Insulin Resistance, Hyperglycemia, and Risk of Developing Obstructive Sleep Apnea in Men and Women in the United States

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Abstract

Rationale: Recent prospective studies suggest diabetes as a risk factor for the development of obstructive sleep apnea (OSA). However, the extent to which diabetes-related traits, such as hyperglycemia and insulin resistance, are related to OSA risk remains uncertain.

Objectives: To examine the risk of developing OSA according to baseline concentrations of fasting insulin and hemoglobin A1c (HbA1c).

Methods: Participants from four prospective U.S. cohorts were included: NHS (Nurses' Health Study; 2002–2012), NHSII (Nurses' Health Study II; 1995–2013), HPFS (Health Professionals Follow-up Study; 1996–2012), and MESA (Multi-Ethnic Study of Atherosclerosis; 2000–2012). OSA was assessed by self-reported clinical diagnosis in NHS/NHSII/HPFS and at-home polysomnography in MESA (defined as Apnea–Hypopnea Index $\geqslant$30).

Results: Of 9,283 participants with fasting insulin data, 790 (8.5%) developed OSA over 10 to 18 years of follow-up. After adjusting for sociodemographic, lifestyle, and comorbidity factors, the odds ratio for incident OSA comparing the extreme quintiles of fasting insulin was 3.59 (95% confidence interval, 2.67–4.82; P-trend < 0.0001). Of 6,342 participants with HbA1c data, 715 (11.3%) developed OSA. The comparable odds ratio for HbA1c was 2.21 (95% confidence interval, 1.69–2.89; P-trend < 0.0001). Additional adjustment for body mass index and waist circumference attenuated the associations for fasting insulin (P-trend = 0.005) and HbA1c (P-trend = 0.03). In the fully adjusted model simultaneously including both biomarkers, only fasting insulin but not HbA1c was associated with OSA risk.

Conclusions: Independent of obesity, insulin resistance may play a more important role than hyperglycemia in the pathogenesis of OSA. Given the limitation of using self-reported diagnosis to exclude baseline prevalent OSA cases, additional studies are needed to further establish the temporal relationship and assess whether improving insulin resistance may reduce OSA risk.

Keywords: obstructive sleep apnea; diabetes; insulin resistance; hyperglycemia; prospective study

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A large body of observational studies in the past 2 decades has shown that obstructive sleep apnea (OSA) induces insulin resistance, alters glucose homeostasis, and increases diabetes risk, likely via intermittent hypoxia, sleep fragmentation, and sympathetic hyperactivity (1–5). This has led to multiple randomized controlled trials (RCTs) evaluating whether OSA treatment using continuous positive airway pressure (CPAP) improves insulin resistance and glycemic control among individuals with comorbid diabetes (6–8). These RCTs, however, did not demonstrate a strong effect of CPAP treatment on glycemic traits and insulin resistance. Recent evidence also suggests the possibility of a bidirectional relationship between OSA and diabetes (9, 10), with several prospective studies supporting diabetes as a risk factor for incident OSA (11, 12).

Diabetes is characterized by increased insulin resistance, impaired insulin secretion, and progressively worsening glycemic control. These metabolic alterations can adversely impact a wide variety of physiologic processes, including mechanistic factors for OSA such as ventilatory control and upper airway patency (13, 14). Animal models suggest that diabetes and insulin resistance lead to abnormal ventilatory responses to hypoxia and hypercapnia that can be reversed by enhancing insulin sensitivity (15–19). In women without frank diabetes and OSA, insulin resistance was significantly positively correlated with measures of pharyngeal collapsibility (20), suggesting that insulin resistance may increase OSA risk through increasing upper airway collapsibility. Furthermore, chronic hyperglycemia may damage peripheral nerves, impairing neuromuscular control of breathing. Diabetic autonomic neuropathy has been linked to increased OSA prevalence (21–23).

Despite these plausible mechanisms, there are few prospective, epidemiologic studies quantifying to what extent insulin resistance and hyperglycemia may promote OSA development. One prospective study with 6 years of follow-up for incidence of observed sleep apnea reported positive associations with fasting insulin and the homeostasis model assessment of insulin resistance (HOMA-IR), but no associations with fasting glucose or hemoglobin A1c (HbA1c) (24). However, given the use of OSA symptoms as the outcome and limited covariate adjustment that only considered age, sex, and waist circumference in this study, there was potential for bias because of misclassification and confounding. To rigorously assess the role of insulin resistance and hyperglycemia in OSA pathogenesis, we evaluated the associations of fasting insulin and HbA1c at baseline with incident OSA risk over 10 to 18 years of follow-up in four U.S. prospective studies with a comprehensive assessment of potential confounders and evaluation of validated clinically diagnosed OSA or physiologically ascertained OSA.

Methods

Study Population

The NHS (Nurses' Health Study), NHSII (Nurses' Health Study II), and the HPFS (Health Professionals Follow-up Study) are three ongoing prospective studies in the United States. A total of 121,700 female registered nurses (30–55 yr) were enrolled in NHS in 1976; 116,429 female nurses (25–42 yr) were enrolled in NHSII in 1989; and 51,529 male health professionals (40–75 yr) were enrolled in HPFS in 1986. Information on medical history and lifestyle factors was collected by a self-administered baseline questionnaire and updated by biennial follow-up questionnaires. From 2000 to 2002, 18,743 NHS women provided a blood sample (89% fasting, defined as more than 8 hours since last meal) using a mailed collection kit and returned the specimen with an ice pack via overnight courier to our laboratory. Using a similar protocol, 29,611 NHSII women provided a blood sample from 1996 to 1999 (72% fasting), and 18,159 HPFS men provided a sample from 1993 to 1995 (58% fasting). For the current study, we included participants who had a fasting insulin or HbA1c assayed previously in multiple nested case-control or cross-sectional studies and answered the question on clinical diagnosis of OSA. We further excluded those who had OSA diagnoses before blood collection, resulting in an analytical sample of 7,360 for fasting insulin (NHS: 2,377; NHSII: 3,734; HPFS: 1,249) and 4,427 for HbA1c (NHS: 1,312; NHSII: 2,135; HPFS: 980), respectively. The study was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

MESA (Multi-Ethnic Study of Atherosclerosis) recruited 6,814 men and women (45–84 yr) who identified themselves as White (38%), Black (28%), Hispanic (22%), or Chinese (12%) from six U.S. communities between 2000 and 2002 (25). Baseline and follow-up clinical examinations, together with standardized questionnaires and periodic telephone contacts, were conducted to collect fasting blood samples and health-related information. At MESA Exam 5 (2010–2013), sleep-disordered breathing was measured by in-home polysomnography (PSG) in 2,261 participants. Our analysis included participants who had fasting insulin (Exam 1) or HbA1c (Exam 2, ∼16 mo after Exam 1) data and successful PSG data (Exam 5) and excluded those who reported physician-diagnosed OSA at Exam 2, leaving 1,923 participants for fasting insulin analysis and 1,915 for HbA1c analysis. Institutional review boards from all participating institutions approved the study, and participants provided written informed consent.

Measurement of Insulin Resistance and Hyperglycemia

As insulin and HbA1c data were available from all four cohorts, we used fasting insulin as a marker for insulin resistance and HbA1c as a marker for hyperglycemia (which reflects glycemic status in the past 2–3 mo). Fasting insulin from all four cohorts was measured by the Linco Human Insulin Specific Radioimmunoassay Kit (Linco Research, Inc.). In NHS/NHSII/HPFS, HbA1c was measured by turbidometric immunoassay in red blood cells using the Hitachi 911 Analyzer (Roche Diagnostics). In MESA, HbA1c was measured by high-performance liquid chromatography using a Tosoh G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc.). The intra-assay coefficients of variation were, in general, less than 10% for fasting insulin and less than 5% for HbA1c. As MESA also measured baseline fasting glucose by the Vitros 950 analyzer (Johnson and Johnson Ortho-Clinical Diagnostics), we used it as a secondary glycemic indicator and calculated HOMA-IR as another index of insulin resistance (fasting glucose [mg/dl] × fasting insulin [μU/ml] / 405).

Assessment of OSA

Methods to assess OSA in these four cohorts have been described previously (26). Briefly, NHS/NHSII/HPFS participants self-reported whether they had clinically diagnosed sleep apnea in 2012–2013 and the year of first

diagnosis. The reliability of the self-reports has previously been validated in a random sample of 108 NHS/NHSII participants (27), among whom all self-reported diagnoses were confirmed on the basis of at least one objective diagnostic method from medical records, and 89% had Apnea–Hypopnea Index (AHI) ≥15. The sex- and body mass index (BMI)-specific prevalence of self-reported OSA diagnosis closely resembles the PSG-measured prevalence of moderate-to-severe OSA in the general U.S. population (27, 28).

In MESA, participants reported whether they had physician-diagnosed sleep apnea at Exam 2, which we used to exclude baseline prevalent cases. At Exam 5, OSA was further assessed by one-night at-home PSG with a 15-channel monitor (Compumedics Ltd.) in a subset of 2,261 participants (29). PSG signals, including apnea and hypopnea events, were scored according to standardized protocols with excellent intra and interscorer reliability (intraclass correlation coefficient greater than 0.94). We included all apnea/hypopnea events associated with a 4% or more drop in oxygen saturation in the calculation of AHI. Our primary OSA definition in MESA was based on an AHI ⩾30 threshold, which gives rise to similar sex- and BMI-adjusted OSA incidence as NHS/NHSII/HPFS and denotes a more severe disease. To assess the associations with OSA severity, we also considered a four-category outcome on the basis of common clinical cutoffs: none (AHI <5), mild (AHI 5–14), moderate (AHI 15–29), and severe (AHI ⩾30). Finally, as described in detail elsewhere (30, 31), we derived several physiological endotypes (i.e., airway collapsibility, arousal threshold, and loop gain) to further subtype different pathogenetic mechanisms in OSA.

Statistical Analysis

In each cohort, logistic regression was used to estimate the odds ratios (ORs) for incident OSA across quintiles of baseline fasting insulin or HbA1c. Given the complex associations of obesity with glucose homeostasis, insulin resistance, and OSA pathogenesis, we considered adiposity measures in a separate model. The first multivariable model adjusted for age, race/ethnicity, sex (MESA only), menopausal status in women, smoking status, sleep duration, diet quality, physical activity, hypertension, and family history of diabetes. The second multivariable model additionally adjusted for BMI (continuous) and waist circumference (continuous). To provide summary estimates of the linear trend, we evaluated the associations with continuous biomarker amounts; log2-transformed fasting insulin values were used in the continuous analysis; thus, a one-unit increment was interpreted as a doubling of the fasting insulin concentration. In the pooled analyses combining data from individual cohorts, we fit the same two multivariable models with additional adjustment for cohort and assessed between-cohort heterogeneity by meta-analyzing the estimates associated with the continuous biomarkers and testing the Q-statistic (32). Given the modest correlation between fasting insulin and HbA1c (Spearman $r = 0.26$; $P < 0.0001$), we considered a third multivariable model in the pooled sample that simultaneously included fasting insulin and HbA1c to evaluate their independent associations with OSA risk.

We used multinomial logistic regression to examine the associations of fasting insulin and HbA1c with OSA severity (four categories) in MESA, adjusted for the same covariates described above. A linear trend was tested by treating severity categories as an ordinal outcome. Stratified analyses by age (≥55, <55 yr), sex, BMI (≥25, <25 kg/m^2), waist circumference (≥102, <102 cm in men; ≥88, <88 cm in women), and menopausal status in women were performed in the pooled sample, and subgroup heterogeneity was evaluated by the likelihood ratio test comparing the models with versus without the crossproduct interaction term. As sensitivity analyses, we repeated all analyses described above, excluding participants who reported diabetes diagnoses or the use of antidiabetic medications.

We conducted several secondary analyses to leverage additional data in MESA. First, we evaluated OSA risk according to baseline fasting glucose and HOMA-IR, which are other commonly used markers of hyperglycemia and insulin resistance. Second, given the diverse study population in MESA, we examined potential racial/ethnic differences in the associations with fasting insulin and HbA1c. Third, we used multinomial logistic regression to evaluate whether the associations differed by excessive daytime sleepiness (EDS) or physiological endotypes (airway collapsibility, arousal threshold, or loop gain) calculated from the polysomnographic measures using validated approaches as described in MESA (30, 31). The EDS analysis was conducted in all four cohorts and defined by self-reported daytime sleepiness 4 or more days/week in NHS/NHSII/HPFS and 3 or more days/week in MESA. Analyses were performed in SAS 9.4 (SAS Institute Inc.).

Results

The distributions of baseline participant characteristics across quintiles of fasting insulin were similar in NHS, NHSII, HPFS, and MESA (Table 1). Compared with participants in the lowest quintile, those in the higher quintiles were more likely to be non-White and have higher BMI, larger waist circumference, lower physical activity, worse diet quality, family history of diabetes, and past clinical diagnosis of hypertension or diabetes. This group was also more likely to report snoring, EDS, and the use of insulin therapy or other hypoglycemic medications. In MESA, there were greater percentages of Black and Hispanic participants in the higher quintiles of fasting insulin. Similar trends of participant characteristics were observed across quintiles of HbA1c (Table E1 in the data supplement).

Of 9,283 participants who did not have clinical diagnoses of OSA at the time of baseline fasting insulin measurement, 790 (8.5%) reported an OSA diagnosis or had an AHI ≥30 during 10 to 18 years of follow-up. OSA risk increased consistently in each cohort with increasing quintiles of fasting insulin (Table 2). After adjustment for multiple risk factors and potential confounders other than BMI and waist circumference, the OR (95% confidence interval [CI]) for OSA comparing participants in the top versus bottom quintile was 3.85 (1.83–8.09) in NHS, 3.86 (2.49–5.98) in NHSII, 1.62 (0.89–2.92) in HPFS, and 4.22 (2.47–7.19) in MESA (P-heterogeneity = 0.01). Although further adjustment of BMI and waist circumference substantially attenuated these associations, there were suggestions of positive associations in NHS, NHSII, and MESA. In the pooled analysis, participants in the highest quintile of fasting insulin had

Table 1. Participant characteristics across cohort-specific quintiles of baseline fasting insulin concentrations

	NHS			NHSII			HPFS			MESA		
	Quintiles of fasting insulin											
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
n	475	474	474	745	744	747	249	250	250	375	388	386
Age, yr	68.5 (6.6)	68.2 (6.4)	67.1 (6.2)	42.2 (4.2)	42.5 (4.1)	42.1 (4.3)	59.7 (7.6)	59.9 (7.9)	60.9 (7.4)	59.3 (9.5)	59.0 (9.4)	58.2 (8.8)
Men, %	0	0	0	0	0	0	100	100	100	44	45	49
Postmenopausal, %	100	100	100	7	6	10	—	—	—	79	79	82
Race and ethnicity, %												
White	96	96	95	96	96	94	97	96	89	45	39	28
Asian	1	1	0	2	1	1	0	0	3	9	13	10
Black	0	0	0	1	1	2	0	0	2	25	25	33
Hispanic	1	1	1	1	1	2	—	—	—	22	23	29
Other/unknown	3	2	3	1	1	2	3	3	5	0	0	0
BMI, kg/m^2	23.7 (3.7)	25.7 (4.0)	30.9 (5.5)	22.8 (3.2)	24.4 (4.1)	30.2 (6.9)	24.3 (2.2)	25.6 (2.3)	26.8 (2.8)	24.9 (3.7)	28.3 (4.9)	32.1 (5.1)
Waist circumference, cm	80.9 (10.8)	86.6 (11.5)	99.3 (12.8)	75.8 (10.3)	79.6 (11.6)	92.7 (17.4)	91.7 (6.8)	97.3 (7.8)	100.0 (8.5)	87.9 (10.6)	97.3 (12.4)	106.9 (13.1)
Current smokers, %	4	4	3	6	7	8	4	3	6	13	12	10
Sleep duration, h	7.2 (1.0)	7.2 (1.2)	7.2 (1.2)	7.1 (1.0)	7.1 (1.0)	7.0 (1.1)	7.2 (1.0)	7.1 (1.0)	7.3 (1.0)	7.2 (1.3)	7.1 (1.5)	7.1 (1.4)
AHI*	—	—	—	—	—	—	—	—	—	9.2 (11.2)	13.9 (16.4)	18.1 (18.1)
Snoring, %†	22	28	45	18	23	40	32	32	47	50	60	66
EDS, %‡	2	3	6	8	9	13	7	12	12	11	14	15
AHEI	55.1 (9.0)	54.1 (9.0)	51.4 (8.1)	49.5 (10.1)	49.5 (9.8)	47.5 (10.1)	55.6 (10.7)	53.7 (10.3)	51.3 (10.2)	53.8 (10.8)	50.7 (8.9)	49.5 (9.3)
Exercise, MET-h/wk	24.0 (19.6)	19.7 (16.0)	15.5 (13.8)	23.3 (26.9)	20.4 (22.4)	17.8 (21.2)	44.3 (37.3)	31.9 (22.0)	29.2 (24.0)	30.2 (36.1)	27.0 (41.2)	19.6 (38.0)
Hypertension, %	26	41	66	5	8	28	6	6	13	29	40	55
Diabetes, %	2	3	8	0	0	1	0	1	3	5	8	18
Insulin therapy, %§	0	0	2	0	0	1	0	0	4	0	1	4
Other hypoglycemic agents, %§	1	2	9	1	1	5	1	1	5	4	5	10
Family history of diabetes, %	23	34	35	34	34	52	23	24	27	33	39	46
HbA1c, %	5.6 (0.7)	5.6 (0.4)	6.0 (0.7)	5.4 (0.3)	5.4 (0.4)	5.7 (0.5)	5.5 (0.4)	5.4 (0.6)	5.7 (0.9)	5.5 (0.8)	5.6 (0.7)	6.0 (1.3)

Definition of abbreviations: AHEI = Alternate Healthy Eating Index; AHI = Apnea–Hypopnea Index; BMI = body mass index; EDS = excessive daytime sleepiness; HbA1c = hemoglobin A1c; HPFS = Health Professionals Follow-up Study; MESA = Multi-Ethnic Study of Atherosclerosis; MET = metabolic equivalent task; NHS = Nurses' Health Study; NHSII = Nurses' Health Study II.

Data are presented as *n* or mean (standard deviation).

*Included all obstructive apneas plus hypopneas associated with 4% oxygen desaturation.

†Defined as self-reported snoring 4 or more nights/week.

‡Defined as self-reported daytime sleepiness ⩾4 d/wk in NHS/NHSII/HPFS and ⩾3 d/wk in MESA.

§In NHS/NHSII/HPFS, the use of antidiabetic medications was assessed several years after blood collection.

Table 2. Associations between baseline fasting insulin concentrations and risk of developing obstructive sleep apnea

	Quintiles of fasting insulin					Per doubling of fasting insulin	*P*-trend
	Q1	Q2	Q3	Q4	Q5		
NHS							
Median (range)*	1.7 (0.2–2.6)	3.4 (2.6–4.2)	5.0 (4.2–6.0)	7.3 (6.0–9.0)	12.6 (9.0–95.9)	—	—
Cases/*N*	10/475	8/477	17/474	18/477	40/474	—	—
Model 1†	1.00 (ref)	0.78 (0.31–2.02)	1.54 (0.69–3.45)	1.70 (0.76–3.79)	3.85 (1.83–8.09)	1.63 (1.32–2.00)	<0.0001
Model 2‡	1.00 (ref)	0.72 (0.28–1.86)	1.20 (0.53–2.73)	1.09 (0.48–2.50)	1.66 (0.74–3.72)	1.20 (0.96–1.51)	0.11
NHSII							
Median (range)*	2.5 (0.2–3.5)	4.5 (3.5–5.4)	6.3 (5.4–7.3)	8.6 (7.3–10.8)	15.3 (10.8–139.1)	—	—
Cases/*N*	28/745	31/750	42/744	62/748	136/747	—	—
Model 1†	1.00 (ref)	1.09 (0.64–1.84)	1.38 (0.84–2.26)	1.87 (1.17–2.98)	3.86 (2.49–5.98)	1.49 (1.32–1.68)	<0.0001
Model 2‡	1.00 (ref)	0.98 (0.58–1.66)	1.14 (0.69–1.88)	1.29 (0.80–2.09)	1.87 (1.16–3.01)	1.13 (0.99–1.29)	0.07
HPFS							
Median (range)*	2.9 (0.2–3.9)	4.6 (3.9–5.5)	6.4 (5.5–7.3)	8.7 (7.3–10.4)	13.5 (10.4–77.5)	—	—
Cases/*N*	21/249	27/250	22/250	28/250	35/250	—	—
Model 1†	1.00 (ref)	1.27 (0.69–2.34)	1.00 (0.53–1.88)	1.30 (0.71–2.39)	1.62 (0.89–2.92)	1.14 (0.94–1.38)	0.19
Model 2‡	1.00 (ref)	1.19 (0.64–2.19)	0.84 (0.44–1.60)	1.04 (0.56–1.96)	1.15 (0.61–2.16)	1.00 (0.81–1.24)	0.97
MESA							
Median (range)*	4.5 (1.2–5.4)	6.3 (5.5–7.1)	8.2 (7.2–9.4)	10.8 (9.5–12.7)	16.3 (12.8–124.8)	—	—
Cases/*N*	20/375	38/395	51/388	77/379	79/386	—	—
Model 1†	1.00 (ref)	1.92 (1.08–3.39)	2.59 (1.49–4.48)	4.42 (2.60–7.52)	4.22 (2.47–7.19)	1.75 (1.45–2.10)	<0.0001
Model 2‡	1.00 (ref)	1.59 (0.89–2.85)	1.90 (1.08–3.35)	2.83 (1.62–4.95)	2.14 (1.19–3.84)	1.26 (1.01–1.56)	0.03
Pooled analysis§							
Median (range)*	2.5 (0.2–3.6)	4.6 (3.7–5.5)	6.4 (5.5–7.4)	8.8 (7.4–10.9)	14.9 (10.9–139.1)	—	—
Cases/*N*	62/1862	98/1852	124/1864	206/1851	300/1854	—	—
Model 1†	1.00 (ref)	1.36 (0.98–1.89)	1.56 (1.13–2.14)	2.51 (1.86–3.40)	3.59 (2.67–4.82)	1.50 (1.39–1.63)	<0.0001
Model 2‡	1.00 (ref)	1.21 (0.87–1.69)	1.21 (0.88–1.68)	1.66 (1.22–2.27)	1.70 (1.24–2.35)	1.14 (1.04–1.24)	0.005
Model 3‖	1.00 (ref)	1.09 (0.71–1.66)	1.40 (0.94–2.08)	1.92 (1.30–2.82)	1.66 (1.11–2.47)	1.15 (1.02–1.30)	0.02

Definition of abbreviations: HPFS = Health Professionals Follow-up Study; MESA = Multi-Ethnic Study of Atherosclerosis; NHS = Nurses' Health Study; NHSII = Nurses' Health Study II; ref = reference.

*Fasting insulin values were reported as μU/ml.

†Model 1: Adjusted for cohort (pooled analysis), age, race and ethnicity, sex (MESA and pooled analysis), menopausal status in women, smoking, sleep duration, diet quality, physical activity, hypertension, and family history of diabetes.

‡Model 2: Model 1 + continuous body mass index and waist circumference.

§Based on the association estimates per doubling of fasting insulin, there was significant between-cohort heterogeneity in Model 1 ($P = 0.01$) and no significant between-study heterogeneity in Model 2 ($P = 0.52$).

‖Model 3: Model 2 + HbA1c.

Table 3. Associations between baseline hyperglycemia measured by hemoglobin A1c and risk of developing obstructive sleep apnea*

	Quintiles of hemoglobin A1c						
	Q1	Q2	Q3	Q4	Q5	Per 1% increase	*P*-trend
NHS							
Median (range)*	5.1 (3.7–5.3)	5.4 (5.3–5.5)	5.6 (5.5–5.7)	5.8 (5.7–6.0)	6.3 (6.0–10.9)	—	—
Cases/*N*	10/252	13/253	15/298	9/248	20/261	—	—
Model 1†	1.00 (ref)	1.42 (0.60–3.33)	1.38 (0.60–3.20)	1.00 (0.39–2.53)	2.21 (0.98–4.99)	1.46 (1.03–2.07)	0.04
Model 2‡	1.00 (ref)	1.53 (0.64–3.71)	1.13 (0.48–2.69)	0.58 (0.21–1.57)	1.46 (0.63–3.38)	1.20 (0.81–1.78)	0.37
NHSII							
Median (range)*	5.0 (0.3–5.2)	5.2 (5.2–5.3)	5.4 (5.3–5.5)	5.6 (5.5–5.8)	6.0 (5.8–10.3)	—	—
Cases/*N*	18/426	32/428	46/425	59/429	93/427	—	—
Model 1†	1.00 (ref)	1.80 (0.98–3.28)	2.52 (1.42–4.47)	2.89 (1.65–5.07)	4.46 (2.57–7.74)	1.88 (1.50–2.37)	<0.0001
Model 2‡	1.00 (ref)	1.69 (0.91–3.12)	1.97 (1.09–3.55)	1.77 (0.99–3.18)	1.94 (1.08–3.50)	1.20 (0.93–1.56)	0.16
HPFS							
Median (range)*	5.0 (4.2–5.1)	5.3 (5.1–5.4)	5.5 (5.4–5.6)	5.8 (5.6–5.9)	6.1 (5.9–12.1)	—	—
Cases/*N*	29/196	34/196	22/196	19/195	31/197	—	—
Model 1†	1.00 (ref)	1.32 (0.76–2.29)	0.73 (0.40–1.35)	0.62 (0.33–1.17)	1.15 (0.65–2.04)	1.05 (0.78–1.40)	0.76
Model 2‡	1.00 (ref)	1.24 (0.71–2.17)	0.72 (0.39–1.34)	0.60 (0.32–1.13)	0.96 (0.53–1.73)	0.97 (0.72–1.31)	0.84
MESA							
Median (range)*	4.9 (3.9–5.1)	5.3 (5.2–5.3)	5.4 (5.4–5.5)	5.7 (5.6–5.9)	6.5 (6.0–15.9)	—	—
Cases/*N*	41/397	39/346	36/342	68/455	81/375	—	—
Model 1†	1.00 (ref)	1.13 (0.70–1.82)	1.07 (0.66–1.74)	1.52 (0.98–2.36)	2.38 (1.52–3.74)	1.22 (1.08–1.38)	0.002
Model 2‡	1.00 (ref)	1.12 (0.69–1.83)	0.99 (0.60–1.64)	1.33 (0.85–2.09)	1.73 (1.08–2.76)	1.14 (1.01–1.30)	0.04
Pooled analysis§							
Median (range)*	5.0 (0.3–5.2)	5.3 (5.2–5.4)	5.5 (5.4–5.6)	5.7 (5.6–5.9)	6.2 (5.9–15.9)	—	—
Cases/*N*	105/1255	117/1185	116/1267	163/1365	214/1270	—	—
Model 1†	1.00 (ref)	1.24 (0.94–1.64)	1.18 (0.89–1.56)	1.51 (1.16–1.98)	2.21 (1.69–2.89)	1.29 (1.18–1.42)	<0.0001
Model 2‡	1.00 (ref)	1.21 (0.91–1.61)	0.99 (0.74–1.32)	1.13 (0.86–1.49)	1.31 (0.99–1.73)	1.12 (1.01–1.24)	0.03
Model 3‖	1.00 (ref)	1.05 (0.74–1.50)	1.07 (0.75–1.51)	1.15 (0.82–1.62)	1.26 (0.89–1.78)	1.09 (0.97–1.23)	0.14

Definition of abbreviations: HPFS = Health Professionals Follow-up Study; MESA = Multi-Ethnic Study of Atherosclerosis; NHS = Nurses' Health Study; NHSII = Nurses' Health Study II; ref = reference.

*HbA1c values were reported as a percent.

†Model 1: Adjusted for cohort (pooled analysis), age, race and ethnicity, sex (MESA and pooled analysis), menopausal status in women, smoking, sleep duration, diet quality, physical activity, hypertension, and family history of diabetes.

‡Model 2: Model 1 + continuous body mass index and waist circumference.

§Based on the association estimates per 1% hemoglobin A1c increase, there was significant between-cohort heterogeneity in Model 1 ($P = 0.004$) and no significant between-cohort heterogeneity in Model 2 ($P = 0.73$).

‖Model 3: Model 2 + fasting insulin.

Table 4. Associations of fasting insulin and hemoglobin A1c with obstructive sleep apnea severity measured by apnea–hypopnea index in Multi-Ethnic Study of Atherosclerosis

		Model 1*	Model 2†
	n	OR (95% CI)‡	
Fasting insulin§			
AHI <5	688	Reference	Reference
AHI 5–14	623	1.44 (1.22–1.70)	1.09 (0.91–1.32)
AHI 15–29	347	1.71 (1.41–2.08)	1.12 (0.90–1.40)
AHI ⩾30	265	2.32 (1.88–2.87)	1.35 (1.06–1.72)
P-trend		<0.0001	0.03
HbA1c‖			
AHI <5	680	Reference	Reference
AHI 5–14	622	1.19 (1.03–1.38)	1.09 (0.94–1.25)
AHI 15–29	348	1.26 (1.07–1.48)	1.11 (0.95–1.30)
AHI ⩾30	265	1.41 (1.19–1.65)	1.22 (1.04–1.44)
P-trend		<0.0001	0.03

Definition of abbreviations: AHI = Apnea–Hypopnea Index; HbA1c = hemoglobin A1c; CI = confidence interval; OR = odds ratio.
*Model 1: Adjusted for age, race and ethnicity, sex, menopausal status in women, smoking, sleep duration, diet quality, physical activity, hypertension, and family history of diabetes.
†Model 2: Model 1 + continuous body mass index and waist circumference.
‡ORs were obtained from multinomial logistic regression.
§Estimates were expressed for every doubling of fasting insulin.
‖Estimates were expressed for a 1% increase in HbA1c.

Table 5. Pooled subgroup associations of fasting insulin and hemoglobin A1c with obstructive sleep apnea risk by age, sex, menopausal status, body mass index, and waist circumference*

	Fasting insulin†		HbA1c‡	
	OR (95% CI)	*P*-int	OR (95% CI)	*P*-int
Age, yr		0.96		0.66
<55	1.14 (1.01–1.28)	—	1.15 (0.99–1.34)	—
⩾55	1.13 (0.99–1.30)	—	1.13 (0.98–1.30)	—
Sex		0.17		0.98
Men	1.07 (0.90–1.27)	—	1.13 (0.99–1.30)	—
Women	1.16 (1.05–1.30)	—	1.14 (0.98–1.32)	—
Menopausal status		0.34		0.92
Premenopausal	1.12 (0.97–1.29)	—	1.17 (0.94–1.45)	—
Postmenopausal	1.23 (1.04–1.47)	—	1.14 (0.95–1.37)	—
BMI, kg/m^2		0.87		0.47
<25	1.14 (0.95–1.36)	—	1.05 (0.78–1.40)	—
⩾25	1.15 (1.04–1.27)	—	1.15 (1.03–1.28)	—
Waist circumference§		0.09		0.68
Small	1.26 (1.10–1.44)	—	1.13 (0.94–1.36)	—
Large	1.18 (1.04–1.34)	—	1.11 (0.98–1.25)	—

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HbA1c = hemoglobin A1c; OR = odds ratio.
*Adjusted for cohort, age, race and ethnicity, sex, menopausal status in women, smoking, sleep duration, diet quality, physical activity, hypertension, family history of diabetes, BMI, and waist circumference.
†Estimates were expressed for every doubling of fasting insulin.
‡Estimates were expressed for a 1% increase in HbA1c.
§Sex-specific cutoff values were used to define a large waist circumference (⩾102 cm for men and ⩾88 cm for women).

3.59-fold (95% CI, 2.67–4.82) increased odds of OSA before adjusting for BMI (*P*-trend < 0.001) and 1.70-fold (95% CI, 1.24–2.35) increased odds after adjusting for BMI (*P*-trend = 0.005). In a subset of 4,640 participants with both fasting insulin and HbA1c data, fasting insulin was significantly positively associated with OSA risk after additionally adjusting for HbA1c (OR comparing extreme quintiles, 1.66; 95% CI, 1.11–2.47; *P*-trend = 0.02).

A total of 6,342 participants had HbA1c data at baseline, of whom 715 (11.3%) developed OSA during follow-up, according to our case definition. Before adjusting for BMI and waist circumference, baseline HbA1c was significantly associated with increased OSA risk in NHS (*P*-trend = 0.04), NHSII (*P*-trend < 0.001), and MESA (*P*-trend = 0.002) but not HPFS (*P*-trend = 0.76) (Table 3), which resulted in significant between-cohort heterogeneity (*P*-heterogeneity = 0.004). After adjusting for BMI and waist circumference, the positive trend between HbA1c and OSA risk was only significant in MESA (*P*-trend = 0.04). The pooled multivariable-adjusted OR (95% CI) comparing the extreme quintiles of HbA1c was 2.21 (1.69–2.89) before adjusting for BMI (*P*-trend < 0.0001) and 1.31 (0.99–1.73) after adjusting for BMI (*P*-trend = 0.03). Simultaneous adjustment of fasting insulin further attenuated the association (OR comparing extreme quintiles, 1.26; 95% CI, 0.89–1.78; *P*-trend = 0.14).

In MESA, baseline fasting insulin concentrations were associated with the risk of developing more severe OSA in a dose–response fashion (Table 4). Compared with participants with AHI <5, the multivariable-adjusted OR (95% CI) associated with every doubling of fasting insulin was 1.44 (1.22–1.70) for AHI 5–14, 1.71 (1.41–2.08) for AHI 15–29, and 2.32 (1.88–2.87) for AHI ⩾30 (*P*-trend < 0.0001). The associations were weaker after adiposity adjustment, but a modest dose–severity relationship persisted (*P*-trend = 0.03). Similar dose–response associations were observed between HbA1c and OSA severity. In the pooled sample, the associations of fasting insulin and HbA1c with OSA risk did not differ by age, sex, BMI, waist circumference, or menopausal status in women (*P*-interaction > 0.09) (Table 5). A sensitivity analysis excluding participants reporting diabetes diagnoses or antidiabetic medication use yielded similar results for

both the primary associations (Table E2) and the subgroup associations (data not shown).

Several additional analyses were conducted in MESA. First, when we used HOMA-IR and fasting glucose as markers for insulin resistance and hyperglycemia, respectively, both were positively associated with OSA risk (Table E3). However, the association with HOMA-IR appeared more robust than that with fasting glucose, especially after adjusting for adiposity; the fully adjusted OR (95% CI) comparing extreme quintiles was 1.85 (1.05–3.26) for HOMA-IR (P-trend = 0.02) and 1.46 (0.89–2.40) for fasting glucose (P-trend = 0.27). Second, although we did not observe significant subgroup differences by race and ethnicity for fasting insulin (P-interaction = 0.71) or HbA1c (P-interaction = 0.61), suggestive positive trends were observed among White, Black, and Hispanic participants but not among Chinese-Americans (Table E4). Third, the associations with either fasting insulin or HbA1c did not appreciably differ for OSA subtypes defined by EDS, airway collapsibility, loop gain, and arousal threshold (P-heterogeneity $>$ 0.21) (Table E5).

Discussion

Using longitudinal data from four cohorts of men and women in the United States, we found that baseline concentrations of fasting insulin and HbA1c were significantly associated with increased risk of OSA after adjustment for obesity and other OSA risk factors. These positive associations were consistently present in different subgroups defined by age, sex, BMI, and menopausal status in women and exhibited a dose–response pattern with OSA severity. In the model with mutual adjustment of both biomarkers, only fasting insulin remained associated with OSA risk, suggesting a more important role of insulin resistance in the pathogenesis of OSA than hyperglycemia.

Our results were consistent with the only prior prospective study, which reported an increased incidence of OSA symptoms (self-report of ever being told of stopping breathing during sleep) in individuals with higher baseline fasting insulin and HOMA-IR (24). Interestingly, this study also found a positive association with the baseline triglyceride concentration (24), which is known to be a sensitive indicator for insulin resistance (33, 34). Although we observed a similar but more modest association for HbA1c, no associations were observed for either fasting glucose or HbA1c in the prior study (24). In our secondary analysis in MESA, HOMA-IR was more robustly associated with OSA risk than fasting glucose, especially after accounting for BMI. Collectively, these findings suggest that insulin resistance may be a more important pathogenic driver of OSA than hyperglycemia. However, it should be noted that our study, which primarily focused on individuals without diabetes, was not able to discern the potential impact of uncontrolled or poorly controlled hyperglycemia (e.g., HbA1c $\geq$8%) on OSA development and therefore was unable to address potential links between diabetic neuropathy and OSA as reported in previous studies (21–23).

The role of insulin resistance in the pathogenesis of OSA has been implicated by multiple lines of evidence. First, experimental studies have consistently reported ventilatory depression and decreased responses to hypoxia and hypercapnia in mice with drug-induced diabetes (15–19); administration of insulin or metformin, which are common treatment approaches for insulin resistance (35), has been shown to prevent these alterations in ventilatory control (17–19). Second, in prior studies evaluating the prospective relationship between diabetes status and OSA risk (11, 12), diabetes requiring insulin therapy was particularly strongly associated with the risk of developing OSA, suggesting that severe insulin resistance may be a potent OSA risk factor. Third, insulin resistance measured by fasting insulin and HOMA-IR has previously been associated with elevated pharyngeal collapsibility during sleep in morbidly obese women without diabetes (20). Although our endotype analysis in the current study did not detect differential associations by upper airway collapsibility for insulin resistance, our prior investigation in MESA found that inflammation (which is a critical mechanism causing insulin resistance [36] and vice versa [37]) was more strongly associated with the OSA endotype characterized by high airway collapsibility (26). Further detailed physiological and epidemiologic studies with a larger sample size are needed to understand the mechanistic pathways through which insulin resistance increases OSA risk.

The biological plausibility for the positive link between insulin resistance and OSA risk was further supported by the dose–response relationship observed across a wide distribution of insulin-resistance levels, as well as the graded associations with OSA severity. Importantly, our study highlights that increased insulin resistance and hyperglycemia that did not meet the diagnostic criteria for diabetes also conferred higher OSA risk, with apparent increases in risk starting from the middle or the second-highest quintile. These observations corroborate the idea that insulin resistance and hyperglycemia should be evaluated on a continuous spectrum, and treatment of subclinical insulin resistance or prediabetes may have beneficial health outcomes. In parallel with a growing number of RCTs evaluating the effect of CPAP treatment on glycemic control (6–8), future studies are needed to assess whether improving insulin resistance and glycemic control may lower OSA incidence. Notably, in a recent small intervention study, intensified antidiabetic treatment over a 4-month period resulted in significant reductions in AHI and sleep time with oxygen saturation below 90%, which was not entirely attributable to concurrent weight change (38).

The four study cohorts complemented each other and provided a large analytical sample that combined *1*) younger and older men and women; *2*) homogenous occupational cohorts and a racial/ethnically diverse community-based sample; and *3*) subjectively reported OSA diagnosis and objectively measured sleep-disordered breathing. Our efforts to harmonize information from individual cohorts allowed fine control of important covariates in the analysis. Consistency of findings across cohorts, coupled with support from multiple secondary analyses and sensitivity analyses, greatly strengthened our conclusion and advanced our understanding of metabolic pathways in OSA development.

Limitations

However, there were several limitations in the present study. First, because self-reported OSA was used to exclude baseline-prevalent cases, the study sample may include individuals with undiagnosed OSA. Therefore, the observed associations may be partly attributed to the impact of undiagnosed OSA on insulin resistance and glucose homeostasis, limiting our ability to accurately estimate the true incidence of OSA. Future studies with repeated PSG measurements are warranted to confirm our findings. Although self-reported OSA in

NHS/NHSII/HPFS has proved reliable (27), the observed associations may be biased if participants with insulin resistance or glucose dysregulation were more likely to have their OSA clinically recognized. Increasing awareness of OSA, as well as improved sensitivity of recording techniques to detect nocturnal apnea/hypopnea events over time, may introduce additional reporting bias. However, such reporting bias was unlikely to materially alter our results, given that we obtained similar results for PSG-measured OSA in MESA. Second, our study used existing data that did not have fasting insulin and HbA1c on every participant. It is possible that the stronger associations observed for fasting insulin versus HbA1c may be owing to their different analytical samples. However, the mutually adjusted model and the secondary analysis in MESA using fasting glucose and HOMA-IR, both based on the same analytical sample, yielded similar differences. Third, the statistical power may be limited to detect moderate heterogeneity across subgroups or by OSA endotypes. Fourth, there may be residual confounding, particularly by obesity, although we observed similar associations across BMI or waist circumference strata. Finally, our assessment of insulin resistance and hyperglycemia relied on a single baseline measurement, which may not fully capture the long-term exposure. Future studies considering repeated biomarker measures and evaluating changes in biomarkers in relation to OSA risk will provide additional insights.

Conclusions

Higher concentrations of fasting insulin and HbA1c were prospectively associated with increased risk of OSA, and the positive association appeared more robust for measures of insulin resistance than measures of hyperglycemia. These observations were further reinforced by the strong dose–response relationships with OSA severity. However, given our reliance on self-reported diagnosis to exclude baseline-prevalent cases, additional studies, such as those with repeated objective assessments of OSA or using genetic instruments (e.g., Mendelian randomization), are needed to determine the temporal relationship and elucidate the underlying causality. If confirmed by further evidence, our findings suggest a value for future investigations to assess the potential benefits of improving insulin resistance and glycemic control on OSA prevention. ■

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