



A Population-Based Study of the Bidirectional Association Between Obstructive Sleep Apnea and Type 2 Diabetes in Three Prospective U.S. Cohorts

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OBJECTIVE

Multiple lines of evidence support a complex relationship between obstructive sleep apnea (OSA) and diabetes. However, no population-based study has evaluated the potential bidirectional association between these two highly prevalent disorders.

RESEARCH DESIGN AND METHODS

We followed 146,519 participants from the Nurses' Health Study (NHS; 2002–2012), Nurses' Health Study II (NHSII; 1995–2013), and Health Professionals Follow-up Study (HPFS; 1996–2012) who were free of diabetes, cardiovascular disease, and cancer at baseline. Cox proportional hazards models were used to estimate hazard ratios (HRs) for developing diabetes according to OSA status. In parallel, we used similar approaches to estimate risk of developing OSA according to diabetes status among 151,194 participants free of OSA, cardiovascular disease, and cancer at baseline. In all three cohorts, diagnoses of diabetes and OSA were identified by validated self-reports.

RESULTS

Similar results were observed across the three cohorts. In the pooled analysis, 9,029 incident diabetes cases were identified during follow-up. After accounting for potential confounders, the HR (95% CI) for diabetes was 2.06 (1.86, 2.28) comparing those with versus without OSA. The association was attenuated but remained statistically significant after further adjusting for waist circumference and BMI (HR 1.37 [95% CI 1.24, 1.53]), with the highest diabetes risk observed for OSA concomitant with sleepiness (1.78 [1.13, 2.82]). In the second analysis, we documented 9,364 incident OSA cases during follow-up. Compared with those without diabetes, the multivariable HR (95% CI) for OSA was 1.53 (1.32, 1.77) in individuals with diabetes. Adjustment for BMI and waist circumference attenuated the association (1.08 [1.00, 1.16]); however, an increased risk was observed among those with diabetes who used insulin compared with those without diabetes (1.43 [1.11, 1.83]), particularly among women (1.60 [1.34, 1.89]).

CONCLUSIONS

OSA is independently associated with an increased risk of diabetes, whereas insulin-treated diabetes is independently associated with a higher risk of OSA, particularly in women. Clinical awareness of this bidirectional association may improve prevention and treatment of both diseases. Future research aimed at elucidating the mechanisms that underlie each association may identify novel intervention targets.

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Both diabetes and obstructive sleep apnea (OSA) are well-established risk factors for cardiovascular disease and premature death that affect millions of people worldwide. The clinical co-occurrence of diabetes and OSA observed in many cross-sectional studies (1–5) has led to the hypothesis of a recursive relationship between these two highly prevalent disorders. Such a bidirectional link is supported by multiple lines of evidence. Intermittent hypoxemia, autonomic nervous system (ANS) overactivity, and sleep fragmentation resulting from OSA may contribute to diabetes through elevated inflammation, insulin resistance, glucose intolerance, and β -cell dysfunction (6–8). Conversely, preexisting diabetes may promote sleep-disordered breathing through abnormalities in ANS activity and impaired ventilatory control due to diabetic neuropathy or through effects of insulin resistance as well as inflammatory and oxidative stress-activated signaling pathways (6–8). However, observed associations between diabetes and OSA (regardless of the directionality) may be confounded by adiposity, the strongest risk factor for both conditions.

Despite plausible evidence, no large-scale population-based study has simultaneously evaluated/quantified this potential bidirectional association, which is important for targeted prevention of both diabetes and OSA. Prior prospective studies have shown consistent associations between OSA status at baseline and increased diabetes risk during follow-up (9–18). By contrast, only one prospective study has partially addressed the converse relationship, reporting positive associations of baseline fasting insulin and insulin resistance with incidence of reported apneas during sleep (19). There is no direct evidence, to our knowledge, on whether diabetes is prospectively associated with OSA risk. To clarify the complex temporal relationship between diabetes and OSA, we examined in parallel whether OSA predicted higher diabetes incidence and whether diabetes was associated with higher OSA risk over 10–18 years of follow-up among U.S. men and women from three large prospective cohort studies. We further assessed the role of adiposity in this putative bidirectional association.

RESEARCH DESIGN AND METHODS

Study Population

The Nurses' Health Study (NHS, enrolling 121,701 female nurses aged 30–55 years in 1976), the Nurses' Health Study II (NHSII, enrolling 116,429 female nurses aged 25–42 years in 1989), and the Health Professionals Follow-up Study (HPFS, enrolling 51,529 male health professionals aged 40–75 years in 1986) are three ongoing prospective U.S. cohort studies. Participants from all three cohorts completed a baseline health questionnaire and updated information on lifestyle and disease diagnoses through biennial follow-up questionnaires. The current study included 166,588 participants (NHS: 68,590; NHSII: 75,082; HPFS: 22,916) who answered the OSA question in 2012–2013. The study was approved by the institutional review board at Partners HealthCare system.

Assessment of Diabetes

Incident diabetes diagnoses in three cohorts were identified by self-reports on each biennial questionnaire and confirmed by a mailed supplemental questionnaire evaluating symptoms, diagnostic tests, and diabetes treatment. Type 2 diabetes was confirmed if ≥ 1 of the following criteria by the National Diabetes Data Group (20) was met: 1) elevated plasma glucose levels (fasting glucose ≥ 140 mg/dL or random glucose ≥ 200 mg/dL) with ≥ 1 classic symptoms (polydipsia, polyuria, polyphagia, weight loss, or coma); 2) elevated plasma glucose on at least two occasions (fasting glucose ≥ 140 mg/dL, random glucose ≥ 200 mg/dL, and/or glucose ≥ 200 mg/dL after an oral glucose test) with no symptoms; and 3) hypoglycemic therapy with insulin or oral medications. An updated cutoff of 126 mg/dL for fasting glucose was used for diagnoses after 1997 according to the American Diabetes Association diagnostic criteria (21). In a validation study of 62 NHS and 59 HPFS participants ascertained to have diabetes through the supplemental questionnaire, 61 (98%) and 57 (97%), respectively, were confirmed by medical records (22,23). Our primary evaluation of diabetes status was whether participants had a history of confirmed diabetes diagnosis. Secondarily, we characterized participants with diabetes by their glycemic control methods,

including oral hypoglycemic agents, insulin therapy, or no medications, and by duration of the disease.

Assessment of OSA

In 2012, NHS participants were asked to report whether they had been diagnosed with OSA by a sleep study and the year of first diagnosis (24,25). Similar assessments were conducted in 2013 in NHSII and in 2012 in HPFS. The overall prevalence of self-reported diagnosed OSA in 2012–2013 was 13.8% in HPFS men and 6.4% in NHS/NHSII women (24), similar to the projected U.S. prevalence of moderate-to-severe OSA (Apnea-Hypopnea Index [AHI] ≥ 15) measured by polysomnography (26). In a validation study, a random sample of 96 NHS/NHSII women who self-reported OSA were all confirmed by medical records to have the diagnoses through objective monitoring (91% by in-laboratory polysomnography); 94 (98%) were classified as obstructive (24). The agreement in year of diagnosis between self-reports and medical records was 95%. Key OSA symptoms, including snoring and sleepiness, have been assessed multiple times during follow-up. Participants responded to the simple question "Do you snore?" with response categories of "every night," "most nights," "a few nights a week," "occasionally," and "almost never"; those who reported snoring every night or most nights were considered to have habitual snoring. Participants who reported ≥ 4 days/week of disrupted daily activities due to sleepiness were considered to have excessive daytime sleepiness (EDS). The primary OSA status was based on whether participants reported a clinical OSA diagnosis; we further combined OSA symptoms with clinical diagnoses to categorize OSA status in order to capture potentially undiagnosed OSA or OSA severity, comparing participants without OSA diagnoses who did not report habitual snoring (reference), participants without OSA diagnoses who reported habitual snoring (i.e., potentially undiagnosed, mild OSA), participants with OSA diagnoses who did not report EDS (i.e., potentially less severe OSA), and participants with OSA diagnoses who reported EDS (i.e., potentially more severe OSA).

Assessment of Covariates

Participants reported their birth date, height, and race/ethnicity. Weight, smoking

status, menopausal status, duration and type of postmenopausal hormone therapy, regular physical examination, and diagnosis of hypertension were self-reported biennially. A measuring tape was provided to measure waist circumference twice during follow-up. Self-reported weight, height, and waist circumference have been previously validated with excellent reliability in these cohorts. Physical activity, assessed every 2–4 years, was quantified as MET hours per week integrating activity duration and intensity. The Alternate Healthy Eating Index (AHEI) was derived from validated semi-quantitative food-frequency questionnaires administered every 4 years. Family history of diabetes and habitual sleep duration were repeatedly assessed by self-reports. In NHS, lifetime duration of rotating night shifts (defined as at least 3 nights per month) was assessed in 1988; in NHSII, it was assessed in 1989 with updates every 2–4 years thereafter.

Statistical Analyses

To evaluate the association of OSA with incident type 2 diabetes, we excluded participants with a history of cancer (except nonmelanoma skin cancer), cardiovascular disease (myocardial infarction, stroke, or coronary artery bypass graft), or diabetes (type 1, type 2, or gestational) at baseline, leaving an analytical sample of 146,519 (NHS: 54,069; NHSII: 72,838; HPFS: 19,612). Each participant contributed person-time from baseline (NHS: 2002; NHSII: 1995; HPFS: 1996) until date of diabetes diagnosis or return of the OSA assessment questionnaire in 2012 (NHS/HPFS) or 2013 (NHSII). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for diabetes comparing participants with versus without OSA diagnoses. We modeled OSA history as a time-dependent variable, allowing unexposed participants (i.e., those without OSA diagnoses) to become exposed at the time of OSA diagnosis. Age- (in 5-year age-groups) and calendar year-stratified models were used in all analyses. Proportional hazards assumption was evaluated using cross-product terms of OSA status with calendar time or age. We further adjusted for demographic, lifestyle, and comorbidity factors as detailed in the footnotes of Table 2. These covariates, except for race/ethnicity and

family history of diabetes, were also treated as time-varying variables in the analysis. Because adiposity is a strong predictor for both diabetes and OSA, we additionally adjusted for time-varying BMI and waist circumference in a separate model to assess their impact on the association. We first conducted the analyses in individual cohorts and then pooled the risk estimates using random-effects meta-analysis.

In parallel, after excluding participants diagnosed with OSA, cancer, cardiovascular disease, type 1 diabetes, or gestational diabetes mellitus prior to baseline, a total of 151,194 participants (NHS: 57,597; NHSII: 73,982; HPFS: 19,615) were included in the analysis of incident OSA risk according to type 2 diabetes status. Similarly, we calculated person-years for each participant from baseline to date of OSA diagnosis or return of the 2012–2013 questionnaire. We estimated HRs (95% CIs) of incident OSA associated with diabetes status or diabetes treatment, with both exposures and covariates modeled as time-varying variables in Cox proportional hazards regression. Further, we evaluated the associations between diabetes duration and OSA risk separately among participants receiving different diabetes treatment. We considered the same multivariable models with and without adjustment for BMI and waist circumference as described above. Cohort-specific estimates were pooled through random-effects meta-analysis.

In addition, we evaluated whether the bidirectional association between diabetes and OSA differed by age (<60, ≥60 years), sex (men, women), and BMI (<30, ≥30 kg/m²). Stratum-specific estimates were calculated in each cohort and then meta-analyzed across cohorts for each category of the factors. Potential heterogeneity was tested using a random-effects model. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

OSA and Incident Diabetes

At the midpoint of follow-up in 2005–2006 (Table 1), 878 of 52,309 (1.7%) NHS women, 1,096 of 70,393 (1.6%) NHSII women, and 1,139 of 18,444 (6.2%) HPFS men reported a diagnosis of OSA. Participants who reported the diagnoses compared with those who did not had higher BMI and waist circumference but

lower alcohol consumption and physical activity, and they were more likely to have habitual snoring, EDS, hypertension, and a family history of diabetes. NHS/NHSII women with OSA diagnoses were also more likely to have ever used estrogen-only hormone therapy and to have worked rotating night shifts.

A total of 2,700 NHS women (525,046 person-years), 4,892 NHSII women (1,278,315 person-years) and 1,437 HPFS men (300,223 person-years) developed diabetes during 10–18 years of follow-up. Similar positive associations between OSA status and incident diabetes risk were observed across the three cohorts (Table 2). The pooled age-adjusted HR (95% CI) was 2.97 (2.40, 3.69) comparing participants with versus without OSA diagnoses, which was reduced to 2.06 (1.86, 2.28) after accounting for multiple potential confounders. Additional adjustment for BMI and waist circumference further attenuated the relationship, but the association remained statistically significant (1.37 [1.24, 1.52]). There was no evidence of significant heterogeneity in the association by age, sex, or BMI (*P*-heterogeneity > 0.17) (Supplementary Table 1).

When OSA status and related symptoms were considered jointly (Table 2), participants who did not have clinical diagnoses of OSA but reported habitual snoring were at higher diabetes risk compared with those who reported neither OSA diagnoses nor habitual snoring (pooled HR 1.25 [95% CI 1.19, 1.31] in the fully-adjusted model). Among participants with OSA diagnoses, those who reported EDS (1.78 [1.13, 2.82]) appeared to have even higher diabetes risk than those who did not report EDS (1.48 [1.31, 1.66]), although this difference was apparent in NHS and HPFS but not observed in NHSII.

Diabetes and Incident OSA

At the midpoint of follow-up (Table 3), 4,633 of 57,135 (8.1%) NHS women, 2,205 of 72,613 (3.0%) NHSII women, and 1,118 of 18,723 (6.0%) HPFS men had previously reported diabetes diagnoses. Participants who had diabetes compared with those who did not were more likely to be older and of nonwhite race/ethnicity and to have higher BMI and waist circumference but lower diet quality, alcohol consumption, and physical activity. Habitual snoring, EDS, hypertension, and

Table 1—Population characteristics by OSA status at the midpoint of follow-up

	Self-reported OSA diagnosis					
	NHS (2006)		NHSII (2005)		HPFS (2006)	
	No	Yes	No	Yes	No	Yes
<i>N</i>	51,431	878	69,297	1,096	17,305	1,139
Age, years	70.4 (6.6)	69.4 (6.3)	50.9 (4.6)	51.8 (4.4)	68.9 (7.2)	68.7 (6.8)
Postmenopausal	100	100	46	51	–	–
Ever E-only HT ^a	43	52	19	22	–	–
Duration of E-only HT, months ^{a,b}	108.6 (88.9)	106.0 (91.0)	6.8 (5.1)	6.5 (5.1)	–	–
Ever E+P HT ^a	41	42	16	13	–	–
Duration of E+P HT, months ^{a,b}	72.3 (51.0)	69.5 (51.0)	3.6 (3.0)	3.8 (3.0)	–	–
Nonwhite	6	5	5	6	4	4
BMI, kg/m ²	26.2 (4.9)	30.8 (6.9)	26.7 (5.9)	34.3 (8.2)	24.7 (6.6)	27.1 (7.9)
Waist circumference, cm	85.5 (12.8)	94.7 (15.6)	85.7 (14.1)	102.2 (17.5)	99.2 (10.2)	106.1 (12.4)
Current smokers	6	4	7	7	3	2
AHEI-2010	57.9 (11.0)	57.4 (10.9)	51.5 (9.9)	48.7 (9.6)	55.5 (9.9)	54.5 (9.7)
Alcohol, g/day	5.8 (8.5)	4.2 (6.6)	4.1 (6.4)	2.7 (5.1)	11.6 (12.8)	10.1 (12.1)
Sleep duration, h/day	7.1 (1.1)	7.2 (1.3)	7.0 (1.0)	7.0 (1.3)	7.1 (1.0)	7.1 (1.1)
Habitual snoring	15	50	16	61	32	67
EDS	3	11	10	30	9	14
Ever night-shift work	48	55	70	74	–	–
Duration of shift work, years ^c	5.5 (6.4)	6.1 (6.8)	5.6 (7.2)	5.7 (6.9)	–	–
Physical activity, MET-h/week	19.5 (17.8)	15.1 (13.7)	21.6 (21.3)	15.4 (15.4)	38.0 (29.3)	31.5 (25.6)
History of hypertension	56	74	24	50	49	64
Family history of diabetes	25	28	34	43	20	23
Regular physical exam	95	96	91	94	85	89

Data are mean (SD) or percent unless otherwise indicated. E-only HT, estrogen-only hormone therapy; E+P HT, estrogen plus progestin hormone therapy. ^aAmong postmenopausal women. ^bAmong ever users. ^cAmong ever night-shift workers.

family history of diabetes were also more common among participants with diabetes. In NHS/NHSII, women with diabetes had shorter duration of estrogen plus progestin hormone therapy and longer duration of night-shift work. Further, among participants with diabetes, those treated with insulin therapy had higher BMI and waist circumference and were more likely to have a family history of diabetes than those treated with oral hypoglycemic medications or those receiving no antidiabetes medications (Supplementary Table 2).

During follow-up, there were 1,926 incident OSA diagnoses in NHS (573,328 person-years), 5,333 diagnoses in NHSII (1,307,468 person-years), and 2,105 diagnoses in HPFS (300,546 person-years). In the pooled age-adjusted analysis (Table 4), diabetes was associated with a 2.14-fold (95% CI 1.49, 3.07) increased risk of developing OSA. Adjustment for potential confounders substantially attenuated the association (HR 1.53 [95% CI 1.32, 1.77]). A weak positive association was observed after controlling for BMI and waist circumference (1.08 [1.00, 1.16]).

This association did not differ significantly by age, sex, or BMI (*P*-heterogeneity > 0.45) (Supplementary Table 1).

Further analysis by diabetes treatment showed higher OSA risk among individuals with diabetes treated with insulin therapy than among individuals with diabetes treated with oral hypoglycemic agents only or those who did not use antidiabetes medications (Table 4). Compared with those without diabetes in the fully adjusted model, individuals with insulin-treated diabetes had 43% higher OSA risk (95% CI 1.11, 1.83), whereas the associations were null for individuals with diabetes treated with oral hypoglycemic agents (pooled HR 0.97 [95% CI 0.87, 1.09]) or without antidiabetes medication use (1.06 [0.95, 1.18]). Notably, the increased OSA risk associated with insulin therapy after full adjustment was only observed in NHS/NHSII women but not in HPFS men, resulting in a significant sex difference in the association (HR in women 1.60 [1.34, 1.89]; HR in men 1.01 [0.69, 1.49]; *P*-heterogeneity = 0.03). Overall, the risk estimates did not differ substantially by duration of diabetes

after accounting for diabetes treatment (Supplementary Table 3). For example, among participants receiving insulin therapy, the fully adjusted HRs (95% CIs) for OSA were 1.49 (0.97, 2.29) for diabetes duration <5 years, 1.21 (0.88, 1.66) for diabetes duration 5–10 years, and 1.45 (1.19, 1.77) for diabetes duration ≥10 years, compared with those without diabetes.

CONCLUSIONS

Our results from three large-scale, population-based cohorts of >145,000 U.S. men and women support a bidirectional association between diabetes and OSA. OSA was associated with 37% higher diabetes risk, independent of demographic, lifestyle, comorbidity, and anthropometric factors. Conversely, individuals with diabetes also had a modest increase in risk of developing OSA. After adjusting for adiposity, we observed a 43% higher OSA risk among individuals with diabetes treated with insulin therapy, particularly among women, consistent with literature suggesting that insulin levels and insulin resistance are

Table 2—Risk of developing diabetes according to self-reported OSA status and related symptoms

	Cases	Person-years	Model 1 ^a	Model 2 ^b	Model 3 ^c
NHS					
Self-reported OSA diagnosis					
No	2,592	516,477	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	108	8,569	2.89 (2.37, 3.53)	2.09 (1.70, 2.56)	1.47 (1.20, 1.81)
OSA status by related symptoms					
No OSA diagnosis	1,911	437,103	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
No OSA diagnosis + snoring	681	79,375	1.96 (1.79, 2.14)	1.61 (1.46, 1.76)	1.28 (1.17, 1.41)
OSA diagnosis + no EDS	90	7,621	3.07 (2.46, 3.82)	2.17 (1.73, 2.71)	1.47 (1.17, 1.84)
OSA diagnosis + EDS	18	948	5.50 (3.39, 8.90)	3.86 (2.37, 6.27)	2.57 (1.57, 4.20)
NHSII					
Self-reported OSA diagnosis					
No	4,668	1,265,678	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	224	12,636	3.55 (3.09, 4.09)	2.09 (1.81, 2.41)	1.27 (1.10, 1.47)
OSA status by related symptoms					
No OSA diagnosis	2,972	1,035,781	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
No OSA diagnosis + snoring	1,696	229,898	2.37 (2.23, 2.52)	1.77 (1.66, 1.88)	1.23 (1.15, 1.31)
OSA diagnosis + no EDS	166	9,557	4.51 (3.83, 5.31)	2.60 (2.20, 3.08)	1.43 (1.21, 1.69)
OSA diagnosis + EDS	58	3,079	4.64 (3.52, 6.11)	2.34 (1.77, 3.09)	1.25 (0.94, 1.66)
HPFS					
Self-reported OSA diagnosis					
No	1,309	288,375	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	128	11,848	2.49 (2.04, 3.04)	1.99 (1.63, 2.44)	1.48 (1.20, 1.82)
OSA status by related symptoms					
No OSA diagnosis	744	196,340	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
No OSA diagnosis + snoring	565	92,035	1.65 (1.47, 1.85)	1.48 (1.31, 1.66)	1.26 (1.12, 1.43)
OSA diagnosis + no EDS	107	10,113	2.93 (2.35, 3.65)	2.26 (1.80, 2.83)	1.59 (1.26, 2.00)
OSA diagnosis + EDS	21	1,735	3.33 (2.06, 5.37)	2.76 (1.70, 4.48)	1.97 (1.21, 3.22)
Pooled ^d					
Self-reported OSA diagnosis					
No	8,569	2,070,530	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	460	33,053	2.97 (2.40, 3.69)	2.06 (1.86, 2.28)	1.37 (1.24, 1.52)
OSA status by related symptoms					
No OSA diagnosis	5,627	1,669,224	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
No OSA diagnosis + snoring	2,942	401,308	1.98 (1.60, 2.44)	1.63 (1.47, 1.80)	1.25 (1.19, 1.31)
OSA diagnosis + no EDS	363	27,291	3.46 (2.59, 4.63)	2.39 (2.13, 2.68)	1.48 (1.31, 1.66)
OSA diagnosis + EDS	97	5,762	4.48 (3.55, 5.64)	2.77 (2.08, 3.70)	1.78 (1.13, 2.82)

Data are HR (95% CI) unless otherwise indicated. Ref., reference. ^aStratified by age and calendar time. ^bModel 1 + adjusted for race/ethnicity (white, nonwhite), menopausal status in women (pre-, postmenopausal), family history of diabetes (yes, no), duration of postmenopausal hormone use by type (never, <5.0, 5.0–9.9, ≥10.0 years), smoking status (current, past, never), alcohol consumption (none, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0 g/day), diet quality (measured by AHEI score, in quintiles), regular physical examination (yes, no), sleep duration (≤5, 6, 7, 8, ≥9 h/day), duration of night-shift work (never, <5.0, 5.0–9.9, ≥10.0 years), physical activity (measured by MET-h/week, in quintiles), and history of hypertension (yes, no). ^cModel 2 + adjusted for BMI (<20.0, 20–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m²) and waist circumference (<80, 80–87, 88–95, ≥96 cm for women and <94, 94–101, 102–111, ≥112 cm for men). ^dPooled using random-effects meta-analysis.

associated with an increased incidence of OSA (19,27). Our study provides direct evidence at the population level on the reciprocal association between diabetes and OSA.

OSA and Incident Diabetes

While prior prospective studies reported positive associations between OSA and incident diabetes, multiple differences exist across studies regarding study populations, length of follow-up, covariate adjustment, and OSA assessment/definition (including self-reports, AHI, oxygen desaturation index, and respiratory disturbance index). In particular, five

studies only detected significant associations for moderate-to-severe OSA (9–13), and one study only found the association in women (16). Despite these differences, a recent meta-analysis of nine prospective cohort studies including 64,101 participants yielded an adjusted pooled relative risk of 1.35 (95% CI 1.24, 1.47) with moderate between-study heterogeneity ($I^2 = 44.4\%$, $P = 0.072$) (7). This summary result is highly comparable to our adjusted pooled estimate for the association between OSA and incident diabetes (HR 1.37 [95% CI 1.24, 1.52]). Notably, our study sample was >2 times the size of this meta-analysis,

with individual-level data to control for confounding and evaluate subgroup heterogeneity.

Similar to most previous studies (7), there was notable attenuation in the association after adjustment for lifestyle and anthropometric covariates, which to some extent reflected strong confounding by these factors given that they are important precipitating factors for both conditions. However, adjusting for lifestyle and anthropometric factors may also partially account for some mediating mechanisms, such as inflammation, impaired glucose tolerance, and insulin resistance, which have been hypothesized

Table 3—Population characteristics by diabetes status at the midpoint of follow-up

	Diabetes status					
	NHS (2006)		NHSII (2005)		HPFS (2006)	
	No	Yes	No	Yes	No	Yes
<i>N</i>	52,502	4,633	70,408	2,205	17,605	1,118
Age, years	70.4 (6.6)	70.9 (6.3)	50.9 (4.6)	52.8 (4.3)	68.9 (7.2)	70.3 (7.1)
Postmenopausal	100	100	46	52	–	–
Ever E-only HT ^a	43	43	19	23	–	–
Duration of E-only HT, months ^{a,b}	118.5 (97.8)	112.5 (92.1)	6.8 (5.1)	6.8 (4.9)	–	–
Ever E+P HT ^a	41	34	16	12	–	–
Duration of E+P HT, months ^{a,b}	77.0 (55.3)	68.4 (51.4)	3.6 (3.0)	3.3 (2.6)	–	–
Nonwhite	6	8	5	10	4	7
BMI, kg/m ²	26.3 (5.0)	30.7 (6.3)	26.8 (5.9)	35.2 (7.7)	24.7 (6.6)	26.8 (8.0)
Waist circumference, cm	85.7 (12.9)	97.1 (14.1)	85.7 (14.1)	105.2 (17.2)	99.3 (10.2)	106.3 (12.4)
Current smokers	6	5	7	8	3	5
AHEI-2010	54.3 (9.3)	52.6 (8.8)	51.5 (9.9)	48.8 (9.2)	55.5 (9.9)	53.9 (9.5)
Alcohol, g/day	5.8 (8.5)	3.0 (6.1)	4.1 (6.4)	1.9 (4.5)	11.5 (12.8)	9.5 (12.2)
Sleep duration, h/day	7.1 (1.1)	7.1 (1.2)	7.0 (1.1)	6.9 (1.2)	7.1 (1.0)	7.1 (1.0)
Habitual snoring	26	38	26	47	32	42
EDS	3	5	10	17	9	13
Ever night-shift work	48	50	70	74	–	–
Duration of shift work, years ^c	5.5 (6.4)	6.8 (7.5)	5.6 (7.3)	6.7 (8.3)	–	–
Physical activity, MET-h/week	19.5 (17.8)	14.4 (15.4)	21.6 (21.3)	15.7 (17.9)	37.9 (29.3)	29.3 (24.7)
History of hypertension	57	85	24	68	50	76
Family history of diabetes	25	47	34	68	20	39
Regular physical exam	95	97	91	96	85	90

Data are mean (SD) or percent unless otherwise indicated. E-only HT, estrogen-only hormone therapy; E+P HT, estrogen plus progestin hormone therapy. ^aAmong postmenopausal women. ^bAmong ever users. ^cAmong ever night-shift workers.

as the biologic pathways linking OSA to the development of diabetes (6–8) and are strongly correlated with adiposity and lifestyle factors (28–31). The significant association after full adjustment for demographic, lifestyle, comorbidity, and anthropometric factors suggests that there may be other independent pathways underlying the observed association. For example, intermittent hypoxemia and recurrent arousals in OSA can stimulate the ANS, leading to augmented catecholamine production, which impairs glucose metabolism, reduces insulin sensitivity, and induces β -cell dysfunction (32).

Further, the symptom-based categorization of OSA status showed that OSA concomitant with EDS, a marker commonly used to indicate clinically significant OSA, was associated with greater diabetes risk compared with OSA without EDS (78% vs. 48% increased risk). The stronger association for a phenotype that includes EDS is also consistent with the hypothesis that EDS is a marker of the persistent proinflammatory condition associated with visceral obesity and OSA (27). By contrast, simple snoring without

clinical diagnosis of OSA, although to a lesser extent, was also significantly associated with 25% higher risk of diabetes in all three cohorts, consistent with several existing studies that have identified snoring (regardless of OSA) as a risk factor for diabetes (33,34). These results suggest a potential dose-response association between OSA severity and diabetes risk and provide additional evidence on a biological gradient corroborating a causal relationship.

Diabetes and Incident OSA

Although only one population-based, prospective study has linked insulin resistance with a higher incidence of OSA, as inferred by reported apneas during sleep (19), multiple plausible mechanisms have been suggested for diabetes contributing to increased OSA risk (6–8). First, insulin resistance, a hallmark of diabetes, has been shown in rat models to desensitize ventilatory responses to hypercapnia and increase susceptibility to OSA (35,36). Second, leptin resistance, another metabolic abnormality common in diabetes, can impair neuromechanical

control of upper airway muscles and increase pharyngeal collapsibility during sleep (37), with effects most prominent in women (38). Third, diabetes is associated with elevated systemic inflammation and oxidative stress, which may weaken respiratory muscles and reduce muscle contractility, predisposing to OSA (39,40). Overall, we only observed a very weak, although statistically significant, association between diabetes and incident OSA after adjustment for BMI and waist circumference, perhaps because adiposity is a good proxy for these diabetes-associated biologic alterations potentially involved in OSA development.

In addition, several cross-sectional studies reported substantially higher OSA prevalence among diabetes patients with autonomic or peripheral neuropathy (41,42), suggesting that diabetic neuropathy may undermine the reflex mechanisms protecting the upper airway from collapse during sleep and may serve as another potential pathway through which diabetes promotes development and progression of OSA.

Table 4—Risk of developing OSA according to diabetes status and antidiabetes medication use

	Cases	Person-years	Model 1 ^a	Model 2 ^b	Model 3 ^c
NHS					
Diabetes status					
No	1,631	528,966	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	295	44,272	2.05 (1.81, 2.32)	1.59 (1.39, 1.81)	1.12 (0.98, 1.27)
Status by diabetes treatment					
No diabetes	1,631	528,966	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Diabetes + no medications	91	16,559	1.81 (1.46, 2.24)	1.46 (1.18, 1.81)	1.07 (0.86, 1.33)
Diabetes + oral hypoglycemic agents only	135	22,264	1.81 (1.51, 2.16)	1.39 (1.16, 1.66)	0.99 (0.82, 1.18)
Diabetes + insulin therapy	69	5,450	3.66 (2.87, 4.68)	2.67 (2.08, 3.42)	1.68 (1.30, 2.16)
NHSII					
Diabetes status					
No	4,885	1,283,581	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	448	23,887	2.99 (2.70, 3.30)	1.68 (1.52, 1.86)	1.08 (0.97, 1.19)
Status by diabetes treatment					
No diabetes	4,885	1,283,581	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Diabetes + no medications	212	13,245	2.66 (2.31, 3.06)	1.55 (1.34, 1.79)	1.03 (0.90, 1.19)
Diabetes + oral hypoglycemic agents only	161	8,234	2.97 (2.53, 3.48)	1.62 (1.38, 1.90)	1.00 (0.85, 1.17)
Diabetes + insulin therapy	75	2,409	4.65 (3.69, 5.85)	2.54 (2.01, 3.20)	1.52 (1.20, 1.92)
HPFS					
Diabetes status					
No	1,964	290,488	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	141	10,058	1.57 (1.32, 1.87)	1.28 (1.07, 1.52)	1.01 (0.84, 1.21)
Status by diabetes treatment					
No diabetes	1,964	290,488	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Diabetes + no medications	78	5,455	1.64 (1.30, 2.06)	1.34 (1.06, 1.69)	1.13 (0.89, 1.42)
Diabetes + oral hypoglycemic agents only	35	2,682	1.29 (0.92, 1.80)	1.04 (0.74, 1.46)	0.82 (0.58, 1.15)
Diabetes + insulin therapy	28	1,922	1.88 (1.29, 2.75)	1.53 (1.04, 2.24)	1.01 (0.69, 1.49)
Pooled ^d					
Diabetes status					
No	8,480	2,103,035	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Yes	884	78,217	2.14 (1.49, 3.07)	1.53 (1.32, 1.77)	1.08 (1.00, 1.16)
Status by diabetes treatment					
No diabetes	8,480	2,103,035	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Diabetes + no medications	381	35,259	2.01 (1.46, 2.77)	1.48 (1.33, 1.65)	1.06 (0.95, 1.18)
Diabetes + oral hypoglycemic agents only	331	33,180	1.94 (1.24, 3.04)	1.38 (1.12, 1.70)	0.97 (0.87, 1.09)
Diabetes + insulin therapy	172	9,781	3.25 (2.07, 5.11)	2.26 (1.70, 3.01)	1.43 (1.11, 1.83)

Data are HR (95% CI) unless otherwise indicated. Ref., reference. ^aStratified by age and calendar time ^bModel 1 + adjusted for race/ethnicity (white, nonwhite), menopausal status in women (pre-, postmenopausal), family history of diabetes (yes, no), duration of postmenopausal hormone use by type (never, <5.0, 5.0–9.9, ≥10.0 years), smoking status (current, past, never), alcohol consumption (none, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0 g/day), diet quality (measured by AHEI score, in quintiles), regular physical examination (yes, no), sleep duration (≤5, 6, 7, 8, ≥9 h/day), duration of night-shift work (never, <5.0, 5.0–9.9, ≥10.0 years), physical activity (measured by MET-h/week, in quintiles), and history of hypertension (yes, no). ^cModel 2 + adjusted for BMI (<20.0, 20–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40.0 kg/m²) and waist circumference (<80, 80–87, 88–95, ≥96 cm for women and <94, 94–101, 102–111, ≥112 cm for men). ^dPooled using random-effects meta-analysis.

This could explain the higher OSA risk associated with insulin therapy that we consistently observed, as insulin therapy may indicate long-standing diabetes with uncontrolled glycemia that requires intensive glucose lowering (43). Thus, these patients were more likely to have complications of diabetes, such as neuropathy, leading to increased OSA risk. Alternatively, insulin levels per se may play a pathogenic role in OSA susceptibility.

We found that the excess OSA risk associated with insulin therapy was remarkably higher in women than in men (60% vs. 1% increased risk),

consistent with our previous cross-sectional study (24). This study clarifies that this sex difference is likely due to the differential impact of insulin-treated diabetes on OSA risk, but not OSA on diabetes risk. Similar sex differences have been well elucidated for cardiovascular outcomes, with women with diabetes more likely to develop coronary heart disease, stroke, and heart failure than men with diabetes (44,45). Our results add to the growing evidence that diabetes-related susceptibility to OSA is also higher in women than men. Interestingly, insulin therapy was more consistently associated with higher OSA

risk than were other treatment strategies in both men and women prior to adjustment of BMI and waist circumference; after the adjustment, this pattern remained similar in women but disappeared in men. This suggests that adiposity may act differently by sex in the pathogenesis of OSA, as supported by previous findings that waist circumference was more strongly associated with OSA in men than in women (24,46). Future studies on sex-specific mechanisms in OSA are needed to fully understand sex differences in the association between diabetes and incident OSA.

Strengths and Limitations

In this study, diabetes and OSA were identified through self-reports with further validation. Given that both diseases tend to be clinically underdiagnosed (47,48), self-reported diagnoses may have misclassified those with mild, asymptomatic diabetes or OSA (i.e., false negatives). This situation could bias the bidirectional association toward the null, if the mild, undiagnosed disease is also associated with the outcome. As mild, undiagnosed disease may exhibit weaker associations compared with clinically diagnosed, more severe disease (e.g., the habitual snoring without OSA diagnosis group), the underestimation is likely to be small. Importantly, we have previously shown that the prevalence of undiagnosed diabetes or OSA is substantially lower in our cohorts of trained health professionals compared with the general population (24,49). Another concern is the possibility of detection bias, in that diagnosis of one condition may elevate the likelihood of clinically diagnosing the other condition. However, this is unlikely to explain the observed bidirectional association because 1) the magnitude/pattern of the association varied by the direction of the association; 2) among clinically diagnosed cases, the association differed considerably by diabetes treatment or by EDS; and 3) adjusting for regular physical examination, an indicator for health care access/motivation, did not alter the observed associations. Further, we did not have information on OSA severity (e.g., AHI), OSA treatment (e.g., continuous positive airway pressure [CPAP] therapy), extent of glycemic control (e.g., hemoglobin A_{1c}), or diabetes complications (e.g., neuropathy). Understanding relationships with these clinical variables will provide important insights into the potential benefits of managing one disorder on the other and should be explored in other studies (50–52). Although we adjusted for both BMI and waist circumference, residual confounding by fat distribution was possible. Specifically, neck circumference, a measure of upper-body fat deposition, is a strong predictor for OSA beyond BMI and abdominal fat (53,54) and is independently associated with inflammation and metabolic factors (55,56). Additional studies are needed to evaluate the impact of neck circumference on this bidirectional

association. Finally, our results based on predominantly white health professionals may not apply to other populations. However, the similarity of our risk estimates with prior studies conducted in diverse samples suggests some common etiology underlying the bidirectional association across populations. Notably, the high-quality health-related information reported by health professionals, including disease diagnoses, greatly enhanced the validity and reliability of our findings.

The strengths of the study include large sample size, long follow-up, and consistent collection of exposure and outcome information across the three cohorts. The retrospective assessment of OSA diagnoses, coupled with biennially updated information on diabetes diagnoses and other risk factors, provides a unique opportunity to elucidate the intricate temporal relationships between OSA and diabetes. This also allowed us to finely control for multiple important factors as time-varying variables, reducing residual confounding and increasing validity.

In conclusion, OSA was independently associated with an increased risk of diabetes, with the highest risk observed for OSA concomitant with EDS. On the other hand, diabetes, particularly insulin-treated diabetes, was associated with a higher risk of OSA, and the association was stronger in women than in men. Clinical awareness of this bidirectional association may improve prevention and treatment of both diseases, and vigilant monitoring of one condition among patients with the other is warranted if our findings are confirmed in other studies. Future research aimed at elucidating the mechanisms that underlie each association may identify novel intervention targets.

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