–1.21]), but not in older men or in women of any age (Gottlieb et al., 2010). Another cohort

study that included 1436 patients who were referred to the Sleep Medicine Center specifically for the evaluation of SDB, showed that OSA was linked to an increased risk of coronary events or CVD death (as a composite end point; Shah et al., 2010). A cohort study of 5990 women found a twofold increase in the risk of incident HF in women with the combination of snoring and excessive daytime sleepiness compared with the reference group without those symptoms (Ljunggren et al., 2016). In the present study, a 29% increased risk of HF was found in participants who reported both snoring and cessation of breathing in the basic model. However, this association was not statistically significant in the fully adjusted model. Our MR finding of a suggestive positive association between genetically predictive OSA and risk of CAD corroborates the results from some observational studies (Gottlieb et al., 2010). Previous cohort studies on SDB in relation to risk of AVS or AAA and MR studies on genetically predicted SDB and the risk of any CVD are limited or lacking.

The mechanisms underlying the link between OSA and CVDs likely involve several pathways specific to each outcome, especially considering shared comorbidities. For instance, sleep apnea may lead to intermittent hypoxia, sleep fragmentation, systemic inflammation, oxidative stress, hypertension, endothelial dysfunction and metabolic dysregulation (Ryan, 2018). All these factors may contribute to the initiation and progression of many of the CVDs. In addition, in a study of 202 patients without clinical coronary disease, the presence and severity of OSA (defined by AHI ≥ 5) was associated with the presence and amount of coronary artery calcification, used as surrogate marker of subclinical coronary disease (Sorajja et al., 2008). OSA may predispose to AF, the most common cardiac arrhythmia, through several mechanisms such as hypoxaemia, hypercapnia and consequent increases in blood pressure and heart rate (Marulanda-Londono & Chaturvedi, 2017). Intermittent hypoxia, periodic alternating exposures to hypoxia and normoxia, may trigger oxidative stress and inflammation (Lavie, 2008), which are related to increased susceptibility to arrhythmias (January et al., 2014). The observed positive association between SDB and AF might also be attributable to common risk factors, such as obesity and hypertension, and the mutually persisting pathophysiological relationship among these conditions (Anter et al., 2017). However, obesity and hypertension are also risk factor for other CVDs for which we found no association with SDB symptoms.

Important strengths of our cohort study are the large sample size; a broad range of CVD outcomes, objectively assessed through linkage to nationwide population-based registers; complete case identification and no loss to follow-up, inclusion of both men and women, and the ability to adjust for important confounders. Several limitations, however, apply to the present study. In this large cohort, we have not investigated clinically diagnosed SDB. Instead, the presence of SDB-related symptoms was determined based on self-reports and therefore measurement error in the exposure assessment was inevitable. For example, some participants lived alone and may not have been aware of snoring or sleep apnea, therefore they did not report these symptoms. Although we made an additional adjustment for cohabitation status, some participants with SDB symptoms may have been overlooked. Given the prospective cohort design, measurement error of reported SDB-related symptoms would rather attenuate the association with risk of CVDs. In addition, we could not properly account for the severity of the SDB. This could also explain the smaller magnitude of associations between SDB symptoms and, for example, AF compared with other studies based on objective measures (e.g. polysomnography). We have not used information on ICD-10 codes for SDB due to the low coverage of SDB diagnoses in the Swedish National Patient register. The objective validation of self-reported SDB symptoms might be difficult. A study of 1409 patients referred to a sleep clinic evaluated the relative validity of self-reported snoring as an indicator of sleep apnea (Bliwise et al., 1991). For example, for the question about snoring, sensitivity for sleep apnea in men was approximately 90%, whereas the specificity was about 50%. The combination of self-reported snoring and breath holding had higher specificity (99%) while the sensitivity was 30%. Although this study did not demonstrate both high specificity and high sensitivity for the combination of self-reported snoring and breath holding as indicators of sleep apnea, the authors pointed out that such self-reported symptoms are useful for population-based studies where objective measurements are not possible (Bliwise et al., 1991). In addition, such symptoms as snoring and breathing cessation are always included in the screening tools for OSA (e.g. Berlin questionnaire and STOP-Bang Questionnaire). A study of 157 adults divided into the development or validation group examined the predictive value of a two-stage screening model including a questionnaire and home oximetry. From the Berlin questionnaire items, self-reported snoring and witnessed sleep apnea were predictive factors for moderate and severe OSA, and were therefore used as a first-stage screening tool along with waist circumference and age (Chai-Coetzer et al., 2011). The prevalence of reported sleep apnea/cessation of breathing in our study is comparable to that in studies conducted over the same time period and utilizing objectively measured sleep apnea (Lyons et al., 2020). In addition, we cannot rule out that some incident CVD cases in this study occurred after the follow-up period. Finally, in view of the observational nature of this study, we cannot rule out residual and unmeasured confounding.

The main strength of our MR study is that such an approach is less prone to confounding, reverse causation bias and measurement error (Davies et al., 2018). Another strength is inclusion of several CVD outcomes and use of summary-level data derived from large-scale genetic consortia or studies with large sample size, which ensures high statistical power to detect weak associations. In addition, we restricted our MR analysis to European descent individuals, which reduced potential bias due to population stratification. However, our MR study has several limitations as well. We observed evidence of pleiotropy, that is, when a genetic variant is associated with more than one phenotype that affects the outcome, in the analyses of sleep apnea in relation to CAD and MI. A possible explanation for the observed pleiotropic effects could be that some of sleep-apnea-SNPs may have stronger association with, for example, BMI or other cardiovascular risk factors. However, SNPs used as instrumental variables were BMI-adjusted and therefore are

expected to be related to apnea independent of BMI. In addition, MR analyses for AAA and AVS were not performed because no large genetic data were available for these outcomes. Thus, further large MR studies using accurate measures of sleep apnea and including other populations are needed.

5 | CONCLUSIONS

Results from this large-scale cohort study of middle-aged and older individuals suggest that self-reported SDB-related symptoms such as disturbing snoring and breathing cessations are associated with an increased risk of AF. However, MR analysis did not support a causal relationship of sleep apnea with AF, HF or MI, but provided suggestive evidence that genetically predicted sleep apnea is associated with an increased risk of CAD.

ACKNOWLEDGEMENTS

The authors would like to thank the national research infrastructure SIMPLER for provisioning of facilities and experimental support. The computations were performed on resources provided by the Swedish National Infrastructure for Computing's (www.snic.se) support for sensitive data SNIC-SENS through the Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX). The authors thank the CARDIoGRAMplusC4D and HERMES consortia for providing summary statistics data for CVD outcomes.

FUNDING INFORMATION

Work of the authors is supported by grants from the Börjeson, Emil and Ragna Foundation (to O.E.T.), the Swedish Research Council for Health, Working Life and Welfare (Forte; grant number 2018-00123; to S.C.L.), the Swedish Research Council (Vetenskapsrådet; grant number 2016-01042 and 2019-00977; to S.C.L.), and the Swedish Heart-Lung Foundation (Hjärt-Lungfonden; grant number 20190247; to S.C.L.). The study was also supported by additional grants from the Swedish Research Council (https://www.vr.se; grant no. 2015-03257, 2017-00644 and 2017-06100 to KM). SIMPLER receives funding through the Swedish Research Council under the grant no. 2017-00644 (to Uppsala University and KM). SNIC is financially supported by the Swedish Research Council. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTIONS

O.E.T. and S.C.L. contributed to the data acquisition, conception and design of the study; O.E.T. and S.Y. conducted the statistical analyses; O.E.T. drafted the first manuscript and prepared a figure. All authors contributed substantially to the interpretation of the results and critical revision of the article for important intellectual content, and approved the final version of the article.

DATA AVAILABILITY STATEMENT

The data that support findings of this prospective cohort study are available upon application to the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER; https://www.simpler4health.se). Data used for the MR analyses are based on publicly available summary statistics data provided by genetic consortia.

ORCID

Olga E. Titova https://orcid.org/0000-0003-2747-1606
Susanna C. Larsson https://orcid.org/0000-0003-0118-0341

REFERENCES

Al Lawati, N. M., Patel, S. R., & Ayas, N. T. (2009). Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Progress in Cardiovascular Diseases*, *51*(4), 285–293. https://doi.org/10.1016/j.pcad.2008.08.001

Anter, E., Di Biase, L., Contreras-Valdes, F. M., Gianni, C., Mohanty, S., Tschabrunn, C. M., Viles-Gonzalez, J. F., Leshem, E., Buxton, A. E., Kulbak, G., & Josephson, M. E. (2017). Atrial substrate and triggers of paroxysmal atrial fibrillation in patients with obstructive sleep apnea. *Circulation. Arrhythmia and Electrophysiology*, *10*(11), e005407. https://doi.org/10.1161/CIRCEP.117.005407

Bliwise, D. L., Nekich, J. C., & Dement, W. C. (1991). Relative validity of self-reported snoring as a symptom of sleep apnea in a sleep clinic population. *Chest*, *99*(3), 600–608. https://doi.org/10.1378/chest.99.3.600

Bowden, J., Davey Smith, G., & Burgess, S. (2015). Mendelian randomization with invalid instruments: Effect estimation and bias detection through egger regression. *International Journal of Epidemiology*, *44*(2), 512–525. https://doi.org/10.1093/ije/dyv080

Burgess, S., Bowden, J., Fall, T., Ingelsson, E., & Thompson, S. G. (2017). Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology*, *28*(1), 30–42. https://doi.org/10.1097/EDE.0000000000000559

Campos, A. I., Ingold, N., Huang, Y., Kho, P. F., Han, X., Ong, J.-S., García-Marín, L. M., Law, M. H., Martin, N. G., Dong, X., & Renteria, M. E. (2020). Genome-wide analyses in 1,987,836 participants identify 39 genetic loci associated with sleep apnoea. *medRxiv*, 2020.2009.2029.20199893. https://doi.org/10.1101/2020.09.29.20199893

Chai-Coetzer, C. L., Antic, N. A., Rowland, L. S., Catcheside, P. G., Esterman, A., Reed, R. L., Williams, H., Dunn, S., & McEvoy, R. D. (2011). A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care. *Thorax*, *66*(3), 213–219. https://doi.org/10.1136/thx.2010.152801

Cuspidi, C., Tadic, M., Sala, C., Gherbesi, E., Grassi, G., & Mancia, G. (2019). Blood pressure non-dipping and obstructive sleep apnea syndrome: A meta-analysis. *Journal of Clinical Medicine*, *8*(9), 1367. https://doi.org/10.3390/jcm8091367

Davies, N. M., Holmes, M. V., & Davey Smith, G. (2018). Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. *BMJ*, *362*, k601. https://doi.org/10.1136/bmj.k601

Gottlieb, D. J., & Punjabi, N. M. (2020). Diagnosis and Management of Obstructive Sleep Apnea: A review. *JAMA*, *323*(14), 1389–1400. https://doi.org/10.1001/jama.2020.3514

Gottlieb, D. J., Yenokyan, G., Newman, A. B., O'Connor, G. T., Punjabi, N. M., Quan, S. F., Redline, S., Resnick, H. E., Tong, E. K., Diener-West, M., & Shahar, E. (2010). Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The

sleep heart health study. *Circulation*, *122*(4), 352–360. https://doi.org/10.1161/CIRCULATIONAHA.109.901801

January, C. T., Wann, L. S., Alpert, J. S., Calkins, H., Cigarroa, J. E., Cleveland, J. C., Jr., Conti, J. B., Ellinor, P. T., Ezekowitz, M. D., Field, M. E., & Members, A. A. T. F. (2014). 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Heart Rhythm Society. *Circulation*, *130*(23), 2071–2104. https://doi.org/10.1161/CIR.0000000000000040

Kitakata, H., Kohno, T., & Fukuda, K. (2018). Sleep-disordered breathing in the elderly: Is it distinct from that in the younger or middle-aged populations? *Journal of Thoracic Disease*, *10*(Suppl 9), S1102–S1107. https://doi.org/10.21037/jtd.2018.03.179

Lavie, L. (2008). Intermittent hypoxia: The culprit of oxidative stress, vascular inflammation and dyslipidemia in obstructive sleep apnea. *Expert Review of Respiratory Medicine*, *2*(1), 75–84. https://doi.org/10.1586/17476348.2.1.75

Lin, G. M., Colangelo, L. A., Lloyd-Jones, D. M., Redline, S., Yeboah, J., Heckbert, S. R., Nazarian, S., Alonso, A., Bluemke, D. A., Punjabi, N. M., & Liu, K. (2015). Association of Sleep Apnea and Snoring with Incident Atrial Fibrillation in the multi-ethnic study of atherosclerosis. *American Journal of Epidemiology*, *182*(1), 49–57. https://doi.org/10.1093/aje/kwv004

Ljunggren, M., Byberg, L., Theorell-Haglow, J., Lindahl, B., Michaelsson, K., & Lindberg, E. (2016). Increased risk of heart failure in women with symptoms of sleep-disordered breathing. *Sleep Medicine*, *17*, 32–37. https://doi.org/10.1016/j.sleep.2015.09.018

Lyons, M. M., Bhatt, N. Y., Pack, A. I., & Magalang, U. J. (2020). Global burden of sleep-disordered breathing and its implications. *Respirology*, *25*(7), 690–702. https://doi.org/10.1111/resp.13838

Marulanda-Londono, E., & Chaturvedi, S. (2017). The interplay between obstructive sleep apnea and atrial fibrillation. *Frontiers in Neurology*, *8*, 668. https://doi.org/10.3389/fneur.2017.00668

Nielsen, J. B., Thorolfsdottir, R. B., Fritsche, L. G., Zhou, W., Skov, M. W., Graham, S. E., Herron, T. J., McCarthy, S., Schmidt, E. M., Sveinbjornsson, G., & Willer, C. J. (2018). Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nature Genetics*, *50*(9), 1234–1239. https://doi.org/10.1038/s41588-018-0171-3

Nikpay, M., Goel, A., Won, H. H., Hall, L. M., Willenborg, C., Kanoni, S., Saleheen, D., Kyriakou, T., Nelson, C. P., Hopewell, J. C., Webb, T. R., Zeng, L., Dehghan, A., Alver, M., Armasu, S. M., Auro, K., Bjonnes, A., Chasman, D. I., Chen, S., … Farrall, M. (2015). A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. *Nature Genetics*, *47*(10), 1121–1130. https://doi.org/10.1038/ng.3396

Oldenburg, O., Costanzo, M. R., Germany, R., McKane, S., Meyer, T. E., & Fox, H. (2021). Improving nocturnal hypoxemic burden with Transvenous phrenic nerve stimulation for the treatment of central sleep apnea. *Journal of Cardiovascular Translational Research*, *14*(2), 377–385. https://doi.org/10.1007/s12265-020-10061-0

Oldenburg, O., Wellmann, B., Buchholz, A., Bitter, T., Fox, H., Thiem, U., Horstkotte, D., & Wegscheider, K. (2016). Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. *European Heart Journal*, *37*(21), 1695–1703. https://doi.org/10.1093/eurheartj/ehv624

Osman, A. M., Carter, S. G., Carberry, J. C., & Eckert, D. J. (2018). Obstructive sleep apnea: current perspectives. *Nat Sci Sleep*, *10*, 21–34. https://doi.org/10.2147/NSS.S124657

Ryan, S. (2018). Mechanisms of cardiovascular disease in obstructive sleep apnoea. *Journal of Thoracic Disease*, *10*(Suppl 34), S4201–S4211. https://doi.org/10.21037/jtd.2018.08.56

Semelka, M., Wilson, J., & Floyd, R. (2016). Diagnosis and treatment of obstructive sleep apnea in adults. *American Family Physician*, *94*(5), 355–360.

Shah, N. A., Yaggi, H. K., Concato, J., & Mohsenin, V. (2010). Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep & Breathing*, *14*(2), 131–136. https://doi.org/10.1007/s11325-009-0298-7

Shah, S., Henry, A., Roselli, C., Lin, H., Sveinbjornsson, G., Fatemifar, G., Hedman, Å. K., Wilk, J. B., Morley, M. P., Chaffin, M. D., & Lumbers, R. T. (2020). Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nature Communications*, *11*(1), 163. https://doi.org/10.1038/s41467-019-13690-5

Sorajja, D., Gami, A. S., Somers, V. K., Behrenbeck, T. R., Garcia-Touchard, A., & Lopez-Jimenez, F. (2008). Independent association between obstructive sleep apnea and subclinical coronary artery disease. *Chest*, *133*(4), 927–933. https://doi.org/10.1378/chest.07-2544

Spiller, W., Davies, N. M., & Palmer, T. M. (2019). Software application profile: Mrrobust - a tool for performing two-sample summary Mendelian randomization analyses. *International Journal of Epidemiology*, *48*, 684–690. https://doi.org/10.1101/142125

Stewart, J., Manmathan, G., & Wilkinson, P. (2017). Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. *JRSM Cardiovascular Disease*, *6*, 2048004016687211. https://doi.org/10.1177/2048004016687211

Textor, J., & Hardt, J. (2011). DAGitty: A graphical tool for analyzing causal diagrams. *Epidemiology*, *22*(5), 745. https://doi.org/10.1097/EDE.0b013e318225c2be

Tung, P., Levitzky, Y. S., Wang, R., Weng, J., Quan, S. F., Gottlieb, D. J., Rueschman, M., Punjabi, N. M., Mehra, R., Bertisch, S., & Redline, S. (2017). Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *Journal of the American Heart Association*, *6*(7), e004500. https://doi.org/10.1161/JAHA.116.004500

van der Harst, P., & Verweij, N. (2018). Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease. *Circulation Research*, *122*(3), 433–443. https://doi.org/10.1161/CIRCRESAHA.117.312086

Verbanck, M., Chen, C. Y., Neale, B., & Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics*, *50*(5), 693–698. https://doi.org/10.1038/s41588-018-0099-7

Wu, Z., Chen, F., Yu, F., Wang, Y., & Guo, Z. (2018). A meta-analysis of obstructive sleep apnea in patients with cerebrovascular disease. *Sleep & Breathing*, *22*(3), 729–742. https://doi.org/10.1007/s11325-017-1604-4

Yavorska, O. O., & Burgess, S. (2017). MendelianRandomization: An R package for performing Mendelian randomization analyses using summarized data. *International Journal of Epidemiology*, *46*(6), 1734–1739. https://doi.org/10.1093/ije/dyx034

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Titova, O. E., Yuan, S., Baron, J. A., Lindberg, E., Michaëlsson, K., & Larsson, S. C. (2022). Self-reported symptoms of sleep-disordered breathing and risk of cardiovascular diseases: Observational and Mendelian randomization findings. *Journal of Sleep Research*, *31*(6), e13681. https://doi.org/10.1111/jsr.13681