Cardiovascular Risk in Young Patients Diagnosed With Obstructive Sleep Apnea

Albertsen, Ida E; Bille, Jesper; Piazza, Gregory; Lip, Gregory Y. H.; Nielsen, Peter B.

Published in:
Journal of the American Heart Association

DOI (link to publication from Publisher):
10.1161/JAHA.123.033506

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Journal of the American Heart Association

ORIGINAL RESEARCH

Cardiovascular Risk in Young Patients Diagnosed With Obstructive Sleep Apnea

Ida E. Albertsen, MD, PhD; Jesper Bille, MD; Gregory Piazza, MD, MS; Gregory Y. H. Lip, MD; Peter B. Nielsen, MPH, PhD

BACKGROUND: In older adults, obstructive sleep apnea (OSA) has been associated with several cardiovascular complications. Whether young patients diagnosed with OSA also are at higher risk of developing subsequent cardiovascular disease is uncertain. We aimed to estimate the risk of developing an incident cardiovascular event among young patients diagnosed with OSA.

METHODS AND RESULTS: We linked nationwide Danish health registries to identify a cohort of patients aged ≤50 years with OSA using data from 2010 through 2018. Cases without OSA from the general population were matched as controls (1:5). The main outcome was any cardiovascular event (including hypertension, diabetes, atrial fibrillation, ischemic heart disease, ischemic stroke, heart failure, and venous thromboembolism). All-cause mortality was a secondary outcome. The study included 20 240 patients aged ≤50 years with OSA (19.6% female; mean±SD age 39.9±7.7 years) and 80 314 controls. After 5-year follow-up, 31.8% of the patients with OSA developed any cardiovascular event compared with 16.5% of the controls, with a corresponding relative risk (RR) of 1.96 (95% CI, 1.90–2.02). At 5-year follow-up, 27.3% of patients with OSA developed incident hypertension compared with 15.0% of the controls (RR, 1.84 [95% CI, 1.78–1.90]). Incident diabetes occurred in 6.8% of the patients with OSA and 1.4% of controls (RR, 5.05 [95% CI, 4.60–5.54]).

CONCLUSIONS: Similar to older adults, young adults with OSA demonstrate increased risk of developing cardiovascular events. To prevent cardiovascular disease progression, accumulation of cardiovascular risk factors, and mortality, risk stratification and prevention strategies should be considered for these patients.

Key Words: cardiovascular disease ■ diabetes ■ hypertension ■ obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by obstructive apnea, hypopnea, and respiratory effort-related arousals caused by repetitive collapse of the upper airway during sleep.[1] OSA is a common disorder occurring in up to 20% of adults.[2] Additionally, the disease is widely underdiagnosed: 86% to 95% of individuals found in population surveys with clinically significant obstructive sleep apnea report no prior OSA diagnosis.[3] Several factors are associated with OSA including older age, male sex, and obesity.[4] With a growing global burden of obesity and overweight, it is recognized that the clinical and public health burden of OSA is increasing.[2]

The episodic cycles of breathing disruption in sleep apnea are associated with a profile of perturbations that include intermittent hypoxia, oxidative stress, sympathetic activation, and endothelial dysfunction, all of which are critical mediators of cardiovascular disease. Hence, besides causing daytime impairment, the health consequences of OSA include development or worsening of cardiovascular diseases.[1] Indeed, OSA has been associated with a broad array of adverse

Correspondence to: Ida E. Albertsen, MD, PhD, Department of Otolaryngology, Head and Neck Surgery and Audiology, Aalborg University Hospital, Hobrovej 18-22, DK-9000 Aalborg, Denmark. Email: i.albertsen@rn.dk; idaehlers@gmail.com

This article was sent to Tazeen H. Jafar, MD MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.033506

For Sources of Funding and Disclosures, see page 9.

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

CLINICAL PERSPECTIVE

What Is New?

- In patients with obstructive sleep apnea, the risk of subsequent cardiovascular disease is not limited to older adults.
- In patients aged ≤50 years with obstructive sleep apnea, the risk of developing incident cardiovascular risk factors or overt cardiovascular disease is substantial compared with healthy controls.

What Are the Clinical Implications?

- To prevent cardiovascular disease progression, accumulation of cardiovascular risk factors, and mortality, risk stratification and prevention strategies should be considered for young patients diagnosed with obstructive sleep apnea.

cardiovascular risk factors or overt disease, including systemic arterial hypertension, cardiac arrhythmias, heart failure, coronary artery disease, stroke, pulmonary hypertension, metabolic syndrome, diabetes, and cardiovascular mortality.[5–7] In more than 5000 participants followed in 7.5 years without prevalent cardiovascular disease, a diagnosis of obstructive sleep apnea was associated with an adjusted hazard ratio (HR) of 2.6 (95% CI, 1.5–4.6) for all-cause mortality, and an adjusted HR of 1.9 (95% CI, 1.2–3.0) for cardiovascular disease incidence.[8]

For patients with cardiovascular disease, the prevalence of OSA is as high as 40% to 80%.[9] However, accumulating evidence suggests that successful treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) can improve cardiovascular outcomes.[5,10] Thus, a scientific statement from the American Heart Association emphasized that better cardiovascular risk stratification on the patient with OSA is warranted.[5]

The association of OSA and cardiovascular disease has primarily been described in cohorts including patients aged greater than 60 years. Whether young patients diagnosed with OSA also carry a high risk of developing subsequent cardiovascular diseases is uncertain. To address this, we aimed to estimate the risk of developing incident cardiovascular risk factors or overt cardiovascular disease (ie, hypertension, diabetes, atrial fibrillation, ischemic heart disease, ischemic stroke, heart failure, and venous thromboembolism) and all-cause death among young patients diagnosed with OSA, using contemporary data from a nationwide Danish cohort.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers may be sent to Danmarks Statistik at dst@dst.dk.

This study was an observational cohort study analyzing Danish nationwide administrative registry data. We searched the registries to obtain a cohort of young patients diagnosed with OSA based on hospital diagnoses to estimate risk of incident cardiovascular disease between year 2010 and 2018.

Setting and Data Sources

This study was based on linkage of 3 nationwide Danish registries: (1) the Danish National Patient Registry, which has tracked hospitalizations since 1977 and outpatient and emergency department visits at all hospitals in Denmark since 1995[11]; (2) the National Prescription Register, which holds detailed information on purchase date, Anatomical Therapeutic Chemical classification code, package size, and dosage for every prescription withdrawal in Denmark since 1994[11]; and (3) the Danish Person Registry, which contains data on sex, date of birth, and vital and emigration status.[12] All codes used in this study are presented in Table S1.

Study Population

Using the National Patient Register, we identified all patients diagnosed with OSA (*International Classification of Diseases, Tenth Revision* [*ICD-10*] code DG4732) and all patients diagnosed with sleep apnea (*ICD-10* code DG473*) also receiving CPAP treatment (ZZ3915) from2010 through 2018. For sleep apnea patients (DG473*) the CPAP treatment code was restricted to 6 months before/after diagnosis date of sleep apnea. According to a recent validation study from the Danish nationwide registries, the *ICD-10* diagnosis code DG4732 has a positive predictive value of 94% making it a suitable source of data on OSA.[13] The diagnosis code for sleep apnea (DG473*) in combination with the code for receiving CPAP treatment has been validated and resulted in a positive predictive value of 89%. We assessed study eligibility criteria for adult patients aged ≤50 years at time of diagnosis. The date of diagnosis was used as index date and defined the date of follow-up. Patients with a history (up 5 years before the date of diagnosis) of cardiovascular disorders, including hypertension, diabetes, ischemic heart disease, ischemic stroke, heart failure, venous thromboembolism, and atrial fibrillation were excluded. To ensure possible coding of patient characteristics in the registries before OSA, we excluded patients who had lived in Denmark for <1 year.

Baseline Characteristics and Comorbidity

Selected baseline characteristics and comorbidities were identified from the National Patient Register using primary and secondary *ICD-10* and Anatomical Therapeutic Chemical codes. Some patients with hypertension and diabetes are treated solely at their general practitioner and may not have received a diagnosis with an *ICD-10* code in the National Patient Registry. Therefore, patients with previous hypertension and diabetes were defined based on information on prescription claims of antihypertensive or antidiabetic medicine within 1 year of OSA diagnosis, or patients who were coded with a relevant *ICD-10* diagnosis in the National Patient Registry within 5 years of diagnosis. The remaining cardiovascular outcomes, including previous ischemic heart disease (covering angina pectoris, acute myocardial infarction, subsequent myocardial infarction, complications following acute myocardial infarction, other acute ischemic heart diseases, and chronic ischemic heart disease), ischemic stroke, atrial fibrillation, venous thromboembolism, and heart failure, were identified through primary and secondary *ICD-10* discharge diagnosis codes.

Outcomes

The primary outcome was a composite outcome defined as any cardiovascular event, covering incident cardiovascular risk factors or overt disease associated with the cardiovascular system (including hypertension, diabetes, atrial fibrillation, ischemic heart disease [as defined previously], ischemic stroke, heart failure, and venous thromboembolism). To ensure validity of the cardiovascular event as an outcome, hospital discharge diagnoses were required to be a primary diagnosis code. All-cause mortality was investigated as a secondary outcome. Separate analyses were performed for the components of the primary composite end point.

Population Controls

We compared the risk of any cardiovascular event for patients with OSA with matched controls free from cardiovascular disease from the general population. Specifically, we used the Danish Civil Registration System to select up to 5 population controls for each case, matched on age (within 5 years of the birth year) and sex. We selected controls using risk-set sampling with replacement: each control had to be alive and at risk of a cardiovascular disease on the index date of the case to whom he/she was matched.[14] Controls were assigned an index date identical to that of each corresponding case, and cases were allowed to act as controls before the diagnosis of OSA.

Statistical Analysis

In the main analysis, we applied time-to-event analyses to calculate cardiovascular risk for patients with and without OSA. Patients were followed until a cardiovascular event, death, emigration, or end of the study, whichever occurred first. Additionally, the risks of the individual cardiovascular components were investigated separately. When investigating the individual cardiovascular outcomes from the primary outcome, patients were not censored if they encountered other cardiovascular outcomes. For comparison, we calculated relative risks (RR) of cardiovascular events for patients with OSA comparing with controls, using a log-link function fulfilling the assumptions for binomial distribution.[15] We reported results at 1- and 5-year follow-up. Cumulative incidence functions by means of the Aalen-Johansen estimator, assuming death as competing risk, were used to depict the absolute risk development over time for the cardiovascular outcomes and all-cause mortality. Analyses were performed using SAS (version 9.4), and STATA/MP (version 17). According to Danish legislation, institutional review board approval and informed consent were not necessary for this type of study.

Sensitivity and Additional Analyses

To investigate if the cardiovascular risk for OSA was modified by sex and by obesity, the main analysis was repeated and stratified by sex and by obesity, respectively. Of note, obesity was defined as body mass index ≥30, see Table S1. Although cardiovascular outcomes were restricted to primary *ICD-10* codes in the main analysis, we investigated risk of cardiovascular outcomes using both primary and secondary codes in a sensitivity analysis. An age-stratified analysis was included to allow for insights on the development of cardiovascular outcomes in different age strata.

RESULTS

After exclusions, the study population comprised 20 240 patients with OSA (19.6% female; mean±SD age 39.9±7.7 years; Figure 1). Baseline characteristics are presented in Table 1. A higher proportion of female patients were diagnosed with obesity (17.4% versus 3.1%) and asthma (6.4% versus 2.5%).

A total of 5283 patients with OSA had an incident cardiovascular event during follow-up, see Table 2. A total of 80 314 sex- and age-matched individuals constituted the control cohort, 98.3% had 5 controls, and 1.7% had 4 controls available for comparisons.

At 1-year follow-up, 9.8% of the patients with obstructive sleep apnea suffered any cardiovascular event compared with 4.0% of controls, corresponding to a RR of 2.45 (95% CI, 2.32–2.59; see Table 3). At 5-year follow-up, 31.8% of the obstructive sleep apnea

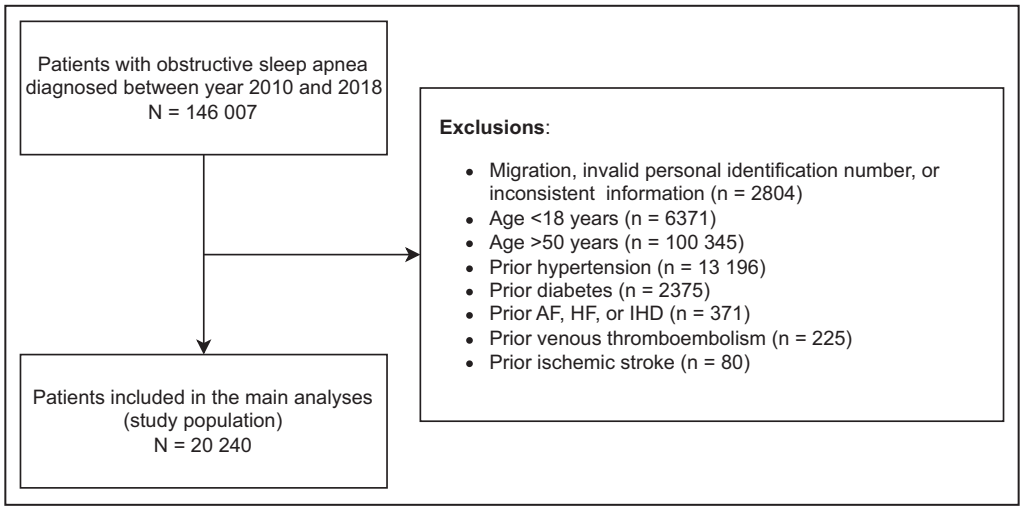

Figure 1. Flow chart of the study population.
AF indicates atrial fibrillation; HF, heart failure; and IHD, ischemic heart disease.

patients experienced any cardiovascular event compared with 16.5% of controls, RR 1.96 (95% CI, 1.90–2.02; see Figure 2).

The most frequent individual outcomes were hypertension and diabetes (see Table 2). After 1 year, 8.3% of the patients with OSA and 3.7% of the controls had incident hypertension (RR, 2.28 [95% CI, 2.15–2.42]) for patients with OSA compared with controls. At 5-year follow-up, the risk for incident hypertension was 27.3% for patients with OSA and 15.0% for controls (RR, 1.84 [95% CI, 1.78–1.90]). The risk of developing diabetes after 1-year follow-up was 1.4% for the patients with OSA and 0.2% for the controls (RR, 5.45 [95% CI, 4.54–6.55]). At 5-year follow-up, 6.8% of the patients with OSA had diabetes and 1.4% of the controls corresponding to an RR of 5.05 (95% CI, 4.60–5.54).

During follow-up, the risk of the remaining cardiovascular outcomes (atrial fibrillation, ischemic heart disease, ischemic stroke, heart failure, and venous thromboembolism) ranged between 1.7% for ischemic heart disease and 0.4% for heart failure. The corresponding risk for controls after 5-year follow-up was 0.9% for ischemic heart disease and 0.1% for heart failure. The cumulative risk of the cardiovascular subtypes and all-cause mortality is depicted in Figure 3. A total of 168 patients with OSA died during follow-up. After 5-year follow-up, 1.1% of the patients with OSA had died compared with 0.6% of the controls (RR, 1.81 [95% CI, 1.50–2.20]).

Sensitivity and Additional Analyses

In the sensitivity analysis stratifying on sex, both female and male patients with OSA had the highest risk of suffering any cardiovascular event compared with their controls (see Figure S1). After 5-year follow-up, 37.4% female patients had experienced a cardiovascular event

Table 1. Descriptive Characteristics of Patients Aged ≤50 Years With Obstructive Sleep Apnea

	Male patients with OSA	Female patients with OSA	All patients with OSA
No. (%)	16277	3963	20240
Age, y, mean±SD	39.9±7.6	39.9±8.3	39.9±7.7
18–29	11.6 (1883)	13.9 (549)	12.0 (2432)
30–39	29.9 (4869)	26.6 (1055)	29.3 (5924)
39–45	29.1 (4738)	27.0 (1071)	28.7 (5809)
46–50	29.4 (4787)	32.5 (1288)	30.0 (6075)
Asthma, % (N)	2.5 (407)	6.4 (254)	3.3 (661)
Chronic obstructive pulmonary disease, % (N)	0.7 (106)	1.2 (46)	0.8 (152)
Alcohol related liver disease, % (N)	n/a*	n/a*	0.1 (21)
Obesity, % (N)	3.1 (509)	17.4 (689)	5.9 (1198)
Statin treatment, % (N)	3.7 (598)	3.5 (137)	3.6 (735)

*Cells are masked owing to data legislation requirements of not presenting cells below 5 subjects.
n/a indicates not available; and OSA, obstructive sleep apnea.

Table 2. Cumulative 1- and 5-Year Risk of Cardiovascular Disease or Death by Obstructive Sleep Apnea Status

	1-y Follow-up				5-y Follow-up			
	OSA patients		Controls		OSA patients		Controls	
	Events (n)	Risk (%) (95% CI)	Events (n)	Risk (%) (95% CI)	Events (n)	Risk (%) (95% CI)	Events (n)	Risk (%) (95% CI)
Any cardiovascular event	1943	9.8 (9.4–10.2)	3110	4.0 (3.9–4.2)	5283	31.8 (31.1–32.6)	10026	16.5 (16.2–16.8)
Hypertension	1656	8.4 (8.0–8.7)	2826	3.7 (3.6–3.8)	4523	27.3 (26.6–28.0)	9116	15.0 (14.7–15.3)
Diabetes	270	1.4 (1.2–1.5)	179	0.3 (0.2–0.3)	1070	6.8 (6.4–7.3)	798	1.4 (1.3–1.5)
Atrial fibrillation	12	0.1 (0.0–0.1)	43	0.1 (0.0–0.1)	75	0.5 (0.4–0.6)	188	0.3 (0.3–0.4)
Ischemic heart disease	74	0.4 (0.3–0.5)	129	0.2 (0.1–0.2)	257	1.7 (1.5–1.9)	539	0.9 (0.8–0.9)
Ischemic stroke	10	0.1 (0.0–0.1)	33	-	73	0.5 (0.4–0.6)	196	0.3 (0.3–0.4)
Heart failure	20	0.1 (0.1–0.2)	26	-	68	0.4 (0.3–0.5)	100	0.2 (0.2–0.2)
Venous thromboembolism	29	0.1 (0.1–0.2)	63	0.1 (0.0–0.1)	149	1.0 (0.8–1.1)	280	0.4 (0.4–0.5)
All-cause mortality	43	0.2 (0.2–0.3)	50	0.1 (0.0–0.1)	168	1.1 (0.9–1.3)	334	0.6 (0.5–0.7)

OSA indicates obstructive sleep apnea.

(RR, 1.84 [95% CI, 1.74–1.96]) and 30.6% of the male patients (RR, 2.02 [95% CI, 1.95–2.09]; Figure S2; Table S2). When stratifying on obesity, patients with OSA had the highest risk of suffering any cardiovascular event regardless of obesity status. After 5-year follow-up, 41.2% of the patients with obesity and OSA had an event compared with 27.5% of the controls with obesity (RR, 1.44 [95% CI, 1.18–1.77]). For participants who were nonobese, the numbers were 31.4% and 16.5%, respectively (RR, 1.93 [95% CI, 1.87–1.99]). In the analysis using both primary and secondary codes for the cardiovascular diseases, similar risk estimates were found as in the primary analysis (data not shown). The age-stratified analysis showed that the risk of any cardiovascular events was highest among those aged 46 to 50 years (see Figure S3).

DISCUSSION

In this large nationwide cohort of adult patients aged ≤50 years with OSA, a total of 5283 patients experienced a cardiovascular event during 5 years of follow-up with a corresponding risk of 31.8% for the patients with OSA compared with 16.5% among the matched controls. The combined outcome was predominantly driven by incident hypertension and diabetes. For all cardiovascular outcomes and all-cause mortality, the risk was highest for patients with OSA compared with matched controls.

Adults with OSA not only have an increased risk of developing comorbid cardiovascular disease but also have worse outcomes related to cardiovascular disease.[16] Yet, in many studies investigating cardiovascular

Table 3. Relative Risk (95% CI) of Cardiovascular Events for Patients with Obstructive Sleep Apnea Compared With Controls

	Relative Risk* (95% CI)	
	1-y Follow-up	5-y Follow-up
Any cardiovascular event	2.45 (2.32–2.59)	1.96 (1.90–2.02)
Hypertension	2.28 (2.15–2.42)	1.84 (1.78–1.90)
Diabetes	5.45 (4.54–6.55)	5.05 (4.60–5.54)
Atrial fibrillation	1.20 (0.62–2.31)	1.32 (1.00–1.74)
Ischemic heart disease	2.16 (1.63–2.88)	1.96 (1.67–2.29)
Ischemic stroke	1.45 (0.70–3.01)	1.51 (1.14–2.01)
Heart failure	3.19 (1.76–5.77)	1.79 (1.29–2.50)
Venous thromboembolism	2.50 (1.57–3.99)	2.31 (1.87–2.86)
All-cause mortality	3.38 (2.24–5.12)	1.81 (1.50–2.20)

*Patients without obstructive sleep apnea (controls) as the reference in all categories.

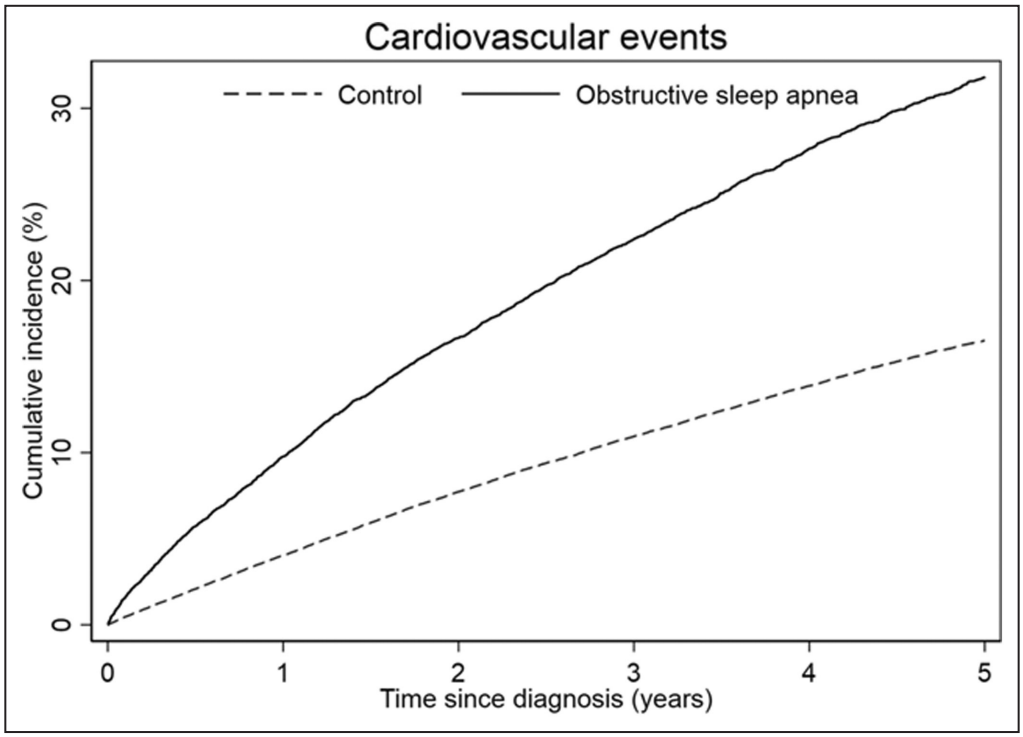

Figure 2. Cumulative incidence of any cardiovascular event by obstructive sleep apnea status at 5-year follow-up.

risk in patients with OSA, the cohorts studied were middle aged or older.[8,17–19] However, the disease is not restricted to individuals with advanced age. In a large French cohort study on more than 20 000 participants, an estimated prevalence of treated sleep apnea or high risk of OSA among 40- to 49-year-olds was 19.1%.[20] Given our study aim, we studied a relatively young cohort with a mean age of 40 years. Despite this selection of a presumably healthier group of patients with OSA, we observed a clear pattern in cardiovascular risk. The absolute risks for hypertension and diabetes were highest, and lower for atrial fibrillation, ischemic heart disease, ischemic stroke, heart failure, and venous thromboembolism. However, disregarding outcome subtype, cardiovascular event risk was consistently highest for patients with OSA and close to double that observed in controls.

The high cardiovascular event risk for patients with OSA is underscored when further focusing on all-cause mortality. Despite our relatively young cohort, the risk of all-cause mortality was close to double for patients with OSA compared with controls (RR, 1.81 [95% CI, 1.50–2.20] for patients with OSA). A higher mortality risk for patients with OSA has been described previously in older cohorts. In an observational study[21] of male patients followed up for a mean of 10.1 years after referral to sleep centers, untreated severe OSA was associated with an odds ratio (OR) of 2.87 (95% CI, 1.17–7.51) for fatal cardiovascular events compared with untreated healthy participants.[21] In the Wisconsin Sleep Study, individuals with severe OSA had an adjusted HR of 3.0 (95% CI, 1.4–6.3) for all-cause mortality compared with those with no OSA.[18] After excluding persons who had used CPAP treatment, the adjusted HR for severe versus no OSA was 5.2 (95% CI, 1.4–19.2).[18] The study participants were relatively young compared with other studies with a mean age of 48 years.

OSA and cardiovascular disease commonly cooccur, probably reflecting both causal relationships and shared prognostic factors, such as male sex, older age, and obesity. In our sensitivity analysis stratifying on obesity, both patients with and without obesity with OSA had the highest risk of suffering an event. The patients with obesity and OSA compared with controls with obesity had a 5-year RR of 1.44 indicating, that the higher risk of cardiovascular events among patients with OSA cannot solely be explained by obesity.

Of all the cardiovascular disease processes associated with OSA, the relationship with hypertension is possibly the best established. It has been shown that in patients with resistant hypertension, up to 80% may have OSA.[22] A dose-dependent relationship between the severity of OSA at baseline and the relative risk of developing hypertension during follow-up was described using the Wisconsin Sleep Cohort.[23] Relative to a reference category of an apnea–hypopnea index of 0, the ORs for the presence of hypertension during follow-up

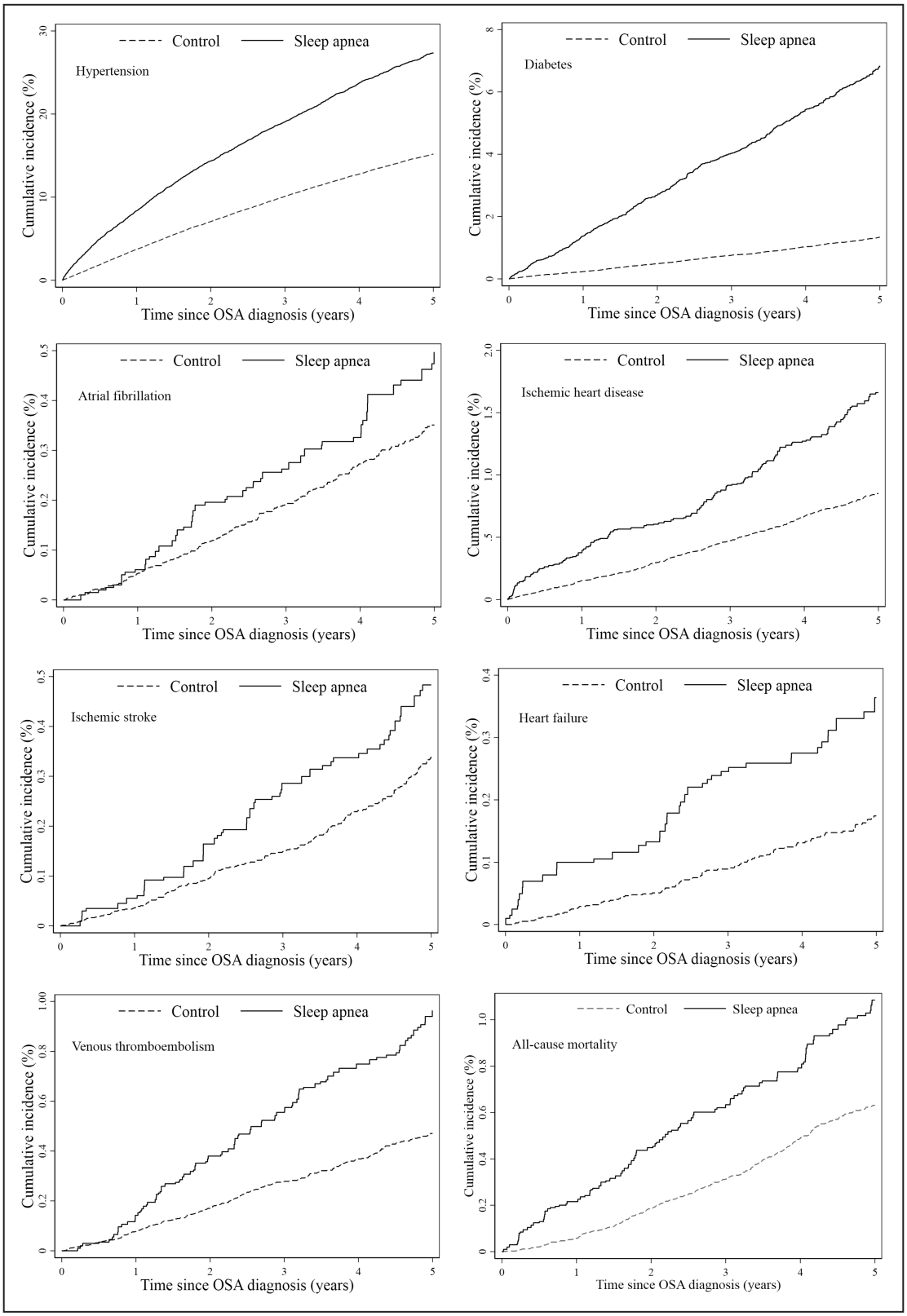

Figure 3. Cumulative incidence of individual cardiovascular events and all-cause mortality by obstructive sleep apnea status.

Please note, different scaling on the *y* axes. Ischemic heart disease including angina pectoris, acute myocardial infarction, subsequent myocardial infarction, complications following acute myocardial infarction, other acute ischemic heart diseases, and chronic ischemic heart disease. OSA indicates obstructive sleep apnea.

for patients with mild sleep apnea (apnea–hypopnea index of 5 to 15) was 2.03 (95% CI, 1.29–3.17), and 2.89 (95% CI, 1.46–5.64) for patients with an apnea–hypopnea index ≥15.0.[23] In our study, hypertension was the most frequent cardiovascular outcome, developed in more than a third of the patients with OSA during follow-up. OSA is a condition with potential for negative feedback in which it worsens conditions that may in turn worsen the OSA making defensive actions highly relevant.[5] Hypertension can easily be detected and often easily treated. Protective actions are required from several specialties ranging from general practitioners measuring and controlling the blood pressure or diabetes, otolaryngologists diagnosing and treating the OSA, and cardiologist diagnosing and treating the cardiovascular complications. Importantly, the aim of our study was descriptive rather than assessing causality. Therefore, a conclusion of a beneficial effect of OSA treatment or general disease avoidance on future risk of cardiovascular risk cannot be drawn from the study.

The second most frequent outcome in our study was diabetes. OSA has previously been associated with a greater likelihood of metabolic syndrome and type 2 diabetes, independently of adiposity level.[24] In a meta-analysis from 2015, the pooled ORs of metabolic syndrome in individuals with OSA for cross-sectional and case–control studies were 2.87 (95% CI, 2.41–3.42) and 2.56 (95% CI, 1.98–3.31), respectively. In a cohort study on 544 patients referred to a sleep center, an association was found between OSA and incident diabetes with an HR per quartile of 1.43 (95% CI, 1.10–1.86).[19] However, the sleep apnea group was older, with a mean age of 62.9 years versus 57.6 years, respectively. Among patients with more severe sleep apnea (upper 2 quartiles of severity), 60% had evidence of regular positive airway pressure use, and this treatment was associated with an attenuation of the risk of diabetes.[19]

Previous studies have demonstrated that atrial fibrillation and OSA often coexist.[6] Independently of obesity and other established risk factors, OSA diagnosis and severity have been independently associated with developing incident atrial fibrillation.[25] In management guidelines, OSA is highlighted as a risk factor in atrial fibrillation and recommends a sleep monitoring procedure for patients with atrial fibrillation suspected for obstructive sleep apnea.[26] In a Danish cross-sectional study from 2023, 126 unselected patients with atrial fibrillation without known OSA were recruited from an outpatient clinic.[17] The median age of the patients was 68 years. The study detected moderate to severe OSA in 56% of the patients.[17] In our study, 0.5% of the sleep apnea patients and 0.3% of the controls developed atrial fibrillation during follow-up. We suspect this relatively low risk in our study to be closely linked to our younger cohort.

In an American Heart Association scientific statement from 2021, patients with OSA should be treated with the goal of preventing or mitigating cardiovascular disease.[5] Our study indicates that this goal should not be limited to middle-aged and older patients usually included in studies but rather extended to also apply to younger patients. Of note, more studies on causal interference between OSA and cardiovascular disease is needed. However, we suspect that to finally achieve this goal an interdisciplinary action from both general practitioners, otolaryngologists, and cardiologists is needed to mitigate the consequences of cardiovascular disease in patients with OSA.

Limitations

With OSA being a recognized and often underdiagnosed disease, we expect some degree of misclassification stemming from undiagnosed OSA in the control group. This may cause an overestimation of the cardiovascular risk in the control group. Conversely, misclassification in the group with OSA may lead to underestimation of the associated cardiovascular risk. Whether misclassification is influenced by age is unknown. However, the misclassification was limited using diagnosis codes recently validated, ensuring a positive predictive value of at least 89%.[13] Also, we recognize some degree of misclassification between the outcome categories based on an overlap of medical indications and diagnosis. For obesity, there is a recognized high validity of the *ICD-10* codes for overweight/obesity when recorded; however, completeness of coding is low.[27] Finally, we were not able to differentiate in types of diabetes. The diabetic outcome was defined using *ICD-10* codes and use of antidiabetic medication. We excluded patients aged <18 years and patients with existing diabetes and therefore expect most patients to develop type 2 diabetes during follow-up.[28]

The disease severity (apnea–hypopnea index) and the oxygen desaturation index among the patients with OSA was unknown. Therefore, we were not able to investigate the association of severity of OSA and risk of cardiovascular disease.

The nationwide Danish health registries have been demonstrated to have nearly complete follow-up reducing the likelihood of bias introduced by subjects lost to follow-up. Our study included a large number of events, which further minimizes the risk of random variation.

CONCLUSIONS

In this large nationwide cohort, the risk of developing cardiovascular events for young patients diagnosed with OSA is substantial. To prevent cardiovascular disease progression, accumulation of cardiovascular risk

factors, and mortality, risk stratification and prevention strategies should be considered for these patients.

ARTICLE INFORMATION

Received November 10, 2023; accepted March 11, 2024.

Affiliations

Department of Otolaryngology, Head and Neck Surgery and Audiology, Aalborg University Hospital, Aalborg, Denmark (I.E.A.); Department of Otolaryngology, Head and Neck Surgery and Audiology, Aarhus University Hospital, Aarhus, Denmark (J.B.); Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (G.P.); Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK (G.Y.L.); Department of Clinical Medicine, Danish Center for Health Services Research, Aalborg University, Aalborg, Denmark (G.Y.L., P.B.N.); and Department of Cardiology (P.B.N.), Aalborg University Hospital, Aalborg, Denmark.

Sources of Funding

None.

Disclosures

Gregory Piazza has received research grant support from BMS/Pfizer, Janssen, Alexion, Bayer, Amgen, BSC, Esperion, 1R01HL164717–01; and has an advisory role with BSC, Amgen, BCRI, PERC, NAMSA, BMS, Janssen, Regeneron. Gregory Y. H. Lip is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in atrial fibrillation, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 899871. Peter B. Nielsen has received speaking fees from Daiichi-Sankyo; consulting fees from Daiichi-Sankyo and Bayer; and grant support from BMS/Pfizer and Daiichi-Sankyo. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S2
Figures S1–S3

REFERENCES

1. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5:136–143. doi: 10.1513/pats.200709-155MG
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165:1217–1239. doi: 10.1164/rccm.2109080
3. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcántara C, Jackson CL, Williams MA, Redline S. Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep*. 2015;38:877–888. doi: 10.5665/sleep.4732
4. Jennum P, Larsen P, Cerqueira CS, Schmidt T, Tønnesen P. The Danish national database for obstructive sleep apnea. *Clin Epidemiol*. 2016;8:573–576. doi: 10.2147/CLEP.S101969
5. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, Mehra R, Bozkurt B, Ndumele CE, Somers VK. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;144:E56–E67. doi: 10.1161/CIR.0000000000000988
6. Manuel A. Obstructive sleep apnoea and atrial fibrillation: a key omission in guidelines. *Br J Cardiol*. 2022;29:10. doi: 10.5837/bjc.2022.010
7. Butt M, Dwivedi G, Khair O, Lip GYH. Obstructive sleep apnea and cardiovascular disease. *Int J Cardiol*. 2010;139:7–16. doi: 10.1016/j.ijcard.2009.05.021
8. Yeboah J, Redline S, Johnson C, Tracy R, Ouyang P, Blumenthal RS, Burke GL, Herrington DM. Association between sleep apnea, snoring, incident cardiovascular events and all-cause mortality in an adult population: MESA. *Atherosclerosis*. 2011;219:963–968. doi: 10.1016/j.atherosclerosis.2011.08.021
9. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehra R, Pack AI, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol*. 2017;69:841–858. doi: 10.1016/j.jacc.2016.11.069
10. Melamed KH, Goldhaber SZ. Obstructive sleep apnea. *Circulation*. 2015;132:e114–e116. doi: 10.1161/CIRCULATIONAHA.114.014458
11. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39:30–33. doi: 10.1177/1403494811401482
12. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi: 10.1007/s10654-014-9930-3
13. Ofverlind E, Bille J, Overvad TF, Nielsen PB, Albertsen IE. Validity of obstructive sleep apnea diagnoses in the Danish National Patient Register. *Dan Med J*. In press.
14. Wacholder S, Mclaughlin JK, Silverman DT, Mandel JS, Wacholer S, Mclaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies I. *Principles. Am J Epidemiol*. 1992;135:1019–1028. doi: 10.1093/oxfordjournals.aje.a116396
15. Cummings P. The relative merits of risk ratios and odds ratios. *Arch Pediatr Adolesc Med*. 2009;163:438–445. doi: 10.1001/archpediatrics.2009.31
16. Yaggi H, Mohsenin V. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001;163:19–25. doi: 10.1164/ajrccm.163.1.2001008
17. Jensen MH, Dalgaard F, Rude Laub R, Gottlieb V, Nielsen OW, Hansen J, Hansen ML, Jennum P, Lamberts M. Prevalence of sleep apnea in unselected patients with atrial fibrillation by a home-monitoring device: the DAN-APNO study. *IJC Heart Vasc* 2023;47:0 101219, DOI: 10.1016/j.ijcha.2023.101219.
18. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*. 2008;31:1071–1078.
19. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. *Am J Med*. 2009;122:1122–1127. doi: 10.1016/j.amjmed.2009.04.026
20. Balagny P, Vidal-Petiot E, Renuy A, Matta J, Frija-Masson J, Steg PG, Goldberg M, Zins M, D'Ortho M-P, Wiernik E. Prevalence, treatment and determinants of obstructive sleep apnoea and its symptoms in a population-based French cohort. *ERJ Open Res*. 2023;9:00053-02023. doi: 10.1183/23120541.00053-2023
21. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365:1046–1053. doi: 10.1016/S0140-6736(05)71141-7
22. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, Leung RST, Bradley TD. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens*. 2001;19:2271–2277. doi: 10.1097/00004872-200112000-00022
23. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378–1384. doi: 10.1056/NEJM200005113421901
24. Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, Ji Q. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. *BMC Pulm Med*. 2015;15:105. doi: 10.1186/s12890-015-0102-3
25. Cadby G, McArdle N, Briffa T, Hillman DR, Simpson L, Knuiman M, Hung J. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. *Chest*. 2015;148:945–952. doi: 10.1378/chest.15-0229
26. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
27. Gribsholt SB, Pedersen L, Richelsen B, Thomsen RW. Validity of ICD-10 diagnoses of overweight and obesity in Danish hospitals. *Clin Epidemiol*. 2019;11:845–854. doi: 10.2147/CLEP.S214909
28. Xu G, Liu B, Sun Y, Du Y, Snetselaar LG, Hu FB, Bao W. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. *BMJ*. 2018;362:k1497. doi: 10.1136/bmj.k1497