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Cardiovascular consequences of obstructive sleep apnea in women: a historical cohort study☆

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Abstract

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Author's contributions

All co-authors were involved in the following: study conception and design, interpretation of data, revising the dataset creation plan and the manuscript critically for the accuracy and important intellectual content and/or final approval of the version to be published.
TK additionally was involved in the following: literature search, obtaining administrative data, analyses of data and drafting of the manuscript.
AG additionally was involved in ethics board' application and obtaining administrative data.
AM participated in data synthesis/interpretation and manuscript preparation/revisions.
RL additionally was involved in ethics boards' application and is a custodian of the sleep laboratory dataset from which the study sample was extracted.
RL, AG and TK had access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

All authors have no potential conflict of interest to disclose.
The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.08.021.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.08.021.

Guarantor statement

The lead and senior authors, Drs. Tetyana Kendzerska and Andrea Gershon, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Objective/Background: Evidence on sex differences in the association between obstructive sleep apnea (OSA) and cardiovascular outcomes is limited and controversial. We conducted a historical cohort study to investigate this relationship.

Patients/methods: Clinical data on adults who underwent sleep study at a large urban academic hospital (Toronto, Canada) between 1994 and 2010 were linked to provincial health administrative data from 1991 to 2015. We fit Cox regressions to investigate the association between OSA severity and a cardiovascular composite outcome (all-cause mortality or hospitalization due to myocardial infarction, stroke, heart failure or atrial fibrillation), controlling for risk factors and stratifying by sex.

Results: A total of 10,149 subjects were included: median age of 49 years, 38% women. Over a median of 9.3 years, 1782 (18%) participants developed an outcome. The association between percentage of sleep time spent with oxygen saturation <90% and outcome was stronger for women (HR for IQR, 3 vs 0% = 1.30, 1.19–1.42) than for men (HR for IQR = 1.13, 1.06–1.21) (p for interaction = 0.01) in the adjusted model. Stratifying by sex, oxygen desaturations and heart rate in sleep were significant predictors in both men and women, while presence of daytime sleepiness, sleep efficiency and periodic leg movements in sleep were predictive in women but not in men.

Conclusions: In a large clinical cohort with suspected OSA, the impact of OSA as measured by the degree of nocturnal oxygen desaturation on the composite outcome was found to be greater in women than in men. We also found a different predictive ability of OSA-related factors by sex.

Keywords

Obstructive sleep apnea; Cardiovascular events; Nocturnal oxygen desaturation; Sex difference; Prognosis

1. Introduction

Obstructive sleep apnea (OSA) is a prevalent chronic sleep disorder characterized by repetitive episodes of complete or partial obstruction of the upper airway resulting in oxygen desaturation or arousal from sleep. OSA affects 34% of men and 17% of women between the ages of 30 and 70 years [1]. There is growing evidence that sex differences exist with respect to the mechanisms of OSA development [2–8], presenting OSA symptoms [9,10], polysomnographic (PSG) features, treatment effects and long-term health consequences [11].

OSA has been shown to be associated with cardiovascular consequences, a relationship which could be mediated via intermittent hypoxemia, arousals from sleep, and intrathoracic pressure swings [12,13]. Prior studies indicate that OSA is an independent risk factor for cardiovascular disease and all-cause mortality among men [14]. However, the data are less definitive for these associations amongst women with some studies demonstrating no increased cardiovascular risk among women with OSA (the Sleep Heart Health Study [SHHS]) [15–17], and others demonstrating either the same (the Spanish prospective clinical cohort, the Multi Ethnic Study of Atherosclerosis [MESA] cohort) [18,19] or even higher risk in women than men with OSA (the Atherosclerosis Risk in Communities (ARIC) Study, the SHHS, and the Wisconsin Sleep Cohort Study) [20,21]. Potential explanations for the

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variability in results include lack of statistical power due to inclusion of small numbers of women and a lower cardiovascular event rate in women versus men, differential effects of OSA on CV events in men versus women [14], and the chance finding of an association in a non-prespecified subgroup analyses. Previously, we found an association between time spent with oxygen saturation (SaO_2)<90% and a composite outcome being significantly stronger for women than for men [22]; however, the event rate in women was insufficient to evaluate the association between OSA and our composite outcomes in women alone. Nor did our composite outcome include atrial fibrillation (AF) which has been shown to be associated with OSA [23,24].

We conducted the current study to evaluate the association between OSA severity (as measured by AHI, degree of nocturnal oxygen desaturation and other OSA-related factors) and long-term cardiovascular outcomes in women as compared to men. We hypothesized that in women, severity of OSA as measured by the degree of nocturnal oxygen desaturation would be independently associated with long-term CV consequences and that the impact of OSA would be greater than in men. We also hypothesized, that insomnia, arousals and periodic leg movement in sleep would be more likely to predict cardiovascular outcome in women [25,26] than in men.

2. Material and methods

2.1. Study design

We conducted a historical cohort study using linked clinical and provincial health administrative data. Participants were followed from their first diagnostic sleep study to the end of March 2015, or the occurrence of the primary outcome, whichever occurred first.

The ethics committees of St. Michael's Hospital (REB#11–124c) and Sunnybrook Research Institute (Data Sharing Agreement #601) approved the study.

2.2. Population of interest

The St. Michael's Hospital (Toronto, Canada) sleep database includes a large set of clinical and demographic variables as well as variables from full in-laboratory polysomnography (PSG) prospectively collected from all consecutive adults with suspected OSA who underwent a first diagnostic sleep study between 1994 and 2010. Details about this cohort are reported previously [22]. Details on definitions of key variables collected in the sleep laboratory are presented in the Appendix (Table A.1).

2.3. Provincial health administrative databases

ICES as a not-for-profit research institute holds copies of high-quality health administrative datasets (https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx) which are routinely evaluated for data quality [27,28]. As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data. Residents of Ontario have universal public health insurance under the Ontario Health Insurance Plan (OHIP), the single payer for all medically necessary services. Hospital and emergency department visits, surgical procedures were identified using the Canadian Institute for Health

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Information (CIHI) Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System [29]. The DAD Abstracting Manual [30] is available on CIHI's website. The manual provides standardized data element definitions, collection instructions, valid data values, validation rules and edits. Claims data for positive airway pressure (PAP) therapy were obtained through the Ontario Assistive Devices Program (ADP) database [31] (details on PAP therapy prescription in Ontario are provided in the Appendix, Text A.1). Mortality and demographic data were determined from the Registered Persons Database. These datasets were linked using unique encoded identifiers.

2.4. Outcomes

The primary composite outcome was defined using provincial health administrative data as the first of (i) hospitalization due to myocardial infarction (MI), stroke, AF [32] or exacerbation of chronic heart failure; (ii) a cardiac revascularization procedure; or (iii) all-cause death. Hospitalization was chosen as a validated, well-defined, reproducible and standardized measure of interest to patients, physicians, and policy decision-makers. We included mortality in our primary outcome because deaths (a competing event) may preclude cardiovascular events or greatly alter the chances to observe them, resulting in a biased estimate of risk for cardiovascular events as a stand-alone outcome. Details on outcome definitions were utilized in our previous studies [22,24] and are presented in the Appendix (Table A.2).

2.5. Predictors

The following OSA-related variables, derived from the clinical data, were potential predictors in our statistical models: (i) clinical symptoms of OSA, (ii) family history of snoring or OSA, (iii) neck circumference, and (iv) all available indices from the PSG. To avoid choosing arbitrary thresholds for PSG indices, they were kept as continuous variables.

OSA severity was defined by both (i) apnea-hypopnea index (AHI), and (ii) percentage of sleep time spent with SaO_2< 90%.

The AHI was defined as the number of apneas and hypopneas per hour of sleep. The definition of hypopnea consisted of: (i) a clear decrease of more than 50% of the baseline amplitude of breathing during sleep for at least 10 s (regardless of oxygen saturations); or (ii) a clear amplitude reduction of breathing during sleep for at least 10 s, that does not reach the above criterion but is associated with either an SaO_2 drop of ≥3% or an arousal [33]. Severity of OSA by AHI was categorized as mild (AHI of 5–14.9/h), moderate (AHI of 15e30/h), or severe (AHI >30/h) OSA [34].

To replicate the effect of previously identified predictors, we considered sleep time spent with SaO_2 as both a continuous and categorical variable (>9 min vs ≤ 9 min). At least 10 min of sleep time spent with SaO_2 <90% corresponds to the 75th percentile of the variable distribution [22].

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2.6. Potential confounders and risk factors

The following variables extracted from clinical data were considered as potential confounders and risk factors: age, sex, body mass index (BMI), and self-reported smoking (current, ex-smoker and never smoked). Comorbidities at baseline (hypertension, diabetes, stroke, MI, chronic heart failure [CHF], depression, COPD, asthma, arrythmias, and cancer) and alcohol use disorder were identified from health administrative data [35–41] in the five-year period before the diagnostic sleep study. Neighborhood income [42] and rural vs urban status were derived from health administrative data at the time of the diagnostic sleep study. Information on acceptance of PAP treatment [43], was derived from the ADP database. Definitions used in our previous study were utilized [22,24] and provided in the Appendix (Table A.2).

2.7. Statistical analysis

We used statistical approaches similar to those of our previously published studies [22]. Descriptive statistics were stratified by sex. We used multivariable Cox regression models to investigate the relationships between predictors and our composite outcome. For continuous explanatory variables, we used log transformations if nonlinearity was observed; the resulting standardized HRs compared the 75th and 25th percentiles (interquartile range, IQR) of a variable distribution, allowing comparison of the HRs on a common scale [44,45].

We previously found that sleep time spent with SaO_2<90%, total sleep time, number of awakenings per night, periodic leg movements in sleep, heart rate in sleep, and daytime sleepiness were significant predictors of the composite outcome controlling for known cardiovascular risk factors: age, sex, smoking status and comorbidities at baseline (hypertension, diabetes, stroke, MI, CHF and COPD) [22]. Thus, first we confirmed the effect of these variables using extended follow-up time and the updated definition of the outcome as we view the stability of our findings as important (details on the importance of replicating a predictive model are provided in the Appendix, Text A.2). Next, given that the predictive ability of the selected previously variables may change with extended follow-up time and the updated definition of the outcome, we replicated our previous approach for variable selection, using a systematic review [14], expert opinion and backward step-down variable deletion [46] (details on the variable selection process are provided in the Appendix, Text A.3), to update statistical models for the total sample and stratifying by sex. We evaluated a priori-defined interactions between measures of OSA severity and sex [44]. Model performance was assessed using R^2 and Harrell's C-index [44]. We used the bootstrap for internal validation and reported bootstrap-corrected C index and R^2.

2.8. Secondary analyses

Given that information on acceptance, but not adherence with PAP treatment was available, the final models were refitted on untreated individuals.

Missingness ranged from 0.69% (AHI) to 10.1% (time spent with SaO_2<90%). Previously we used multivariate imputation by chained equations approach to impute missing values [47]. Given that our results were previously confirmed on imputed datasets [22] and for a

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unified presentation, we presented our findings on the original dataset (completed case analyses).

All statistical analyses were performed in the secure environment following provincial privacy standards using R Version 3.1.2 (www.r-project.org).

3. Results

3.1. Cohort description

In total, 10,149 subjects were included: median age 49 (IQR: 39–59) years, 38% women, median BMI 29 kg/m^2 (IQR: 25–33), and median apnea-hypopnea index (AHI) 16/h (IQR: 6–35) with 21% (30% of women and 16% of men) of individuals with AHI < 5/h and 30% (18% of women and 36% of men) of individuals with AHI > 30/h. Details on this cohort are available elsewhere [22]. At baseline, women were of similar age and BMI but were more likely to have severe comorbidity and were less likely to be current smokers than men (Table 1). In terms of OSA related characteristics, women were more likely to report waking unrefreshed, morning headaches and restless legs; men were more likely to report snoring and witnessed apnea. Women tended to have a milder REM-predominant OSA, while men were more likely to have severe position-dependent OSA given similar age and BMI: the total AHI: 10.5/h in women vs. 20.1/h in men; REM AHI: 23.7/h in women vs. 26.2/h in men; supine AHI: 12.6/h in women vs. 33.0/h in men (Table 1).

3.2. Survival analyses

3.2.1. Unadjusted—Over a median follow-up of 9.3 years, 1782 (17.6%) participants (516 [13.3%] of women) developed the cardiovascular outcome. Among those who developed the outcome, men had significantly more severe OSA as measured by total AHI and while supine, but women tended to have more severe OSA in REM sleep (Table 1). Importantly, there was no significant difference in the degree of nocturnal hypoxemia between sexes. In the total sample, unadjusted ten-year event-free survival was significantly ($p < 0.0001$) lower in men (80.4%, 79.3–81.4) as compared to women (86.6%, 85.4–87.8). Event-free survival differed significantly (p values < 0.01) by sex among those with no OSA or with mild OSA (Fig. 1). However, among those with moderate and severe OSA (Fig. 1), event-free survival was not significantly different in men and women ($p > 0.12$). Similar patterns were observed for the degree of nocturnal oxygen desaturations (Fig. 2).

3.2.2. Adjusted: multivariable Cox regression models—Aside from awakenings in sleep, we confirmed previous findings that time spent with SaO_2 <90%, sleep time, periodic leg movements, heart rate in sleep, and daytime sleepiness were significant predictors for an outcome in the fully adjusted model (Table A.3). We also confirmed that the association between measures of the degree of nocturnal oxygen desaturation and the composite outcome was significantly (p values for interactions ≤0.01) stronger for women than for men (Table A.3). Specifically, controlling for confounders, the association between percentage of sleep time spent with SaO_2<90% and the composite outcome was significantly (p value for interaction = 0.01) stronger for women (HR for IQR, 3 vs 0% = 1.30, 1.19–1.42) than for men (HR for IQR = 1.13, 1.06–1.21). Stratifying by sex, the degree of nocturnal

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oxygen desaturation and heart rate in sleep remained significantly associated with the outcome in both sexes controlling for age, smoking and income status, alcohol use disorder, BMI, and comorbidities at baseline (hypertension, diabetes, stroke, MI, CHF, COPD, arrythmias, and cancer) (Table 2). Other sleep-related factors such as daytime sleepiness, sleep efficiency and periodic leg movements in sleep were significant predictors in women but not in men (Table 2, Figure A.1). Income status was a significant predictor in men but not in women, while smoking was more strongly associated with the composite outcome in women as compared to men.

Controlling for total sleep time, number of awakenings, periodic leg movements and mean heart rate in sleep, daytime sleepiness and traditional cardiovascular risk factors, the effect of AHI on cardiovascular outcome was non-significant (HR for IQR, 35 vs 6 = 1.04, 0.94–1.14) in the total sample, contrasting with a significant association with individuals untreated with PAP (HR = 1.14, 1.01–1.30). This finding suggests a potential protective effect of PAP treatment. The interaction term between AHI and sex was not significant (p = 0.17).

4. Discussion

In a large clinical cohort with suspected sleep apnea, we confirmed our hypothesis that in women, severity of OSA as measured by degree of nocturnal oxygen desaturation is associated with cardiovascular consequences after accounting for other traditional cardiovascular risk factors. Further, the association in women is significantly stronger than in men suggesting that women may be more susceptible to the impact of nocturnal hypoxemia. We also found other important sex-based differences in the association between other OSA-related factors and cardiovascular outcomes. Degree of nocturnal hypoxemia and heart rate in sleep were significant predictors in both men and women, while presence of daytime sleepiness, sleep efficiency and periodic leg movements in sleep were predictors in women but not in men. These results should be considered in future studies and clinical practice supporting growing evidence that routine PSG data can be used to identify physiological phenotypes that capture risk of cardiovascular outcomes otherwise missed by conventional OSA severity classification as based on AHI [48].

Our study adds important new information to the body of evidence supporting both the greater impact of OSA in women and the development of predictive models separately for women and men. A limited number of studies have specifically investigated the association between OSA and cardiovascular outcomes and mortality in women. As we reported previously this variability may be explained by limited statistical power due to small numbers of women with severe OSA and a lower cardiovascular event rate in women versus men [14]. Findings from the overall SHHS suggested that OSA severity may be associated with all-cause mortality [15], incident coronary artery disease and HF [16] or stroke [17] in men but not in women. Important differences in study design and cohort could explain these dissimilar findings. The SHHS is a community-based cohort study where most participants had a milder or no OSA, while we have studied a clinical cohort referred with suspected OSA with diverse of severity. In addition, different outcome measures may also have influenced the results. Notably, in a later study using both the SHHS and ARIC cohorts, the opposite results have been shown. Specifically, that among women, but not men, OSA

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severity was independently associated with the composite of mortality, incident cardiovascular disease, or left ventricular hypertrophy [21]. One of the possible explanations of this controversy proposed by authors was that the SHHS combined sample was younger and experienced lower overall event rates in comparison with the sample in ARIC [21]. Our findings are also consistent with the Wisconsin Sleep Cohort Study where greater mortality was reported for middle-aged women with OSA, but not for men [20].

The observed differential effects by sex of OSA on our composite outcome may be explained by multiple factors. Sex difference has been shown in cardiac adaptation [49,50]. Women with OSA have demonstrated greater endothelial dysfunction [51], platelet activation [52], higher propensity to develop pulmonary [53] and systemic hypertension, and greater heart rate response associated with arousals [49] than men. Women were also more likely to have REM predominant OSA which has been shown to be independently associated with hypertension [54,55] and in those with prevalent cardiovascular disease with a higher incidence of a composite cardiovascular outcome [56]. In addition, sub-optimal compliance with a PAP treatment in women with OSA compared to men [57] might explain our findings. Although speculative, we cannot exclude the possibility that earlier presentation of OSA in men as compared to women combined with a longer lifetime exposure to OSA may offer some protection from OSA-related injury. Finally, a higher hazard associated with nocturnal oxygen desaturation in women may be largely a function of their superior survival in the absence of significant nocturnal oxygen desaturation as compared to men (Fig. 2).

To our knowledge, this is the first study to address the association between various metrics associated with OSA and cardiovascular outcomes in a large cohort of women and men with suspected OSA. Low sleep efficiency by itself has been shown to be associated with an increased risk of cardiovascular events and all-cause mortality [58]. Results from a meta-analysis based on prospective cohort studies suggested that the risk of cardio-cerebral vascular events associated with some insomnia symptoms may be greater for women than for men [59]. The underlying mechanism of this finding is not completely understood, but one of the potential explanations is the impact of OSA which has been shown to cause most awakenings in individuals with chronic insomnia [60]. An increase in periodic leg movements in sleep associated with arousals has been shown to be associated with an increase cardiovascular risk [61,62], and potentially can be considered as a separate OSA-phenotype [48]. It is noteworthy that women whose AHI worsened over time have been also shown had an increase in periodic leg movements in sleep; this relationship was not found in men [63]. Available data also suggest an association between excessive daytime sleepiness and mortality [64] as well increased risk for prevalent and incident cardiovascular events [65]. Men and women have been shown to answer questions on daytime sleepiness differently [66,67] with depression and insomnia contributing more to daytime sleepiness in women than in men [67]. We also found a higher level of depression/anxiety in women than in men in our cohort (84% vs 68%) as well as a higher use of hypnotics (36% vs 25%).

Our study has multiple strengths including a large number of women with long follow-up and a large number of cardiovascular events. We used consistent scoring criteria over time, and validated algorithms to define cardiovascular outcomes and comorbidities at baseline

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from health administrative data. Finally, our cohort had a higher proportion of people with severe OSA.

As with any observational study single-center study, there are limitations related to generalizability and availability of data. Data regarding certain potential confounders (eg, presence of obesity hypoventilation syndrome, level of cholesterol, race, and adherence to PAP therapy) were not available. Although we used validated algorithms to define some variables from health administrative data, these algorithms are characterized by certain specificity and sensitivity resulting in possible misclassification bias. If differential, this bias could go in either direction, while if non-differential, the estimated effect is more likely to fall below the true value. However, our statistical model with traditional cardiovascular risk factors had high predictive and discriminative ability, indicating that the majority of important predictors were included. Furthermore, we do not have accepted definitions of intermittent nocturnal hypoxemia that includes both SaO_2 variability and severity. As such, we cannot exclude the possibility that nocturnal oxygen desaturation in our cohort was related to underlying cardiopulmonary disease such as CHF and COPD. However, the association between nocturnal hypoxemia and our composite outcome remained significant after controlling for the presence of CHF, COPD, smoking status and other comorbidities. Night-to-night variability and instrumentation errors may be involved in the assessment of OSA; however, OSA classification has been shown to remain largely stable over several months to years [68,69].

Using population data we recently demonstrated that female sex was associated with longer wait times for both PSG and CPAP in Ontario (Canada) [70], which may be explained by non-classical OSA presentation in women as compared to men (eg, with symptoms of restless legs or insomnia) [71–73]. Our findings of higher risk for all-cause mortality and cardiovascular hospitalizations in women with untreated OSA, suggests the need for a screening tool for OSA in women and increasing awareness in primary health care physicians to better recognize presentation of OSA in this population. Given that OSA-related factors other than AHI are potentially important predictors of the cardiovascular outcomes in women, even those with low AHI may benefit from PAP treatment. This requires confirmation in future studies.

5. Conclusions

This study provides further insight into the sex variation of the OSA outcome. In a large clinical cohort with suspected sleep apnea, severity of OSA (as measured by the degree of nocturnal oxygen desaturation) was independently associated with cardiovascular consequences in women. This association was stronger in women as compared to men. Further, a different predictive ability of OSA-related factors by sex was found. These findings have potential implications for screening, risk stratification and treatment of OSA in both women and men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Other contributions

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Abbreviations list

ADG	Aggregated diagnosis groups (The Johns Hopkins ACG System, Version 10)
ADP	Assistive Devices Program
AF	Atrial fibrillation
AHI	Apnea-hypopnea index
ArI	Arousal index
ARIC	The Atherosclerosis Risk in Communities Study
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
ESS	The Epworth Sleepiness Score
HR	Hazard ratio
ICES	The former Institute for Clinical Evaluative Sciences: https://www.ices.on.ca/About-ICES/Mission-vision-and-values

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IQR	Interquartile range
MESA	The Multi Ethnic Study of Atherosclerosis cohort
OHIP	Ontario Health Insurance Plan
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PLMI	Periodic leg movement index
PSG	Polysomnography
REM	Rapid eye movement sleep
SaO_2	Oxygen saturation
SHHS	The Sleep Heart Health Study
TST	Total sleep time

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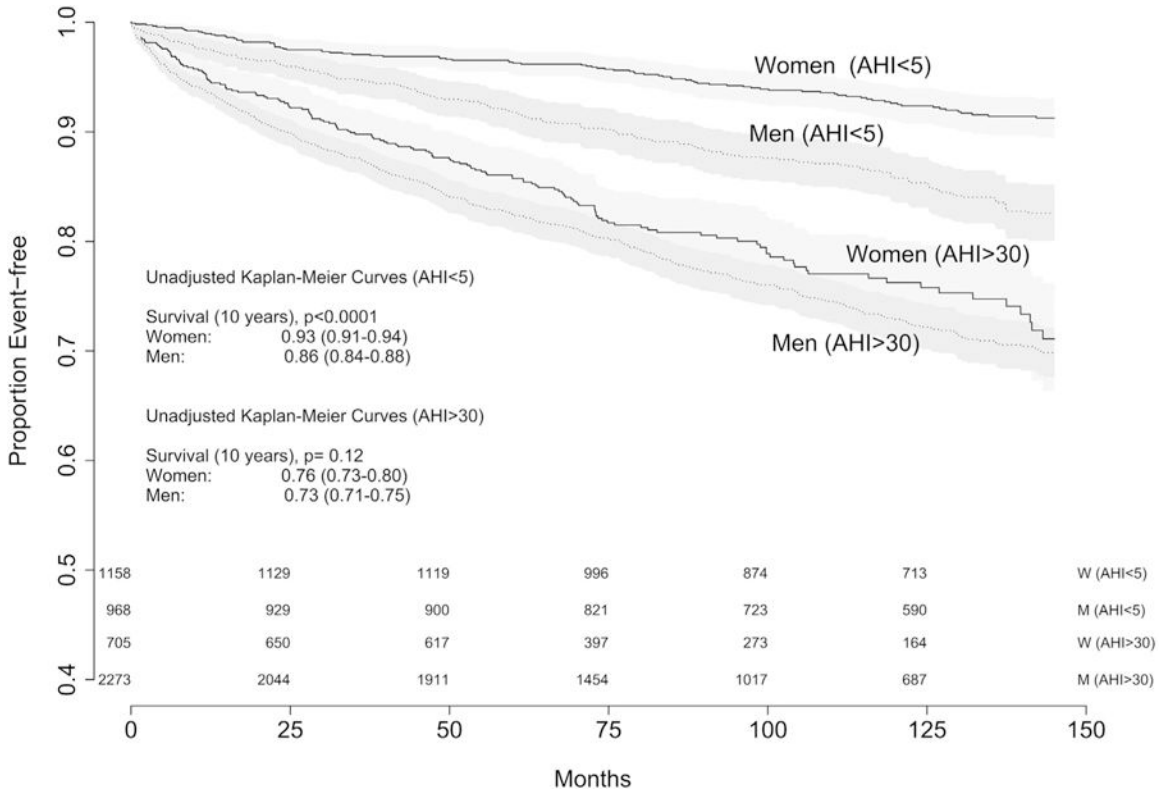

Fig. 1.

Unadjusted Kaplan–Meier survival curves stratified by sex in individuals: (i) without obstructive sleep apnea (apnea-hypopnea index [AHI] < 5 events per hour); (ii) with severe obstructive sleep apnea (apnea-hypopnea index >30 events per hour). The numbers at risk are presented above the x-axis.

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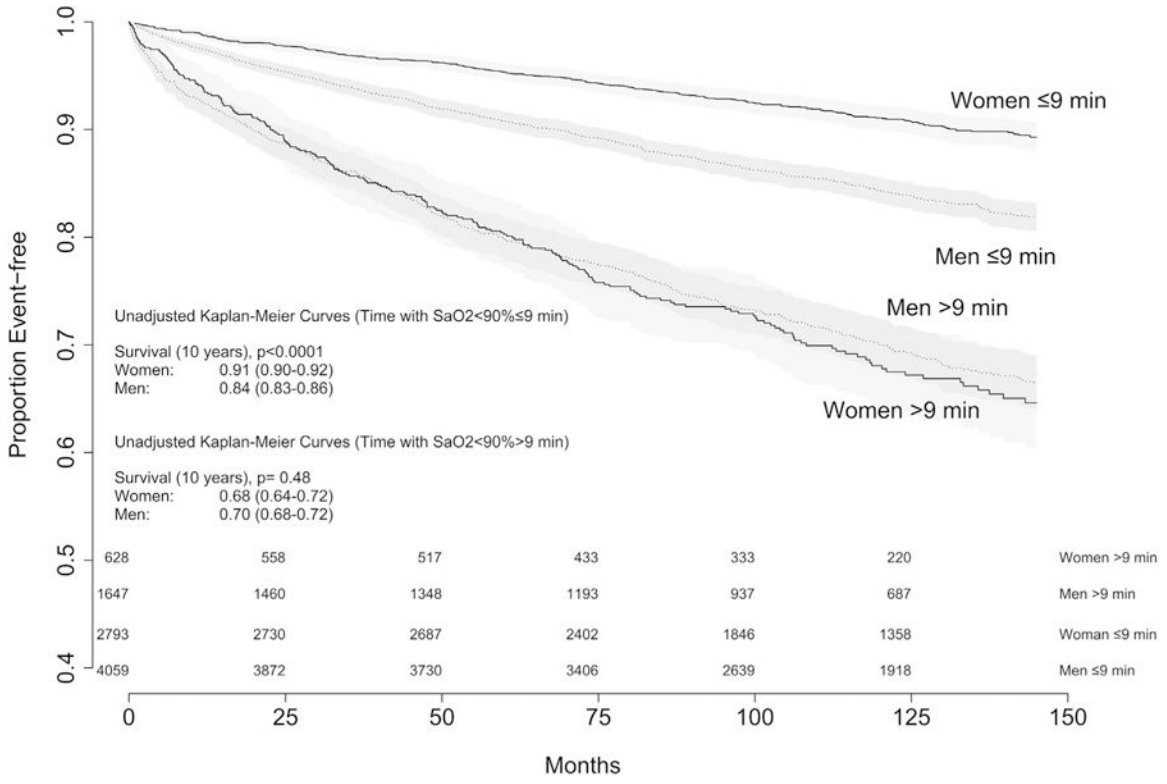

Fig. 2.

Unadjusted Kaplan–Meier survival curves stratified by sex in individuals who spent: (i) ≤ 9 min with oxygen saturation below 90%; (ii) > 9 min with oxygen saturation below 90%. The numbers at risk are presented above the x-axis.

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Table 1

Characteristics of individuals with suspected obstructive sleep apnea at the time of a full-night diagnostic sleep study (baseline) and among those who developed a composite cardiovascular outcome stratified by sex.[a]

Characteristics	Total Sample		Individuals who developed a composite cardiovascular outcome	
	Women (n = 3865)	Men (n = 6284)	Women (n = 516)	Men (n = 1266)
Demographics				
Age, years, median (IQR)	50 (40–59)	49 (39–59)	63 (52–74)	62 (53–71)
BMI, median (IQR)	29 (25–36)	29 (26–33)	32 (27–39)	30 (27–34)
Social History, n (%)				
Smoking status				
Current	614 (17)	1225 (21)	99 (21)	219 (19)
Ex-smokers	554 (16)	1315 (23)	93 (20)	393 (35)
Income status				
Lowest quintile (Q1)	841 (22)	1149 (18)	141 (27)	261 (21)
Highest quintile (Q5)	963 (25)	1902 (31)	108 (21)	358 (28)
Alcohol use disorder	169 (4.4)	447 (7.1)	31 (0.6)	114 (0.9)
Prior comorbidity, n (%)				
Hypertension	1352 (35.0)	2240 (35.7)	313 (60.7)	774 (61.1)
Diabetes	563 (14.6)	911 (14.5)	180 (34.9)	410 (32.4)
Stroke	83 (2.1)	140 (2.2)	35 (0.7)	71 (0.6)
Myocardial infarction	81 (2.1)	319 (5.1)	43 (0.8)	190 (1.5)
Chronic heart failure	188 (4.9)	438 (7.0)	131 (2.5)	325 (2.6)
COPD	485 (12.6)	773 (12.3)	192 (3.7)	372 (2.9)
Arrhythmias	705 (18.2)	1082 (17.2)	189 (3.7)	496 (3.9)
Cancer	210 (5.4)	310 (4.9)	75 (1.5)	136 (1.1)
Level of comorbidities per ADG category				
Low	680 (18)	2191 (35)	34 (7)	226 (18)
Moderate	1608 (42)	2512 (40)	166 (32)	463 (37)
High	1577 (41)	1581 (25)	316 (61)	577 (46)
Polysomnographic indices, median (IQR)				
Sleep efficiency, %	81.9 (70.3–89.3)	81.3 (68.9–89.1)	74.0 (59.0–85.2)	72.7 (58.2–83.0)

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Characteristics	Total Sample		Individuals who developed a composite cardiovascular outcome	
	Women (n = 3865)	Men (n = 6284)	Women (n = 516)	Men (n = 1266)
Total sleep time, hours	5.8 (5.0–6.5)	5.7 (4.8–6.4)	5.2 (4.1–6.0)	5.1 (4.2–6.0)
Sleep latency, min	13.4 (6.3–26.3)	9.9 (5.0–19.8)	15.2 (7.1–30.2)	11.0 (5.6–21.9)
REM, %	16.9 (12.0–21.4)	16.8 (11.8–21.3)	14.7 (8.5–20.2)	14.9 (8.9–20.1)
Supine, %	34.9 (13.9–58.7)	33.6 (14.1–58.3)	28.2 (6.6–59.5)	25.8 (7.0–54.7)
AHI in TST, events/hour	10.5 (3.8–23.9)	20.1 (8.5–40.7)	16.0 (6.3–36.2)	26.9 (10.2–49.7)
REM AHI, events/hour	23.7 (7.0–47.7)	26.2 (9.4–49.1)	30.0 (5.3–54.9)	26.5 (8.4–49.7)
Supine AHI, events/hour	12.6 (2.3–34.2)	33.0 (10.6–67.6)	17.6 (1.7–49.8)	41.2 (11.2–74.8)
Mean SaO_2 in TST, %	95.3 (93.8–96.5)	94.7 (93.3–95.8)	93.6 (91.5–95.3)	93.8 (92.0–95.1)
Time spent with SaO_2<90%, min	0.1 (0.0–3.8)	0.9 (0.0–13.2)	5.4 (0.2–45.2)	5.2 (0.3–37.5)
Time spent with SaO_2<90%, %	0.0 (0.0–1.3)	0.3 (0.0–4.2)	1.9 (0.1–16.9)	1.9 (0.1–14.8)
PLMI in TST, events/hour	0.9 (0.0–10.7)	1.2 (0.0–14.4)	5.2 (0.0–25.9)	7.0 (0.0–32.8)
ArI in TST, events/hour	18.7 (11.8–30.6)	26.5 (15.9–43.7)	25.3 (13.7–45.0)	32.6 (19.7–53.6)
Number of awakenings in TST	23 (16–31)	27 (19–38)	25 (17–34)	30 (21–47)
Sleep apnea related self-reported symptoms, n (%)				
The total ESS, 0–24	8 (5–12)	8 (5–12)	8 (4–12)	8 (4–12)
Daytime sleepiness	1350 (38)	2307 (39)	239 (52)	563 (49)
Snoring	2883 (81)	5357 (91)	379 (83)	1011 (89)
Stopping breathing	1021 (30)	2867 (50)	129 (31)	532 (48)
Wake unrefreshed	2980 (83)	3979 (68)	349 (75)	678 (60)
Morning headaches	1490 (41)	1251 (21)	186 (40)	202 (17)
Restless Legs	1538 (43)	1864 (32)	248 (53)	443 (39)
Memory impact	2420 (68)	2996 (51)	297 (64)	568 (50)
Treatment, n (%)				
Hypnotic medications at baseline	1321 (36)	1484 (25)	195 (41)	344 (29)
Treated with PAP, n (%)	1253 (32)	2763 (44)	209 (41)	549 (43)

Abbreviations: ADG, aggregated diagnosis groups (The Johns Hopkins ACG System, Version 10); AHI, apnea-hypopnea index; ArI – arousal index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESS, the Epworth Sleepiness Score; IQR, interquartile range; PAP, positive airway pressure treatment; PLMI, periodic leg movement index; REM, rapid eye movement sleep; SaO_2, oxygen saturation; TST, total sleep time.

[a]Numbers may not add to total because of missing values.

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Table 2

The relationship between obstructive sleep apnea related variables adjusted for known cardiovascular risk factors and the composite cardiovascular outcome in the final Cox regression multivariable model applying variable selection techniques. Estimates are presented as hazard ratios and 95% confidence intervals.

	Total Sample	Women	Men
Daytime sleepiness (Yes vs No)	1.22 (1.10–1.37)	–	–
The ESS score/24 (12 vs 5)	–	1.23 (1.07–1.42)	–
% of sleep time spent with SaO_2<90% (3 vs 0)	1.16 (1.10–1.24)	1.27 (1.14–1.42)	1.11 (1.04–1.19)
PLMI, events/h (13 vs 0)	1.12 (1.02–1.23)	1.18 (1.00–1.41)	–
Sleep Efficiency, % (70 vs 89)	–	1.16 (1.02–1.31)	–
Stage 1, % (14 vs 5)	1.04 (1.01–1.08)	–	1.04 (1.00–1.07)
Heart rate, mean/TST, bpm (70 vs 57)	1.27 (1.18–1.36)	1.15 (1.00–1.32)	1.37 (1.26–1.49)
Age, years (59 vs 40)	3.07 (2.74–3.45)	2.64 (2.14–3.25)	3.44 (3.01–3.93)
Sex (M vs F)	1.46 (1.28–1.66)		
BMI, kg/m^2 (33 vs 25)	1.02 (0.95–1.10)	1.05 (0.93–1.17)	1.00 (0.91–1.11)
Ex-smoker vs never	1.12 (0.98–1.28)	1.13 (0.86–1.47)	1.15 (0.99–1.34)
Current vs never	1.65 (1.41–1.93)	2.25 (1.72–2.96)	1.44 (1.19–1.74)
Income Status: Q1 vs Q5	1.24 (1.05–1.46)	–	1.28 (1.06–1.55)
Prior comorbidities			
Hypertension (Yes vs No)	1.20 (1.06–1.37)	1.45 (1.15–1.82)	1.18 (1.02–1.38)
Diabetes (Yes vs No)	1.57 (1.38–1.79)	1.68 (1.33–2.13)	1.54 (1.33–1.79)
Stroke (Yes vs No)	–	1.60 (1.01–2.52)	1.33 (1.00–1.78)
Myocardial infarction (Yes vs No)	1.50 (1.26–1.79)	1.58 (1.08–2.31)	1.45 (1.19–1.77)
Chronic heart failure (Yes vs No)	2.23 (1.90–2.62)	3.03 (2.26–4.05)	2.09 (1.74–2.52)
COPD (Yes vs No)	1.38 (1.20–1.57)	2.03 (1.62–2.56)	1.17 (1.00–1.37)
Arrhythmias (Yes vs No)	1.44 (1.26–1.65)	1.35 (1.06–1.70)	1.49 (1.27–1.75)
Cancer (Yes vs No)	1.23 (1.03–1.46)	1.36 (1.00–1.85)	–
Alcohol use disorder (Yes vs No)	–	–	1.11 (0.88–1.40)
Bootstrap-corrected R^2	0.24	0.24	0.26
Bootstrap-corrected Harrell's C-index	0.84	0.85	0.83

Abbreviations: PLMI, periodic limb movement index; PSG, polysomnography; SaO_2, oxygen saturation; TST, total sleep time.