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SCIENTIFIC INVESTIGATIONS

Prospective association of obstructive sleep apnea risk factors with heart failure and its subtypes in postmenopausal women: The Women's Health Initiative

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Study Objectives: The relationship between obstructive sleep apnea (OSA) and heart failure (HF) incidence in postmenopausal women has been understudied, given the limited representation of women in heart failure studies. We investigated the relationship between OSA risk factors and HF and its subtypes in postmenopausal women.

Methods: We performed a prospective analysis on the adjudicated HF outcomes in the Women's Health Initiative from enrollment (1993–1998) to September 30, 2016. HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) were defined as adjudicated acute HF hospitalization with EF ≥ 45% or < 45%, respectively. We employed Cox regression to examine the association between OSA risk factors and symptoms (individually and using a summary risk score) and time to first hospitalized HF.

Results: Of 42,362 women, 2,205 (5.21%) developed all HF, 1,162 (2.74%) women developed HFpEF, and 679 (1.60%) developed HFrEF. Individual OSA risk factors and symptoms, including obesity (hazard ratio = 1.33, 95% confidence interval [CI] 1.20–1.48), snoring (hazard ratio = 1.30, 95% CI 1.16–1.46), and hypertension (HR = 1.45, 95% CI 1.35–1.56), were positively associated with risk of HF and HFpEF, but only hypertension was associated with HFrEF. When examined as a summary risk score compared with those with none of the OSA risk factors, presence of each additional factor was significantly associated with increased risk of hospitalized HF in a dose-response fashion for HFpEF (*P* trend < .001), but not HFrEF (*P* trend = .26).

Conclusions: OSA risk factors and symptoms were associated with HFpEF, but not HFrEF, among postmenopausal women and are largely dependent on body mass index, snoring, and hypertension.

Keywords: obstructive sleep apnea, postmenopausal women, HFpEF, HFrEF

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) has been associated with cardiovascular mortality and morbidity, including heart failure. Its association with heart failure in postmenopausal women is understudied given the underrepresentation of women in heart failure studies. Given that the prevalence of OSA is high in postmenopausal women, we aim to evaluate the association of risk factors and symptoms of OSA with heart failure in this population.

Study Impact: Findings demonstrated that risk factors and symptoms of OSA were associated with heart failure with preserved ejection fraction but not heart failure with reduced ejection fraction in postmenopausal women. Early recognition of these risk factors and symptoms should be considered, especially in those with heart failure with preserved ejection fraction.

INTRODUCTION

Heart failure (HF) is associated with considerable morbidity, increased mortality, and societal economic burden.[1] HF is different in women compared to men. The onset of HF in women is later compared with men, although the lifetime absolute risk is similar between the 2 groups.[2] Therefore, the investigation of treatable comorbid conditions commonly occurring with HF, such as obstructive sleep apnea (OSA) is particularly important among women.

OSA is a common chronic disorder that often requires lifelong care. If left untreated, OSA may be associated with increased all-cause and cardiovascular mortality even after accounting for adiposity.[3] Furthermore, in addition to OSA being widely underdiagnosed, the prevalence of it in HF is high.[4] Sex-specific differences exist in the association between

OSA and cardiovascular disease.[5] OSA is approximately 2 to 3 times more common in men than women, although the gap narrows at menopause in women.[6] Increase in morbidity and mortality risk due to OSA after menopause may be attributed in part to hormonal changes related to variation in estrogen and progesterone.[7] In women, the diagnosis of OSA may be difficult given presentation of disease at later ages (increase in prevalence after menopause), underreporting of symptoms,[8] and differences in physiologic changes compared with men.[9]

Patients who present to a sleep clinic with OSA commonly complain of symptoms such as loud snoring, choking, gasping for air, periods of breathing cessation, morning headaches, diaphoresis, sleep fragmentation, and excessive daytime sleepiness.[10] Additionally, a patient may have established risk factors of OSA, which include obesity, large neck diameter, large tongue, airway with high Mallampati score, retrognathia, hypertension, and insulin resistance.[10] Although women may present with symptoms such as insomnia, morning headaches, and depression that are different compared with men, typical symptoms and risk factors such as obesity, snoring, and daytime sleepiness are used in validated questionnaires that apply to both sexes.

Overall, research on the relationship between OSA and heart failure incidence in postmenopausal women has been limited, and women have been underrepresented in heart failure studies.[11] Additionally, the prevalence of OSA is high in postmenopausal women. As postmenopausal women have a high risk of undiagnosed OSA, this leads to fewer opportunities for studying these relationships and potentially intervening at an earlier stage. The aim of our study was to investigate the relationship between OSA, as defined by presence of OSA risk factors and symptoms, and HF incidence in postmenopausal women.

METHODS

The Women's Health Initiative (WHI) cohort consists of 161,808 multiethnic women aged 50–79 years recruited in 40 clinical centers nationwide between 1993 and1998 (ClinicalTrials.gov identifier: NCT00000611). All 161,808 women who were enrolled completed the same baseline questionnaire. Detailed information on the recruitment process was published previously.[12–14] Out of the complete cohort, a subset of 44,174 women had adjudicated HF outcomes from enrollment to September 30, 2016. After excluding women with self-reported HF at baseline (n = 684) and those with missing OSA risk factors or covariates (n = 1,128), the final analytical sample consisted of 42,362 women. Institutional review board approval was obtained at the participant's respective institution. The participants completed informed consent documentation.

Reported HF hospitalizations were confirmed by trained adjudicators. It involved extracting health information from hospital records, which included new symptoms of HF, previous history of HF, general medical history, medications, a detailed physical exam, diagnostic blood, radiographic examination, and results of clinical procedures, including cardiac catheterization and coronary angiography. HF was defined as definite acute hospitalized HF, possible acute hospitalized HF, chronic stable HF, HF unlikely, or unclassifiable. Based on available 2-dimensional echocardiography data and other cardiac tests, such as coronary angiography and cardiac magnetic resonance imaging in the medical record, heart failure with reduced ejection fraction (HFrEF) was defined as EF < 45% and HFpEF was defined as EF ≥ 45%. This definition has been used in WHI studies and has good agreement with other population studies.[15]

The following risk factors and symptoms for OSA were examined in this study: obesity, snoring, poor sleep quality, sleep fragmentation (waking up multiple times during the night), daytime sleepiness, and hypertension. These are used in the Berlin and STOP-Bang questionnaires, which have been validated to reliably predict OSA and were used in a previous study.[16,17] The symptoms are part of the WHI Insomnia Rating Scale, which has been previously validated.[18]

Obesity was defined according to National Institutes of Health criterion as having a body mass index (BMI) of greater than 30 kg/m^2.[19] For snoring, poor sleep quality, sleep fragmentation, and daytime sleepiness, participants were asked if they snored; about the sleep quality defined as average, sound or restful, or restless or worse; if they woke up several times a night; and if they fell asleep during quiet activities, respectively. Hypertension was defined either by self-report from participants of having untreated or treated hypertension, being on antihypertensive medications, having a systolic blood pressure of > 139 mm Hg, or having a diastolic blood pressure of > 90 mm Hg.

The following selected covariates were included in our study based on their association with obstructive sleep apnea and HF and their use in previous sleep-related research studies. Race-ethnicity, socioeconomic status, which included education and household income, and marital status were defined the same as previously described.[20]

Age, blood pressure, BMI, and waist-to-hip ratio were defined as continuous variables from measurements obtained at baseline. Pertinent past medical history included diabetes mellitus (on diabetic medications), hyperlipidemia, coronary heart disease, HF, and atrial fibrillation (AF). Renal failure was defined as having an estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2. The Charlson Comorbidity Index[21] was used to predict the 10-year mortality risk based on the following comorbidities: peripheral arterial disease, asthma, emphysema, gastric or duodenal ulcer, systemic lupus erythematosus, rheumatoid arthritis, liver disease, leukemia, lymphoma, and solid tumors. The index score ranged from 1 to 3 (1 = no comorbid condition, 2 = 1 comorbid condition, and 3 = 2 or more comorbid conditions).

The following behavioral risk factors were included: smoking (never, former, current), alcohol consumption (gram standardized servings per day), and recreational physical activity (metabolic equivalent hours per week).

Hormone therapy (HT) use with estrogen and/or progesterone was defined as never, former, or current. Use of sleep medications was defined as taking any kind of sleep aid or alcohol at bedtime. Hysterectomy was defined as having a history of the procedure.

Since the diagnosis of OSA was not available in the WHI, we utilized a summary score consisting of 6 risk factors and symptoms associated with OSA as a proxy for this exposure of interest. Briefly, each of the 6 risk factors was defined as a binary

Table 1—Characteristics of WHI sample by heart failure.

Variable	Overall	No HF	All HF	*P* Value	HFpEF	*P* Value	HFrEF	*P* Value
n	42,362	40,157	2,205		1,162		679	
Age*, year	62.5 (7.2)	62.3 (7.2)	66.8 (6.8)	**< .0001**	67.0 (6.7)	**< .0001**	66.2 (7.1)	
Body mass index*, kg/m^2	29.6 (6.4)	29.6 (6.3)	31.2 (6.9)	**< .0001**	31.8 (7.1)	**< .0001**	30.0 (6.0)	
Systolic BP*, mm Hg	129 (17.7)	129 (17.5)	137 (19.0)	**< .0001**	137 (19.5)	**< .0001**	136 (18.0)	
Diastolic BP*, mm Hg	76 (9.3)	76 (9.3)	76 (9.9)	.2165	76 (10.3)	.0710	77 (9.3)	
Waist/hip ratio*	.823 (.081)	.821 (.081)	.846 (.080)	**< .0001**	.850 (.078)	**< .0001**	.840 (.074)	
Race				**< .0001**		**< .0001**		**< .0001**
Black	13,757 (32.5)	20,057 (50.0)	1,462 (66.3)		801 (68.9)		426 (62.7)	
White	21,519 (50.9)	13,172 (32.9)	585 (26.5)		269 (23.2)		208 (30.6)	
Hispanic	6,070 (14.4)	5,957 (14.9)	113 (5.1)		68 (5.9)		28 (4.1)	
Asian	516 (1.2)	497 (1.2)	19 (0.9)		11 (1.0)		5 (.7)	
Other	445 (1.1)	419 (1.0)	26 (1.2)		13 (1.1)		12 (1.8)	
Education				**< .0001**		**.0009**		**.0218**
Less than high school	4,351 (10.3)	4,129 (10.3)	222 (10.1)		112 (9.6)		71 (10.5)	
High school graduate	7,701 (18.2)	7,250 (18.1)	451 (20.5)		233 (20.1)		149 (21.9)	
Some college	16,611 (39.2)	15,690 (39.1)	921 (41.8)		503 (43.3)		263 (38.7)	
College graduate	13,315 (31.4)	12,725 (31.7)	590 (26.8)		307 (26.4)		186 (27.4)	
Income, % annual household				**< .0001**		**< .0001**		**< .0001**
< $20,000	10,083 (23.8)	9,408 (23.4)	675 (30.6)		346 (29.8)		212 (31.2)	
$20,000–$49,999	18,368 (43.4)	17,344 (43.2)	1,024 (46.4)		547 (47.1)		311 (45.8)	
≥ $50,000	11,080 (26.2)	10,706 (26.7)	374 (17.0)		202 (17.4)		114 (16.8)	
Marital status				**< .0001**		**< .0001**		.0526
Married or partnered	22,873 (54.4)	21,800 (54.7)	1,073 (49.0)		562 (48.5)		341 (50.7)	
Single/divorced/widowed	19,204 (45.6)	18,085 (45.3)	1,119 (51.1)		596 (51.5)		332 (49.3)	
Smoking status				**< .0001**		**< .0001**		**.0009**
Never	21,542 (51.5)	20,551 (51.8)	991 (45.5)		518 (45.2)		310 (46.3)	
Former	16,034 (38.3)	15,131 (38.2)	903 (41.5)		487 (42.5)		266 (39.7)	
Current	4,248 (10.2)	3,966 (10.0)	282 (13.0)		142 (12.4)		94 (14.0)	
Alcohol use*, servings/wk	1.88 (4.82)	1.89 (4.81)	1.88 (5.09)	.9750	1.90 (5.25)	.9540	2.00 (5.13)	
Diabetes mellitus	3,025 (7.2)	2,627 (6.6)	398 (18.1)	**< .0001**	205 (17.7)	**< .0001**	127 (18.7)	**< .0001**
Coronary heart disease	1,256 (3.0)	1,040 (2.6)	216 (9.8)	**< .0001**	104 (9.0)	**< .0001**	81 (11.9)	**< .0001**
Atrial fibrillation	1,570 (3.7)	1,414 (3.5)	156 (7.1)	**< .0001**	78 (6.7)	**< .0001**	43 (6.3)	**.0003**
e-GFR<60 (out of n = 2,2742)	1,225 (3.7)	1,055 (5.0)	170 (10.8)	**< .0001**	95 (11.1)	**< .0001**	43 (9.2)	**.0003**
Modified Charlson Comorbidity Index				**< .0001**		**< .0001**		**<.0001**
0	25,534 (60.3)	24,630 (61.3)	904 (41.0)		489 (42.1)		276 (40.7)	
1	10,385 (24.5)	9,679 (24.1)	706 (32.0)		377 (32.4)		219 (32.3)	
2+	6,443 (15.2)	5,848 (14.6)	595 (27.0)		296 (25.5)		184 (27.1)	
Hysterectomy	18,587 (43.9)	17,502 (43.6)	1,085 (49.2)	**< .0001**	573 (49.3)	.0002	332 (48.9)	**.0079**
Current HT use	7,960 (19.4)	7,720 (19.8)	240 (11.3)	**< .0001**	132 (11.8)	**< .0001**	69 (10.5)	**< .0001**
Use sleep medications				**< .0001**		**< .0001**		.0622
None	32,996 (78.1)	31,372 (78.4)	1,624 (73.8)		852 (73.5)		507 (74.8)	
≤2 times/wk	5,838 (13.8)	5,508 (13.8)	330 (15.0)		173 (14.9)		102 (15.0)	
≥3 times/wk	3,405 (8.1)	3,159 (7.9)	246 (11.2)		135 (11.6)		69 (10.2)	
Physical activity*, metabolic equivalent-h/wk	10.56 (13.17)	10.63 (13.22)	9.28 (12.25)	**< .0001**	9.01 (12.12)	**.0001**	9.15 (11.68)	

(continued on following page)

Table 1—Characteristics of WHI sample by heart failure. (continued)

Variable	Overall	No HF	All HF	*P* Value	HFpEF	*P* Value	HFrEF	*P* Value
Individual OSA risk factors								
Body mass index				**< .0001**		**< .0001**		**.0160**
≥30 kg/m^2	17,429 (41.1)	16,296 (40.6)	1,133 (51.4)		633 (54.5)		310 (45.7)	
Snoring				.0675		.1203		.3869
Yes, ≥ 3 times/wk	8,427 (19.9)	7,955 (19.8)	472 (21.4)		252 (21.7)		144 (21.2)	
Sleep quality				.0533		.1059		.2180
Restless or worse	7,238 (17.1)	6,828 (17.0)	410 (18.6)		219 (18.9)		128 (18.9)	
Sleep fragmentation				**< .0001**		**< .0001**		**.0033**
Yes, ≥ 3 times/wk	16,167 (38.2)	15,169 (37.8)	998 (45.3)		540 (46.5)		296 (43.6)	
Daytime sleepiness				.2107		.3065		.8186
Yes, ≥ 3 times/wk	12,372 (29.2)	11,702 (29.1)	670 (30.4)		355 (30.6)		201 (29.6)	
Hypertension				**< .0001**		**< .0001**		**< .0001**
Yes	16,312 (38.5)	15,076 (37.5)	1236 (56.1)		644 (55.4)		370 (54.5)	
OSA Score (# OSA risks present)				**< .0001**		**< .0001**		**< .0001**
0	7,418 (17.5)	7,196 (17.9)	222 (10.1)		112 (9.6)		80 (11.8)	
1	11,460 (27.1)	10,969 (27.3)	491 (22.3)		249 (21.4)		158 (23.3)	
2	10,932 (25.8)	10,328 (25.7)	604 (27.4)		315 (27.1)		187 (27.5)	
3	7,355 (17.4)	6,866 (17.1)	489 (22.2)		270 (23.2)		141 (20.8)	
4	3,664 (8.7)	3,398 (8.5)	266 (12.1)		139 (12.0)		77 (11.3)	
5	1,298 (3.1)	1,189 (3.0)	109 (4.9)		64 (5.5)		30 (4.4)	
6	235 (.6)	211 (.5)	24 (1.1)		13 (1.1)		6 (.9)	

*Variables are continuous: mean and standard deviation presented. Other variables are categorical: count and percentages presented. Significant *P* values are indicated in bold. BP = blood pressure, eGFR = estimated glomerular filtration rate, HF = heart failure, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HT = hormone therapy, OSA = obstructive sleep apnea.

variable, as follows: BMI ≥ 30 kg/m^2, snoring ≥ 3 times per week, restless or worse sleep quality, waking up at night ≥ 3 times per week, daytime sleepiness ≥ 3 times per week, and previous diagnosis of hypertension. The summary score ranged from 0 to 6, depending on the number of risk factors present in any order.

Continuous variables were summarized as means with their respective standard deviations, and categorical variables were expressed as frequencies with proportions. Each OSA risk factor was dichotomized into the absence and presence of the risk factor, as defined above.

We calculated person-time follow-up from the date of baseline study enrollment in the WHI observational study or randomization in the WHI clinical trials, until first diagnosis of acute hospitalized HF (whichever subtype occurred first), death from any cause, loss to follow-up, or end of the follow-up interval, whichever came first. Incident HF events and person-time follow-up were used to compute age-adjusted incidence rates of each HF endpoint and its respective confidence interval.

Inverse probability weighting of the population was employed to account for the fact that not all participants in the full cohort had HF adjudicated. Multivariable Cox proportional hazards regression models were utilized to examine the relationship between OSA risk factors and symptoms and incident HF hospitalization and account for confounding. Variables kept in the final model were included if they changed the exposure estimates by more than ±10% or were risk factors or symptoms supported by previous studies to obtain a parsimonious model. The risk factor summary score (referent defined as having no risk factors) was used as a proxy to model OSA. To examine for competing risk either due to death or having another type of HF, we conducted an analysis using a competing-risk model as previously described by Fine and Gray.[22]

AF and HT use have been demonstrated to be associated with the risk of OSA and HF.[23,24] We examined effect modification of each of these variables with the OSA score. A *P* value of < .05 for the interaction was considered to be significant.

Since obesity and hypertension are associated with OSA and HF, sensitivity analyses were performed to clarify this association independent of BMI and hypertension. We performed the sensitivity analyses in 2 ways. First, we examined the relationship of daytime sleepiness and snoring with HF after adjusting for only BMI in one model and for BMI and hypertension in another model. Second, we modified the OSA score by excluding BMI and hypertension and then adjusting for only BMI in one model and for BMI and hypertension in another model.

All analyses were conducted using SAS v9.4 (Cary, NC).

RESULTS

Baseline characteristics of the study population are presented in **Table 1**. The average age was 62.5 years, 50.9% were white,

Table 2—Incident and age-adjusted incident rates of heart failure by type.

OSA Risk Factors	Person-Years	Events	Age Adjusted Incidence Rate	95% CI
All heart failure				
Overall	580,595	2,205	3.976	(3.956, 3.995)
Obesity	230,595	1,133	5.101	(5.061, 5.141)
Snore	115,205	472	4.208	(4.162, 4.255)
Daytime sleepiness	166,934	670	4.162	(4.124, 4.199)
Sleep fragmentation	218,929	998	4.762	(4.725, 4.800)
Poor sleep quality	96,348	410	4.449	(4.394, 4.504)
Hypertension	208,752	1,236	6.157	(6.109, 6.206)
Heart failure with preserved ejection fraction				
Overall	580,595	1,162	2.095	(2.085, 2.105)
Obesity	230,595	633	2.851	(2.829, 2.874)
Snore	115,205	252	2.249	(2.225, 2.274)
Daytime sleepiness	166,934	355	2.206	(2.187, 2.227)
Sleep fragmentation	218,929	540	2.581	(2.561, 2.602)
Poor sleep quality	96,348	219	2.374	(2.346, 2.404)
Hypertension	208,752	644	3.210	(3.185, 3.235)
Heart failure with reduced ejection fraction				
Overall	580,595	679	1.219	(1.213, 1.225)
Obesity	230,595	310	1.394	(1.383, 1.406)
Snore	115,205	144	1.272	(1.259, 1.285)
Daytime sleepiness	166,934	201	1.240	(1.229, 1.252)
Sleep fragmentation	218,929	296	1.411	(1.400, 1.422)
Poor sleep quality	96,348	128	1.380	(1.364, 1.397)
Hypertension	208,752	370	1.832	(1.818, 1.846)

CI = confidence interval, OSA = obstructive sleep apnea.

32.5% were black, 14.4% were Hispanic/Latina, and 1.2% were Asian. Mean BMI of the study population was 29.6 kg/m^2. The proportion of women with diabetes mellitus, coronary heart disease, and AF was higher in the HF, HFpEF, and HFrEF groups compared with those without HF. Additionally, women in the HF groups were more likely to be former or current smokers. Women with all HF, HFpEF, or HFrEF had more snoring, sleep fragmentation, and higher prevalence of hypertension compared with those with no HF.

Of the 2,205 all HF participants, 458 had unknown HF type. Of the remaining 1,747 participants, 1,469 had either a transthoracic or a transesophageal echocardiogram to determine HF type. The EF for the other 278 participants were determined through coronary angiography, cardiac radionuclide ventriculogram, cardiac magnetic resonance imaging, cardiac clinical trial, or stress test. The total number of incident HF, HFpEF, and HFrEF events were 2,205, 1,162, and 679, respectively, as presented in **Table 2**. The highest age-adjusted incidence rates of HF, HFpEF, and HFrEF were found in those with hypertension. The individual risk factors were associated with higher age-adjusted incident HFpEF rates compared with the incident HFrEF rates.

Age-adjusted and fully adjusted hazard ratios (HRs) of incident all HF, HFpEF, and HFrEF according to OSA risk factors are presented in **Table 3**. In the fully adjusted models, increasing BMI was associated with all HF and HFpEF but not HFrEF.

Those who snored or who did not know if they snored had a modest increase in the estimated risk of all HF or HFpEF but not HFrEF compared with those who did not snore. The amount of HF risk between those who snored ≤ 2 times per week or ≥ 3 times per week was similar. In the fully adjusted model, restless or worse sleep quality was not associated with an increased risk of all HF, HFpEF, and HFrEF compared with sound or restful sleep quality. Likewise, frequent sleep fragmentation and daytime sleepiness were not associated with an increased risk of all HF or HFpEF but not HFrEF after accounting for confounders. Lastly, those with hypertension had a modest increase in HF risk compared with those without hypertension.

Associations between the OSA risk factor and symptom score (used as a proxy for OSA presence) with all HF, HFpEF, and HFrEF are presented in **Table 4**. In the fully adjusted model for all HF, each incremental increase in the number of OSA risk factors was associated with all HF in a linear dose-response fashion (P trend < .001).

Each additional OSA risk factor compared with no risk factors was significantly associated with increased risk of HFpEF in a linear dose response fashion (P trend < .001). As for HFrEF, each additional OSA risk factor was associated with

Table 3—Unadjusted and adjusted hazard ratios of incident heart failure across OSA risk factors.

OSA Risk Factor	Unadjusted Model			Age-Adjusted Model			Fully Adjusted* Model		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
All heart failure									
Body mass index									
< 25 kg/m^2 (referent)	1.000	—	—	1.000	—	—	1.000	—	—
25 to < 30 kg/m^2	1.228	(1.125, 1.340)	**< .001**	1.251	(1.146, 1.365)	**< .001**	1.149	(1.044, 1.265)	**.005**
30 to < 35 kg/m^2	1.533	(1.399, 1.680)	**< .001**	1.684	(1.537, 1.846)	**< .001**	1.329	(1.198, 1.475)	**< .001**
≥ 35 kg/m^2	2.358	(2.153, 2.583)	**< .001**	3.071	(2.802, 3.367)	**< .001**	2.133	(1.915, 2.376)	**< .001**
Snoring									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	1.242	(1.091, 1.415)	**.001**	1.396	(1.225, 1.589)	**< .001**	1.253	(1.089, 1.442)	**.002**
Yes, ≥ 3 times/wk	1.577	(1.415, 1.758)	**< .001**	1.761	(1.580, 1.963)	**< .001**	1.298	(1.155, 1.458)	**< .001**
Don't know	1.507	(1.369, 1.659)	**< .001**	1.414	(1.284, 1.556)	**< .001**	1.197	(1.080, 1.326)	**.001**
Sleep quality									
Sound or restful (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Average	1.033	(.966, 1.104)	.342	1.030	(.963, 1.101)	.385	0.889	(.826, .955)	**.001**
Restless or worse	1.140	(1.048, 1.240)	**.002**	1.315	(1.209, 1.431)	**< .001**	0.950	(.864, 1.044)	.283
Sleep fragmentation									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	.999	(.917, 1.089)	.987	0.983	(.902, 1.071)	.696	0.927	(.846, 1.016)	.107
Yes, ≥ 3 times/wk	1.357	(1.250, 1.473)	**< .001**	1.271	(1.171, 1.380)	**< .001**	1.051	(.961, 1.148)	.276
Daytime sleepiness									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	.996	(.923, 1.075)	.921	0.934	(.865, 1.009)	.082	1.012	(.932, 1.100)	.772
Yes, ≥ 3 times/wk	1.117	(1.027, 1.215)	**.010**	1.073	(.987, 1.167)	.100	1.079	(.986, 1.181)	.100
Hypertension									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes	2.378	(2.239, 2.525)	**< .001**	2.010	(1.891, 2.135)	**< .001**	1.449	(1.349, 1.557)	**< .001**
HFpEF									
Body mass index									
<25 kg/m^2 (referent)	1.000	—	—	1.000	—	—	1.000	—	—
25 to < 30 kg/m^2	1.367	(1.206, 1.549)	**< .001**	1.393	(1.229, 1.579)	**< .001**	1.26	(1.099, 1.445)	**.001**
30 to < 35 kg/m^2	1.774	(1.558, 2.021)	**< .001**	1.962	(1.722, 2.235)	**< .001**	1.493	(1.289, 1.729)	**< .001**
≥35 kg/m^2	3.101	(2.733, 3.518)	**< .001**	4.111	(3.619, 4.670)	**< .001**	2.842	(2.450, 3.297)	**< .001**
Snoring									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	1.318	(1.108, 1.569)	**.002**	1.488	(1.250, 1.772)	**< .001**	1.304	(1.079, 1.576)	**.006**
Yes, ≥ 3 times/wk	1.563	(1.348, 1.812)	**< .001**	1.752	(1.511, 2.032)	**< .001**	1.245	(1.062, 1.460)	**.007**
Don't know	1.492	(1.309, 1.701)	**< .001**	1.396	(1.224, 1.591)	**< .001**	1.160	(1.009, 1.334)	**.037**
Sleep quality									
Sound or restful (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Average	1.077	(.982, 1.180)	.115	1.074	(.980, 1.177)	.129	0.935	(.846, 1.033)	.184
Restless or worse	1.220	(1.088, 1.368)	**.001**	1.418	(1.264, 1.590)	**< .001**	0.985	(.866, 1.121)	.8219
Sleep fragmentation									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	1.080	(.958, 1.218)	.209	1.063	(.942, 1.199)	.320	0.978	(.861, 1.111)	.732
Yes, ≥ 3 times/wk	1.511	(1.348, 1.695)	**< .001**	1.413	(1.260, 1.585)	**< .001**	1.115	(.985, 1.262)	.084

(continued on following page)

Table 3—Unadjusted and adjusted hazard ratios of incident heart failure across OSA risk factors. (continued)

OSA Risk Factor	Unadjusted Model			Age-Adjusted Model			Fully Adjusted* Model		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Daytime sleepiness									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	.976	(.879, 1.084)	.652	.913	(.822, 1.014)	.088	0.978	(.874, 1.095)	.705
Yes, ≥ 3 times/wk	1.113	(.992, 1.247)	.067	1.067	(.952, 1.196)	.268	1.067	(.944, 1.207)	.298
Hypertension									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes	2.397	(2.207, 2.602)	**< .001**	2.015	(1.855, 2.189)	**< .001**	1.435	(1.302, 1.583)	**< .001**
HFpEF									
Body mass index									
< 25 kg/m^2 (referent)	1.000	—	—	1.000	—	—	1.000	—	—
25 to < 30 kg/m^2	1.367	(1.206, 1.549)	**< .001**	1.393	(1.229, 1.579)	**< .001**	1.26	(1.099, 1.445)	**.001**
30 to < 35 kg/m^2	1.774	(1.558, 2.021)	**< .001**	1.962	(1.722, 2.235)	**< .001**	1.493	(1.289, 1.729)	**< .001**
≥ 35 kg/m^2	3.101	(2.733, 3.518)	**< .001**	4.111	(3.619, 4.670)	**< .001**	2.842	(2.450, 3.297)	**< .001**
Snoring									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	1.318	(1.108, 1.569)	**.002**	1.488	(1.250, 1.772)	**< .001**	1.304	(1.079, 1.576)	**.006**
Yes, ≥ 3 times/wk	1.563	(1.348, 1.812)	**< .001**	1.752	(1.511, 2.032)	**< .001**	1.245	(1.062, 1.460)	**.007**
Don't know	1.492	(1.309, 1.701)	**< .001**	1.396	(1.224, 1.591)	**< .001**	1.160	(1.009, 1.334)	**.037**
Sleep quality									
Sound or restful (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Average	1.077	(.982, 1.180)	.115	1.074	(.980, 1.177)	.129	0.935	(.846, 1.033)	.184
Restless or worse	1.220	(1.088, 1.368)	**.001**	1.418	(1.264, 1.590)	**< .001**	0.985	(.866, 1.121)	.8219
Sleep fragmentation									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	1.080	(.958, 1.218)	.209	1.063	(.942, 1.199)	.320	0.978	(.861, 1.111)	.732
Yes, ≥ 3 times/wk	1.511	(1.348, 1.695)	**< .001**	1.413	(1.260, 1.585)	**< .001**	1.115	(.985, 1.262)	.084
Daytime sleepiness									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	.976	(.879, 1.084)	.652	.913	(.822, 1.014)	.088	0.978	(.874, 1.095)	.705
Yes, ≥ 3 times/wk	1.113	(.992, 1.247)	.067	1.067	(.952, 1.196)	.268	1.067	(.944, 1.207)	.298
Hypertension									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes	2.397	(2.207, 2.602)	**< .001**	2.015	(1.855, 2.189)	**< .001**	1.435	(1.302, 1.583)	**< .001**
HFrEF									
Body mass index									
< 25 kg/m^2 (referent)	1.000	—	—	1.000	—	—	1.000	—	—
25 to < 30 kg/m^2	1.057	(.912, 1.227)	.461	1.074	(.926, 1.246)	.348	0.997	(.846, 1.174)	.968
30 to < 35 kg/m^2	1.311	(1.121, 1.534)	**.001**	1.418	(1.212, 1.658)	**< .001**	1.154	(.965, 1.380)	.117
≥ 35 kg/m^2	1.410	(1.189, 1.671)	**< .001**	1.763	(1.485, 2.093)	**< .001**	1.189	(.971, 1.455)	.093
Snoring									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	1.101	(.871, 1.391)	.420	1.218	(.964, 1.539)	.099	1.028	(.798, 1.323)	.833
Yes, ≥ 3 times/wk	1.459	(1.206, 1.767)	**< .001**	1.607	(1.327, 1.945)	**< .001**	1.206	(.985, 1.477)	.070
Don't know	1.346	(1.137, 1.594)	**.001**	1.268	(1.071, 1.501)	**.006**	1.068	(.894, 1.275)	.467

(continued on following page)

Table 3—Unadjusted and adjusted hazard ratios of incident heart failure across OSA risk factors. (continued)

OSA Risk Factor	Unadjusted Model			Age-Adjusted Model			Fully Adjusted* Model		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Sleep quality									
Sound or restful (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Average	.989	(.876, 1.116)	.855	.986	(.874, 1.113)	.823	0.874	(.767, .997)	**.044**
Restless or worse	1.069	(.916, 1.247)	.400	1.214	(1.040, 1.417)	**.014**	0.933	(.786, 1.107)	.426
Sleep fragmentation									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	.868	(.747, 1.009)	.065	.855	(.735, 0.994)	**.041**	0.852	(.725, 1.001)	.051
Yes, ≥ 3 times/wk	1.135	(.983, 1.310)	.085	1.070	(.926, 1.235)	.359	0.955	(.817, 1.117)	.566
Daytime sleepiness									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes, ≤ 2 times/wk	.950	(.828, 1.091)	.469	.897	(.781, 1.029)	.121	0.982	(.847, 1.140)	.815
Yes, ≥ 3 times/wk	1.047	(.899, 1.218)	.557	1.010	(.868, 1.176)	.894	1.036	(.880, 1.219)	.670
Hypertension									
No (referent)	1.000	—	—	1.000	—	—	1.000	—	—
Yes	2.148	(1.925, 2.397)	**< .001**	1.842	(1.650, 2.057)	**< .001**	1.362	(1.196, 1.552)	**< .001**

*Model adjusted for age, race/ethnicity, education, income, marital status, waist-to-hip ratio, diabetes, coronary heart disease, atrial fibrillation, use of HT, use of sleep medications, modified Charlson Comorbidity Index, smoking, alcohol consumption, physical activity, hysterectomy, systolic blood pressure. Significant *P* values are indicated in bold. CI = confidence interval, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, HT = hormone therapy, OSA = obstructive sleep apnea.

modest increase in risk, but the estimates did not increase in a linear dose response fashion.

After accounting for death as a competing risk, the hazard ratios did not appear to differ compared with the estimates from the original analyses. Additionally, they did not appear to differ after accounting for other HF types (**Table S1** in the supplemental material).

In the fully adjusted model, the interaction terms including AF and HT with OSA risk factors and symptoms were significant ($P = .002$ and $P = .005$, respectively). The association of the OSA score and all HF, HFpEF, and HFrEF stratified by HT and AF are presented in **Table S2** and **Table S3**, respectively. Each additional OSA risk factor was associated with all HF and HFpEF and not HFrEF in a dose response fashion in those who currently use HT. Increasing number of OSA risk factors and having AF demonstrated a linear dose response relationship in the risk of having all HF, HFpEF, and HFrEF.

There was a modest increase in risk of having all HF in those who snore ≥ 3 times per week in the fully adjusted model. The association was attenuated after adjusting for BMI. (**Table S4**) Furthermore, when BMI and hypertension were excluded from the OSA score, each additional OSA risk factor was not associated with a higher risk of having all HF, HFpEF, or HFrEF (*P* trend =.56, .17, and .36, respectively). Adjustment for BMI alone and for BMI and hypertension demonstrated similar nonsignificant results (**Table S5**).

DISCUSSION

We have demonstrated that the presence and number of OSA risk factors and symptoms are associated with risk of HFpEF but not HFrEF in a multiethnic cohort of postmenopausal women. However, these associations are largely dependent on BMI and hypertension. These OSA risk factors and symptoms were more strongly associated with HF risk in those with atrial fibrillation and those who use hormone therapy.

Gottlieb et al[11] had shown in the Sleep Heart Health Study that OSA is associated with increased risk of incident heart failure in men but not women. This was attributed to low prevalence of severe OSA or late onset of symptoms in women. In our study, we evaluate the relationship of OSA risk factors and incident HF in a large cohort of postmenopausal women. We found that the association of OSA risk factors and symptoms and incident HF is observed in postmenopausal women, a population that has higher cardiovascular morbidity and mortality compared to men.[25] Furthermore, disrupted sleep leads to sleep deprivation as commonly seen in patients with OSA, and it increases the risk of inflammation and cardiovascular disease in older women.[26,27]

In this study, we found that the association between the OSA summary score and HF risk is likely a function of hypertension and obesity. Having OSA increases the risk of having hypertension, and in those with hypertension, OSA may be present.[28] A study in Brazil demonstrated that 64% of the study population with resistant hypertension had OSA. Resistant hypertension is 2 times more prevalent in those with OSA compared with those with primary hypertension.[29] The mechanism linking OSA to hypertension is complex and multifactorial, which includes catecholamine surge and alteration of the renin-angiotensin system.[30] The relationship between hypertension and OSA is also evident in the treatment of OSA with continuous positive

Table 4—Adjusted hazard ratios of incident heart failure based on OSA score.

OSA Score (# OSA risks present)	Unadjusted Model			Age-Adjusted Model			Fully Adjusted* Model		
	HR	95% CI	*P* Trend	HR	95% CI	*P* Trend	HR	95% CI	*P* Trend
All HF									
0 (referent)	1.000	—	**< .001**	1.000	—	**< .001**	1.000	—	**< .001**
1	1.549	(1.387, 1.731)		1.450	(1.298, 1.620)		1.266	(1.122, 1.428)	
2	2.035	(1.826, 2.268)		1.926	(1.728, 2.146)		1.489	(1.322, 1.677)	
3	2.559	(2.289, 2.862)		2.522	(2.256, 2.820)		1.737	(1.535, 1.967)	
4	3.020	(2.661, 3.426)		3.098	(2.730, 3.515)		1.828	(1.588, 2.105)	
5	3.130	(2.640, 3.711)		3.412	(2.878, 4.046)		1.725	(1.428, 2.083)	
HFpEF									
0 (referent)	1.000	—	**< .001**	1.000	—	**< .001**	1.000	—	**< .001**
1	1.628	(1.392, 1.904)		1.519	(1.299, 1.777)		1.308	(1.105, 1.547)	
2	2.187	(1.877, 2.547)		2.066	(1.774, 2.407)		1.534	(1.298, 1.812)	
3	3.040	(2.603, 3.549)		3.001	(2.570, 3.504)		2.003	(1.689, 2.375)	
4	3.306	(2.771, 3.943)		3.402	(2.851, 4.058)		1.872	(1.538, 2.278)	
5	3.660	(2.907, 4.608)		4.007	(3.183, 5.045)		1.865	(1.443, 2.412)	
6	5.716	(3.827, 8.537)		6.731	(4.506, 10.054)		2.614	(1.693, 4.035)	
HFrEF									
0 (referent)	1.000	—	**.002**	1.000	—	**< .001**	1.000	—	.342
1	1.316	(1.090, 1.588)		1.240	(1.027, 1.497)		1.144	(.932, 1.405)	
2	1.680	(1.398, 2.019)		1.598	(1.329, 1.920)		1.286	(1.048, 1.578)	
3	1.887	(1.553, 2.292)		1.857	(1.528, 2.256)		1.349	(1.085, 1.679)	
4	2.321	(1.859, 2.899)		2.371	(1.898, 2.960)		1.556	(1.215, 1.992)	
5	2.356	(1.726, 3.216)		2.540	(1.861, 3.467)		1.442	(1.026, 2.027)	
6	2.876	(1.537, 5.382)		3.283	(1.754, 6.146)		1.452	(.741, 2.846)	

*Model adjusted for age, race/ethnicity, education, income, marital status, waist-to-hip ratio, diabetes, coronary heart disease, atrial fibrillation, use of HT, use of sleep medications, modified Charlson Comorbidity Index, smoking, alcohol consumption, physical activity, hysterectomy, systolic blood pressure. Significant *P* values are indicated in bold. CI = confidence interval, HF = heart failure, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, HT = hormone therapy, OSA = obstructive sleep apnea.

airway pressure (CPAP). CPAP is effective in reducing blood pressure in those with hypertension.[31] The link between obesity and OSA has been reconfirmed in many studies and is one of the main risk factors used in screening questionnaires.[16] Addressing reversible causes like obesity could potentially reduce OSA severity and HF incidence.[32]

Bixler et al[33] had shown that one of the significant risk factors for OSA in women is being postmenopausal, and HT use is associated with reduced risk of OSA. However, several large randomized controlled trials examining the relationship between HT and cardiovascular disease risk, including one in the WHI, found no difference in the primary outcome in the treatment arm compared with the placebo arm. There was also evidence suggesting early increase in cardiovascular disease risk with HT use.[34–36] A more recent study that followed postmenopausal women over 10 years showed lower risk of mortality, heart failure, and myocardial infarction due to HT use.[24] In our study, we found that in the fully adjusted models, HT use was associated with increased risk of all HF, HFpEF, and HFrEF incidence in those with OSA risk factors.

In a study by Gami et al[23], half of participants with AF had underlying OSA, and the association of AF with OSA was stronger than that of BMI and hypertension with OSA, both of which are typical OSA risk factors. They also demonstrated that those with coronary heart disease and congestive heart failure were more likely to have OSA. OSA and arrhythmia such as atrial fibrillation are both highly prevalent in patients with HF.[4] In the setting of OSA, intermittent hypoxemia, hypercapnia, severe blood pressure surges, and enhanced sympathetic drive predisposes one to the development of AF.[37] In our study, we found that those with AF and OSA risk factors had increased risk of HF, especially for HFrEF. The mechanisms linking AF to HFrEF were previously described, which include shortened diastolic filling time reducing cardiac output and loss of atrial filling support to the ventricle.[38] Regardless of the type of HF, the risk of death, HF hospitalization, and stroke are all similarly increased in patients with atrial fibrillation.[39]

Our study has several limitations. First, HF was adjudicated based on the woman's presentation to the hospital. Women who had milder exacerbation of HF and were managed in the outpatient setting were not included. Previous research suggests that outpatient HF is less than 25% of HF cases, is equally distributed between HFpEF and HFrEF, and leads subsequent hospitalization in a relatively short time period.[40]

Second, the formal diagnosis of OSA was not available in the WHI due to the lack of polysomnographic data. We used known OSA risk factors and symptoms from validated screening questionnaires to create an OSA score to act as an indicator of OSA, but not all symptoms, such as snort arousals and witnessed apneas were available. Although OSA symptoms and risk factors are not specific to the diagnosis of OSA, in patients with cardiovascular diseases, some of the more sophisticated questionnaires compared to the Epworth Sleepiness Scale demonstrated a higher sensitivity for predicting OSA. The Berlin and STOP-BANG questionnaires demonstrated a sensitivity of 73% and 97%, respectively.[41] Future research using direct measurement of respiratory parameters, such as those in polysomnography would be helpful in further exploring the relationship between OSA and HF.

Despite these limitations, there are several strengths to our study. Our study incorporated a large cohort of postmenopausal women, a population with increased risk of OSA and HF. Heart failure admission were adjudicated by trained physicians from hospital records with good degrees of reproducibility with other epidemiologic algorithms of acute heart failure.[42] Lastly, echocardiography data were used to help differentiate between the different subtypes types of heart failure, which is particularly relevant to older women given the higher rates of HFpEF.

CONCLUSIONS

OSA risk factors and symptoms were associated with higher risk of HFpEF but not HFrEF in postmenopausal women. Hypertension and obesity were strongly associated with OSA and play an important role in other comorbid conditions, including HF. Early recognition and management of OSA risk factors and symptoms may reduce HF risk, especially in postmenopausal women with preserved ejection fractions.

ABBREVIATIONS

AF, atrial fibrillation
BMI, body mass index
CI, confidence interval
CPAP, continuous positive airway pressure
GFR, glomerular filtration rate
HF, heart failure
HFpEF, heart failure with preserved ejection fraction
HFrEF, heart failure with reduced ejection fraction
HR, hazard ratio
HT, hormone therapy
OSA, obstructive sleep apnea
WHI, Women's Health Initiative

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