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Original Contribution

Type of Menopause, Age at Menopause, and Risk of Developing Obstructive Sleep Apnea in Postmenopausal Women

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Despite established sex differences and longstanding hypotheses of sex hormone influence in the etiology of obstructive sleep apnea (OSA), we have found no studies that evaluated type of menopause and age at menopause, which affect postmenopausal hormonal milieu, in relation to OSA risk in women. We followed 50,473 postmenopausal women from the Nurses' Health Study during 2002–2012 and 53,827 postmenopausal women from the Nurses' Health Study II during 1995–2013, with 1,712 and 2,560 incident OSA diagnoses, respectively. Compared with natural menopause, the pooled hazard ratio for OSA was 1.27 (95% confidence interval (CI): 1.17, 1.38) for surgical menopause by hysterectomy/oophorectomy. The association remained the same after further accounting for age at menopause (hazard ratio = 1.26, 95% CI: 1.15, 1.38). The risk associated with surgical menopause was higher among women who were not obese as well as among women who never used hormone therapy (*P* for interaction < 0.05). Earlier menopause was associated with higher OSA risk prior to adjustment for type of menopause (comparing those aged <40 years versus those aged 50–54 years, hazard ratio = 1.21, 95% CI: 1.08, 1.35; *P* for trend = 0.008), although no association was observed after the adjustment. Surgical as compared with natural menopause was independently associated with higher OSA risk in postmenopausal women. Our results provide additional evidence for a role for sex hormones, particularly abrupt hormonal changes, in modulating OSA risk.

age at menopause; hysterectomy; obstructive sleep apnea; oophorectomy; risk factors; sleep epidemiology

Abbreviations: BMI, body mass index; CI, confidence interval; EDS, excessive daytime sleepiness; HR, hazard ratio; HT, hormone therapy; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OSA, obstructive sleep apnea.

Obstructive sleep apnea (OSA) is a chronic and highly prevalent disorder in adults that poses an increased risk for cardiometabolic diseases and premature death (1–3). Prior investigations have consistently reported that OSA is more common among men than women and that there is a significant increase in incidence in women after menopause (4–10). Differences in endogenous sex hormones, such as estrogen and progesterone, are postulated to play a major role in these observations. This hypothesis is further supported by some (11–13), but not all (14–16), studies suggesting that postmenopausal hormone therapy (HT) may be inversely associated with OSA. However, few studies have evaluated other important hormonal factors in relation to OSA risk.

Each year, more than 300,000 US women receive prophylactic oophorectomies, often at the time of hysterectomy (17). Bilateral oophorectomy in premenopausal women results in surgically induced menopause that abruptly reduces the production of endogenous sex hormones (18). Early menopause, either naturally occurring or induced by surgery, radiation, or chemotherapy, is associated with shorter lifetime exposure to endogenous sex hormones. A growing body of evidence suggests that early cessation of the production of endogenous sex hormones, such as estrogen, is detrimental for women's long-term health. Early onset of menopause, particularly as a result of bilateral oophorectomy, has been adversely associated with cardiovascular disease, cognitive decline, and mortality (17, 19–21). It remains unknown whether these menopausal factors also influence OSA risk, given that depletion of estrogen and progesterone may act in the pathogenesis of OSA (10). We therefore examined risk of developing OSA according to type of menopause and age at menopause in 2 independent prospective cohorts of US women. We hypothesized that both surgical menopause (as compared

with natural menopause) and early-onset menopause (regardless of type of menopause) were independently associated with higher OSA risk in postmenopausal women.

METHODS

Study participants

The Nurses' Health Study (NHS) was established in 1976 when 121,700 US female registered nurses aged 30–55 years completed the first questionnaire regarding medical history and lifestyles. The Nurses' Health Study II (NHSII) commenced in 1989 when 116,429 female nurses aged 25–42 years completed a similar questionnaire at enrollment. A biennial follow-up questionnaire was mailed to participants to update their information on disease occurrence and health-related factors. The present study was restricted to women who were postmenopausal and free of known OSA, cancer, and cardiovascular disease before entry into the analysis. We excluded women missing information on menopausal factors or OSA diagnosis or who had menopause due to pelvic irradiation, resulting in 50,473 NHS and 53,827 NHSII participants for analysis.

Assessment of OSA and related symptoms

In 2012, NHS participants reported diagnoses by responding to the question: "Have you ever had sleep apnea diagnosed by clinicians or sleep study?" Those who answered "yes" were further asked to report year of first diagnosis as "before 2002," "2002–2005," "2006–2007," "2008–2009," "2010–2011," or "after 2012." We began follow-up in 2002 in NHS to ensure that all cases had been diagnosed after study baseline. The diagnoses were assessed in a similar manner in NHSII in 2013, with year of diagnosis as "before 1995," "1996–2000," "2001–2005," "2005–2009," or "after 2009." The follow-up period in NHSII was 1995–2013.

In a pilot validation study of 42 NHS and 45 NHSII participants randomly sampled from those who reported diagnoses, all women were confirmed by medical record review to have had their sleep apnea diagnosed by at least one of the following: in-lab polysomnography (91%), home sleep apnea test (9%), or overnight oximetry (20%), with 18% using ≥2 methods; 98% were classified as obstructive, 1% as central, and 1% as mixed. Concordance in year of diagnosis was 95% between self-reports and medical records. Collectively, these results highlight that self-reported OSA among nurses is highly reliable despite its underrecognition in the general population (22).

Snoring was repeatedly assessed during follow-up (NHS: 2000/2002/2008/2012; NHSII: 2001/2013) with possible response categories of "every night," "most nights," "a few nights a week," "occasionally," and "almost never." We defined habitual snoring as snoring every night or most nights. Daytime sleepiness was evaluated in 2008 (NHS) and 2001 (NHSII) with the question: "On average, how often are your daily activities affected because you are sleepy during the day?" Participants who reported ≥4 days/week were considered to have excessive daytime sleepiness (EDS). NHSII participants further reported witnessed apnea by responding "yes" or "no" to the question: "Has anyone noticed that you stop breathing during your sleep?"

Assessment of menopausal factors

On every biennial questionnaire, participants reported whether their menstrual periods had ceased permanently. Women who reported "no menstrual periods" or "had menopause but now have periods induced by hormones" were considered postmenopausal, and they were asked at what age (in years) and for what reason (surgery, radiation/chemotherapy, natural) their periods ceased. Women with surgical menopause provided additional information on the type of surgery. We defined surgical menopause as menopause due to simple hysterectomy (i.e., without oophorectomy) or unilateral/bilateral oophorectomy with or without hysterectomy. Similarly, women with natural menopause were asked about any subsequent postmenopausal surgery to remove ovaries or uterus. Self-reported menopausal factors have previously been proven to be highly accurate (23). In a random sample of 6,591 NHS women, agreement in self-reported age at menopause over a 2-year period was 82% for natural menopause and 95% for surgical menopause. Among 200 women reporting surgical menopause whose medical records were obtained, 198 (99%) had agreement regarding the number of surgically removed ovaries.

Statistical analyses

Due to the distinct age distribution, the analytical strategy implemented in NHS was different from that for NHSII. In NHS, almost all participants were postmenopausal at baseline (2002); our analysis was restricted to postmenopausal women in 2002 who were free of OSA, cancer, and cardiovascular disease. By contrast, 7.2% of NHSII women were postmenopausal at baseline (1995). Thus, we dynamically included women when they became postmenopausal over follow-up.

In the main analyses, person-time of follow-up accrued from the return of the baseline questionnaire (for women who were postmenopausal at baseline) or the return of the first postmenopausal questionnaire (for women who were premenopausal at baseline) until OSA diagnosis or the return of the last questionnaire (NHS: 2012–2014; NHSII: 2013–2015). Cox proportional hazards models were used to estimate the hazard ratios and 95% confidence intervals for OSA according to type of menopause (natural (referent) or surgical) and age at menopause (in years: <40, 40–44, 45–49, 50–54 (referent), or ≥55). We tested for trend by evaluating age at menopause as a continuous variable. All Cox models stratified by age and calendar time. Multivariable analyses further considered OSA risk factors and other relevant covariates (described below in tables). All these variables (except for race/ethnicity) were updated during follow-up and were modeled as time-varying covariates in the analysis. Given the strong interrelationship between type of menopause and age at menopause, we simultaneously adjusted for these 2 factors in a separate model to estimate their independent associations with OSA risk. Analyses were conducted separately in each cohort and were pooled using fixed-effects meta-analysis.

Several sensitivity analyses were conducted to test the robustness of the results. First, because endometriosis and uterine fibroids (assessed in the NHSII only) are 2 primary indications that lead to hysterectomy/oophorectomy, we further considered these 2 benign gynecologic diseases to evaluate their influence on the association with surgical menopause. Second, we also restricted our analyses to naturally postmenopausal women who

Table 1. Age-Standardized Population Characteristics Among Postmenopausal Women Free of Obstructive Sleep Apnea Diagnoses at Baseline in the Nurses' Health Study and Nurses' Health Study II[a], United States

Characteristic	Type of Menopause							
	Nurses' Health Study				Nurses' Health Study II			
	Surgical (n = 17,482)		Natural (n = 32,991)		Surgical (n = 14,338)		Natural (n = 39,489)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	67.0 (6.5)		66.6 (6.8)		51.5 (6.0)		53.9 (3.6)	
Age at menopause, years	47.9 (5.3)		50.7 (3.6)		43.7 (6.7)		49.6 (4.6)	
Nonwhite		6		5		6		6
Married		77		77		79		79
Body mass index[b]	27.1 (5.2)		26.6 (5.1)		28.2 (6.2)		27.0 (6.2)	
Waist circumference, cm	87.3 (13.4)		86.3 (13.3)		86.8 (14.6)		84.2 (14.2)	
Parous		95		95		83		80
No. of children[c]	3.1 (1.4)		3.1 (1.4)		2.2 (0.9)		2.3 (0.9)	
Ever estrogen-only HT use		83		24		53		3
Ever estrogen + progestin HT use		16		52		4		21
Ever oral contraceptive use		58		54		91		88
Current smoker		7		7		9		8
Alcohol use, g/day	5.0 (8.0)		5.6 (8.3)		3.7 (6.3)		4.4 (6.8)	
Habitual sleep duration, hours	7.1 (1.1)		7.2 (1.1)		6.9 (1.1)		7.0 (1.1)	
Habitual snoring		28		27		29		25
Excessive daytime sleepiness		3		3		11		9
Witnessed apneas[d]						8		6
Current shift work		4		4		15		14
Alternate Healthy Eating Index score	53.3 (9.2)		53.2 (9.4)		51.2 (9.7)		52.6 (10.0)	
Physical activity, MET-hours/week	17.9 (16.5)		18.6 (17.7)		19.8 (20.4)		21.1 (21.2)	
History of hypertension		54		47		23		17
History of diabetes		7		5		4		3
History of uterine fibroids[d]						62		25
History of endometriosis[d]						29		9
Regular physical exam		95		93		94		92

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation.

[a] In the Nurses' Health Study, study baseline was 2002; in Nurses' Health Study II, which commenced in 1989, the baseline was the questionnaire cycle during which the participants were first included in the analysis after they became postmenopausal.

[b] Weight (kg)/height (m)^2.

[c] Among parous women.

[d] Assessed only in Nurses' Health Study II.

had never used HT, to examine the association between age at menopause and OSA risk. Third, to address the potential misclassification due to mild, undiagnosed OSA, we further divided women without self-reported OSA into high-risk (i.e., reporting habitual snoring) and low-risk (i.e., reporting no habitual snoring) groups. Similarly, we categorized self-reported OSA cases as those who reported EDS versus those who did not, to assess heterogeneity in associations by OSA severity (24). Because EDS was assessed only once in both cohorts, we estimated the odds ratios and 95% confidence intervals associated with type of menopause using multinomial logistic regression for a symptom-based, 4-category OSA status (no OSA diagnosis without habitual snoring (referent), no OSA diagnosis with habitual snoring, OSA diagnosis without EDS, and OSA diagnosis with EDS), adjusted for baseline covariates.

We performed additional post hoc analyses to characterize the association between surgical treatment and OSA risk in more detail. We evaluated: 1) whether OSA risk differed by the

number of ovaries removed; 2) whether OSA risk differed by hysterectomy with/without oophorectomy; and 3) whether hysterectomy/oophorectomy after natural menopause was also associated with subsequent OSA risk. Subgroup analyses were conducted to evaluate whether the associations with surgical menopause differed by body mass index (BMI, calculated as weight (kg)/height $(m)^2$; categories of <30 and ≥30), waist circumference (in cm: <88 or ≥88), postmenopausal HT (never use, ever use), physical activity (in metabolic equivalent–hours/week: <18 or ≥18), habitual snoring (no, yes), time since menopause (in years: ≤15 or >15), history of endometriosis (no, yes), and history of uterine fibroids (no, yes). Likelihood ratio tests comparing the models with versus without the terms for interaction between the exposure and the stratification variable were used to assess the statistical significance of potential effect modification. All analyses were performed using SAS, version 9.4, for UNIX (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Population characteristics

Compared with naturally postmenopausal women, surgically postmenopausal women were more likely to have menopause at an earlier age and to have ever used estrogen-only HT and oral contraceptives, but they were less likely to have ever used estrogen plus progestin HT. Surgical versus natural menopause was also associated with higher BMI; larger waist circumference; higher prevalence of hypertension, endometriosis, and uterine fibroids; less alcohol consumption; and lower physical activity level (Table 1). We documented 1,712 incident OSA cases in NHS during 12 years of follow-up and 2,560 incident OSA cases in NHSII during 20 years of follow-up. The prevalence of habitual snoring and EDS, as well as the average BMI and waist circumference, were significantly higher in women reporting physician-diagnosed OSA ($P < 0.0001$; Table 2).

Age at menopause and OSA risk

We observed similar associations between menopausal factors and OSA risk in both cohorts (Table 3; P for heterogeneity > 0.27). In the pooled analysis adjusted for age, earlier age at menopause was associated with increased OSA risk (P for trend < 0.0001). Compared with menopausal age during 50–54 years, the hazard ratios (95% confidence intervals (CIs)) were 1.52 (95% CI: 1.37, 1.70) for <40 years, 1.28 (95% CI: 1.15, 1.42) for 40–44 years, 1.03 (95% CI: 0.82, 1.29) for 45–49 years, and 1.10 (95% CI: 0.98, 1.23) for ≥55 years. This inverse association was weaker after adjusting for relevant covariates (P for trend = 0.008). Early menopause was not associated with OSA risk after additional adjustment for type of menopause (P for trend = 0.50). When the analysis was restricted to naturally postmenopausal women who never used HT, there was no association between age at menopause and OSA risk after multivariable adjustment (Web Table 1, available at https://academic.oup.com/aje).

Type of menopause and OSA risk

By contrast, the pooled age-adjusted HR of developing OSA among women with surgical menopause compared with women with natural menopause was 1.48 (95% CI: 1.38, 1.59; Table 3). Adjustment for potential confounders, particularly BMI and waist circumference, attenuated the association (hazard ratio (HR) = 1.27, 95% CI: 1.17, 1.38), although it remained statistically significant. The association was materially unchanged after further accounting for age at menopause (HR = 1.26, 95% CI: 1.15, 1.38). In a sensitivity analysis in NHSII, additional adjustment for history of endometriosis and uterine fibroids only slightly attenuated the hazard ratio for surgical menopause, from 1.22 (95% CI: 1.08, 1.37) to 1.20 (95% CI: 1.06, 1.36).

Compared with postmenopausal women with intact ovaries/uterus, the hazard ratio associated with surgical menopause was 1.43 (95% CI: 1.27, 1.61) for bilateral oophorectomy, 1.44 (95%

Table 2. Symptoms and Risk Factors Comparing Self-Reported Incident Cases of Obstructive Sleep Apnea Versus Noncases, Nurses' Health Study (2002–2012) and Nurses' Health Study II (1995–2013), United States

OSA-Related Factor	Self-Reported OSA[a]							
	Nurses' Health Study				Nurses' Health Study II			
	Yes (n = 1,712)		No (n = 48,761)		Yes (n = 2,560)		No (n = 51,267)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Habitual snoring[b]		65.3		26.3		64.8		24.0
Excessive daytime sleepiness[c]		10.1		3.0		19.0		9.2
Witnessed apneas[d]						63.6		3.3
Body mass index[e]	30.7 (6.3)		26.6 (5.1)		32.3 (7.4)		27.0 (6.0)	
Waist circumference, cm	95.2 (15.0)		86.4 (13.2)		96.4 (16.5)		84.3 (13.9)	

Abbreviations: OSA, obstructive sleep apnea; SD, standard deviation.
[a] $P < 0.0001$ for all comparisons by OSA status in each cohort.
[b] Defined as snoring every night or most nights.
[c] Reporting sleepiness for ≥4 days/week.
[d] Assessed only in Nurses' Health Study II.
[e] Weight (kg)/height $(m)^2$.

Table 3. Postmenopausal Risk of Obstructive Sleep Apnea According to Type of Menopause and Age at Menopause, Nurses' Health Study (2002–2012) and Nurses' Health Study II (1995–2013), United States

Menopausal Factor	No. of Cases	Person-Years	Model 1[a]		Model 2[b]		Model 3[c]	
			HR	95% CI	HR	95% CI	HR	95% CI
Nurses' Health Study								
Type of menopause								
Natural	990	382,797	1.00	Referent	1.00	Referent	1.00	Referent
Surgical	722	201,611	1.42	1.29, 1.56	1.34	1.15, 1.55	1.33	1.15, 1.54
Age at menopause, years								
<40	92	21,696	1.43	1.15, 1.77	1.21	0.97, 1.52	1.16	0.92, 1.45
40–44	134	38,292	1.21	1.01, 1.45	1.06	0.88, 1.28	1.05	0.87, 1.26
45–49	354	134,991	0.92	0.81, 1.03	0.93	0.82, 1.05	0.95	0.84, 1.08
50–54	962	335,977	1.00	Referent	1.00	Referent	1.00	Referent
≥55	170	53,453	1.05	0.89, 1.23	1.12	0.95, 1.32	1.17	0.99, 1.38
P for trend			0.0025		0.35		0.74	
Nurses' Health Study II								
Type of menopause								
Natural	1,558	335,024	1.00	Referent	1.00	Referent	1.00	Referent
Surgical	1,002	155,065	1.53	1.41, 1.66	1.24	1.12, 1.37	1.22	1.08, 1.37
Age at menopause, years								
<40	420	71,520	1.56	1.37, 1.77	1.21	1.05, 1.38	1.07	0.92, 1.25
40–44	378	68,842	1.32	1.16, 1.50	1.13	0.99, 1.28	1.03	0.90, 1.19
45–49	690	129,110	1.15	1.04, 1.28	1.11	0.99, 1.23	1.06	0.95, 1.18
50–54	883	186,235	1.00	Referent	1.00	Referent	1.00	Referent
≥55	189	34,382	1.15	0.98, 1.35	1.08	0.91, 1.26	1.09	0.92, 1.28
P for trend			0.0001		0.01		0.56	
Pooled								
Type of menopause								
Natural	2,548	717,821	1.00	Referent	1.00	Referent	1.00	Referent
Surgical	1,724	356,676	1.48	1.38, 1.59	1.27	1.17, 1.38	1.26	1.15, 1.38
Age at menopause, years								
<40	512	93,216	1.52	1.37, 1.70	1.21	1.08, 1.35	1.10	0.97, 1.25
40–44	512	107,134	1.28	1.15, 1.42	1.10	0.99, 1.23	1.04	0.93, 1.16
45–49	1,044	264,101	1.03	0.82, 1.29	1.02	0.85, 1.21	1.01	0.90, 1.13
50–54	1,845	522,212	1.00	Referent	1.00	Referent	1.00	Referent
≥55	359	87,835	1.10	0.98, 1.23	1.10	0.98, 1.23	1.12	1.00, 1.26
P for trend			<0.0001		0.008		0.50	

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent.

[a] Stratified by age in months and calendar years.

[b] Model 1 with the addition of adjustment for body mass index (calculated as weight (kg)/height (m)^2: <20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0), waist circumference (in cm: <76, 76–87, 88–95, ≥96), smoking (never, past, current), alcohol consumption (in g/day: none, <5.0, 5.0–14.9, 15.0–29.9, ≥30.0), duration of postmenopausal hormone therapy by type (in years: never, <5.0, 5.0–9.9, ≥10.0), race/ethnicity (white, nonwhite), history of diabetes (yes, no), history of hypertension (yes, no), duration of oral contraceptive use (in years: never, <1.0, 1.0–4.9, 5.0–9.9, ≥10.0), parity (continuous), physical activity (in MET-hours/week: <3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0), Alternate Healthy Eating Index (in quintiles), and sleep duration (in hours/day: ≤5, 6, 7, 8, ≥9).

[c] Model 2 with the addition of simultaneous adjustment for age at menopause or type of menopause.

CI: 1.19, 1.75) for unilateral oophorectomy, and 1.24 (95% CI: 1.12, 1.38) for simple hysterectomy without oophorectomy (Table 4). Bilateral oophorectomy in naturally postmenopausal women was also associated with higher OSA risk (HR = 1.21, 95% CI: 1.04, 1.41), although this was not observed for postmenopausal unilateral oophorectomy (HR = 1.15, 95% CI: 0.95, 1.38) or simple hysterectomy (HR = 1.07, 95% CI: 0.86, 1.32). The positive association with surgical menopause appeared stronger for OSA with EDS (odds ratio = 1.80, 95% CI: 1.47, 2.20), a marker of severe OSA, than for OSA without

Table 4. Postmenopausal Risk of Obstructive Sleep Apnea According to Specific Type of Surgery at Menopause or During Postmenopausal Years, Nurses' Health Study (2002–2012) and Nurses' Health Study II (1995–2013)[a], United States

Type of Surgery	No. of Cases	HR	95% CI
Natural menopause			
Intact uterus and ovaries	2,127	1.00	Referent
Postmenopausal simple hysterectomy	92	1.07	0.86, 1.32
Postmenopausal unilateral oophorectomy	120	1.15	0.95, 1.38
Postmenopausal bilateral oophorectomy	209	1.21	1.04, 1.41
Surgical menopause			
Simple hysterectomy	453	1.24	1.12, 1.38
Unilateral oophorectomy	130	1.44	1.19, 1.75
Bilateral oophorectomy	1,141	1.43	1.27, 1.61

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent.

[a] Stratified by age in months and calendar years, and adjusted for age at menopause, body mass index (calculated as weight (kg)/height $(m)^2$: <20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0), waist circumference (in cm: <76, 76–87, 88–95, ≥96), smoking (never, past, current), alcohol consumption (in g/day: none, <5.0, 5.0–14.9, 15.0–29.9, ≥30.0), duration of postmenopausal hormone therapy by type (in years: never, <5.0, 5.0–9.9, ≥10.0), race/ethnicity (white, nonwhite), history of diabetes (yes, no), history of hypertension (yes, no), duration of oral contraceptive use (in years: never, <1.0, 1.0–4.9, 5.0–9.9, ≥10.0), parity (continuous), physical activity (in MET-hours/week: <3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0), Alternate Healthy Eating Index (in quintiles), and sleep duration (in hours/day: ≤5, 6, 7, 8, ≥9).

EDS (odds ratio = 1.48, 95% CI: 1.35, 1.63). Among women who did not report an OSA diagnosis, surgical menopause was also associated with somewhat higher odds of having habitual snoring, which may include mild, potentially undiagnosed OSA (Web Table 2).

Subgroup analyses

In subgroup analyses (Table 5), the association of surgical menopause with OSA risk was more pronounced in women with a BMI of <30 versus ≥30 (P for interaction = 0.04) and in never users versus ever users of postmenopausal HT (P for interaction = 0.01). Although the difference did not reach statistical significance, the association was suggestively stronger in women with a waist circumference of <88 cm versus ≥88 cm and in women with low versus high physical activity level. We observed no significant differences by habitual snoring, time since menopause, history of endometriosis, or history of fibroids (P for interaction > 0.26).

DISCUSSION

In 2 large prospective cohort studies, surgical menopause was associated with a 26% higher risk of developing OSA in postmenopausal women, adjusted for age at menopause and other OSA risk factors. This association appeared to persist for decades after menopause. Women who had had a bilateral oophorectomy after natural menopause were also at slightly higher risk for later development of OSA. Conversely, early onset of menopause after accounting for surgical versus natural menopause was not independently associated with OSA risk. To our knowledge, this is the first population-based study to describe an adverse association between surgical menopause and OSA risk.

Depletion of estrogen and progesterone has been hypothesized to contribute to the increased OSA risk observed among postmenopausal women (10). It is known that a key source of androgens in postmenopausal women is ovarian secretion; androgens can be aromatized to estrogens in peripheral tissues (25, 26). Compared with natural menopause, surgical removal of ovaries among premenopausal women leads to a sudden reduction in endogenous sex hormones (18). The higher OSA risk associated with surgical menopause observed in this study provides further evidence for the potential role of sex hormones in OSA etiology. The increased OSA risk due to surgical menopause that persisted for many years into the postmenopausal period (i.e., surgical menopause was associated with OSA diagnosed >15 years after menopause), as well as the slightly increased OSA risk associated with postmenopausal bilateral oophorectomy, are consistent with prior evidence that the postmenopausal ovary is hormonally active for many years after menopause (26). Interestingly, women who used exogenous hormones, which may help offset the deficiency of endogenous hormones after ovary removal, had a significantly smaller increase in OSA risk associated with surgical menopause. Similarly, the positive associations between surgical menopause and OSA risk were weaker in women with higher BMI or waist circumference; these women also had a higher estrogenic environment given that adipose tissues are the major source of estrogen production in postmenopausal women (27, 28), which could potentially mitigate the negative influence of oophorectomy on OSA development. However, it is possible that the association with surgical menopause is masked in obese women, given that adiposity is such a strong risk factor for OSA (Web Table 3). Further, we observed an attenuated OSA risk

Table 5. Risk of Obstructive Sleep Apnea Associated With Type of Menopause According to Several Risk Factors in the Nurses' Health Study (2002–2012) and Nurses' Health Study II (1995–2013)[a], United States

Risk Factor	No. of Cases	Surgical Vs. Natural Menopause		*P* for Interaction
		HR	95% CI	
Body mass index[b]				0.04
<30	1,838	1.38	1.20, 1.58	
≥30	2,434	1.20	1.07, 1.36	
Waist circumference, cm[c]				0.20
<88	1,246	1.38	1.15, 1.64	
≥88	2,428	1.22	1.07, 1.38	
Hormone therapy[d]				0.01
Never user	1,731	1.42	1.24, 1.63	
Ever user	2,541	1.12	1.03, 1.23	
Physical activity, MET-hours/week				0.10
<18	1,267	1.41	1.19, 1.66	
≥18	3,005	1.23	1.10, 1.36	
Habitual snoring				0.30
No	1,497	1.27	1.09, 1.47	
Yes	2,775	1.23	1.10, 1.38	
Time since menopause, years				0.95
≤15	2,558	1.29	1.14, 1.45	
>15	1,714	1.25	1.08, 1.46	
History of endometriosis[e]				0.42
No	2,038	1.25	1.09, 1.43	
Yes	5,22	1.10	0.84, 1.44	
History of uterine fibroids[e]				0.26
No	1,495	1.20	1.00, 1.45	
Yes	1,065	1.13	0.95, 1.33	

Abbreviations: CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent.

[a] Stratified by age in months and calendar years, and adjusted for (except the stratification variable) age at menopause, body mass index (calculated as weight (kg)/height (m)^2: <20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0), waist circumference (in cm: <76, 76–87, 88–95, ≥96), smoking (never, past, current), alcohol consumption (in g/day: none, <5.0, 5.0–14.9, 15.0–29.9, ≥30.0), duration of postmenopausal hormone therapy by type (in years: never, <5.0, 5.0–9.9, ≥10.0), race/ethnicity (white, nonwhite), history of diabetes (yes, no), history of hypertension (yes, no), duration of oral contraceptive use (in years: never, <1.0, 1.0–4.9, 5.0–9.9, ≥10.0), parity (continuous), physical activity (in MET-hours/week: <3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0), Alternate Healthy Eating Index (in quintiles), and sleep duration (in hours/day: ≤5, 6, 7, 8, ≥9).

[b] Weight (kg)/height (m)^2.

[c] Among a subset of participants with waist circumference measurements.

[d] Includes any hormone therapy use (estrogen-only, estrogen plus progestin, or other hormone therapy).

[e] Among the Nurses' Health Study II participants only.

associated with surgical menopause among more active women, supporting potential benefits of physical activity for OSA independent of obesity (29, 30).

The mechanisms through which sex hormones may influence the development of OSA remain unclear. There is limited evidence that estrogen and progesterone may act upon upper airway dilator muscles to control ventilation and airway collapsibility during sleep (31, 32), which predisposes surgically postmenopausal women to higher susceptibility to OSA. Emerging evidence indicates that OSA is characterized by a continuum of severity symptoms with dose-response patterns similar to other physiologic factors, such as blood pressure (5). The graded relationships of surgical menopause with different outcome categories potentially reflecting OSA severity (Web Table 2) provide additional biologic plausibility to support the observed association.

Existing results are mixed regarding the association of oophorectomy with postmenopausal hormonal profiles. While findings are consistent for short-term hormonal changes after oophorectomy, some long-term epidemiologic studies reported lower circulating testosterone levels but observed no significant differences

in estrone or estradiol levels comparing postmenopausal women with and without oophorectomy, regardless of timing of the surgery (33, 34). Hysterectomy with ovarian conservation has also been associated with lower testosterone and dehydroepiandrosterone sulfate among postmenopausal women (33–35). The increased OSA risk we observed for surgical menopause due to oophorectomy or simple hysterectomy, which both lead to reduction in testosterone levels, suggests that androgens may also be involved in OSA etiology. Additional research is warranted to understand the role of androgen and its potential interaction with other sex hormones in postmenopausal OSA development.

Contrary to our hypothesis, we did not observe an association between age at menopause and OSA risk after adjusting for type of menopause. While both early menopause and surgical menopause reduce exposure to sex hormones, their impact on endocrine regulation and homeostasis may vary substantially. Natural menopause, even when it occurs prematurely, is accompanied by a gradual decrease in estrogen production that extends to many years before and after menopause (36). For example, estrogen levels start to fall several years before natural menopause, and this decrease continues after menopause (36–38). It has been shown that, compared with women with <4 years of menopause, total estradiol concentrations were 23% lower in women >20 years after menopause (39). By contrast, premenopausal bilateral oophorectomy leads to an immediate onset of menopause, with an abrupt fall in circulating estrogens and testosterone levels (18). Our results suggest that sudden alterations in hormonal homeostasis, rather than progressive decline in hormone levels over time, may have a greater long-term influence on OSA development.

One potential limitation of the present study is our reliance on self-reported OSA. Although our validation study suggests high reliability of self-reported OSA diagnosis, other clinical characteristics related to OSA diagnosis, such as underrecognition and differential diagnosis, need to be considered. Given that all study participants were trained health professionals, undiagnosed OSA may be less prevalent than in the general population (22). Notably, the BMI-specific prevalence of self-reported OSA in postmenopausal women of our study populations (Web Table 4) was highly comparable to recent polysomnography-based estimates for moderate-to-severe sleep-disordered breathing (apnea-hypopnea index of ≥15) among US women aged 50–70 years (6). Globally, the prevalence of moderate-to-severe OSA varied considerably across different populations, ranging from 1.2% to 23.4% in women (5–7). The prevalence of mild-to-severe OSA (apnea-hypopnea index of ≥5) was even higher (range, 6.5%–60.8%), with a recent Swiss study estimating that up to 60.8% of women aged >50 years had sleep-disordered breathing of any form (5). These comparisons suggest that self-reported cases in our cohorts may be more likely to represent those with more severe OSA syndromes that led to clinical diagnoses but inadequately capture mild, asymptomatic cases that remained undiagnosed. However, any such underdiagnosis would not alter our conclusions, given that similar positive associations were observed when we separated out women who were at high risk for undiagnosed OSA (i.e., those who reported habitual snoring but did not report clinical OSA diagnosis).

Further, the positive association could have resulted from differential detection if women with surgical menopause were more likely to have clinical diagnoses of OSA. However, we observed no differences in regular physical exams between naturally versus surgically postmenopausal women, and adjusting for this proxy indicator of health motivation and health-care access did not change the estimates. The fact that postmenopausal bilateral oophorectomy was weakly associated with OSA risk while postmenopausal unilateral oophorectomy was not associated with risk further refutes the possibility of bias due to differential diagnoses. However, we cannot fully exclude that interest in prevention or differential patterns of health care may partly explain the association between surgical menopause and OSA risk (15). The homogeneity of the study population, consisting exclusively of registered nurses, despite limiting the generalizability of our findings, also reduces variations in health-seeking behaviors that may render differential OSA detection. It should be noted that the predominance of white women in our study populations may limit extrapolation of the results to other races/ethnicities.

The study has several notable strengths, including large sample size, long follow-up, and validation of self-reported diagnosis, as well as similar results in 2 independent cohorts. Important risk factors for OSA have been repeatedly and consistently assessed during follow-up in the 2 cohorts, allowing us to finely control for confounding. We were able to consider a number of relevant lifestyle factors to minimize the potential for unmeasured confounding. The wide, nonoverlapping age distribution between NHS and NHSII provided a unique opportunity to examine the very long-term associations between menopausal factors and OSA risk.

In conclusion, we found that surgical as compared with natural menopause was independently associated with higher OSA risk in postmenopausal women. Further research is necessary to understand the underlying biology for this association, particularly hormone-related mechanisms, considering the time course and rapidity of hormonal changes. Given the considerably high prevalence of both surgical menopause and OSA in the general population, establishing their link has important public health implications. Our findings add additional support for consideration of ovarian conservation at the time of hysterectomy in low-risk, premenopausal women, and could identify high-risk postmenopausal women, such as those with oophorectomy, who may benefit from further OSA screening.

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