Obstructive Sleep Apnea, Glucose Tolerance, and β-Cell Function in Adults With Prediabetes or Untreated Type 2 Diabetes in the Restoring Insulin Secretion (RISE) Study

Babak Mokhlesi,[1] Ashley H. Tjaden,[2] Karla A. Temple,[1] Sharon L. Edelstein,[2] Susan Sam,[1] Kristen J. Nadeau,[3] Tamara S. Hannon,[4] Shalini Manchanda,[4] Kieren J. Mather,[4] Steven E. Kahn,[5] David A. Ehrmann,[1] and Eve Van Cauter,[1] for the RISE Consortium*

Diabetes Care 2021;44:993–1001 | https://doi.org/10.2337/dc20-2127

OBJECTIVE

Obstructive sleep apnea (OSA) is associated with insulin resistance and has been described as a risk factor for type 2 diabetes. Whether OSA adversely impacts pancreatic islet β-cell function remains unclear. We aimed to investigate the association of OSA and short sleep duration with β-cell function in overweight/obese adults with prediabetes or recently diagnosed, treatment-naive type 2 diabetes.

RESEARCH DESIGN AND METHODS

Two hundred twenty-one adults (57.5% men, age 54.5 ± 8.7 years, BMI 35.1 ± 5.5 kg/m^2) completed 1 week of wrist actigraphy and 1 night of polysomnography before undergoing a 3-h oral glucose tolerance test (OGTT) and a two-step hyperglycemic clamp. Associations of measures of OSA and actigraphy-derived sleep duration with HbA_{1c}, OGTT-derived outcomes, and clamp-derived outcomes were evaluated with adjusted regression models.

RESULTS

Mean ± SD objective sleep duration by actigraphy was 6.6 ± 1.0 h/night. OSA, defined as an apnea-hypopnea index (AHI) of five or more events per hour, was present in 89% of the participants (20% mild, 28% moderate, 41% severe). Higher AHI was associated with higher HbA_{1c} ($P = 0.007$). However, OSA severity, measured either by AHI as a continuous variable or by categories of OSA severity, and sleep duration (continuous or <6 vs. ≥6 h) were not associated with fasting glucose, 2-h glucose, insulin sensitivity, or β-cell responses.

CONCLUSIONS

In this baseline cross-sectional analysis of the RISE clinical trial of adults with prediabetes or recently diagnosed, untreated type 2 diabetes, the prevalence of OSA was high. Although some measures of OSA severity were associated with HbA_{1c}, OSA severity and sleep duration were not associated with measures of insulin sensitivity or β-cell responses.

[1]University of Chicago, Chicago, IL
[2]George Washington University Biostatistics Center (RISE Coordinating Center), Rockville, MD
[3]University of Colorado Anschutz Medical Campus/Children's Hospital Colorado, Denver, CO
[4]Indiana University School of Medicine, Indianapolis, IN
[5]VA Puget Sound Health Care System and University of Washington, Seattle, WA

Corresponding author: Babak Mokhlesi, bmokhles@medicine.bsd.uchicago.edu

Received 25 August 2020 and accepted 12 January 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.13607591.

*A complete list of the RISE Consortium investigators can be found in the supplementary material online.

The Centers for Disease Control and Prevention estimated that in 2018, ~88 million American adults had prediabetes and 34 million had type 2 diabetes (1). The increasing prevalence of obesity has contributed to the diabetes epidemic (2). Obesity is also an important risk factor for obstructive sleep apnea (OSA) (3), a sleep disorder characterized by recurrent episodes of complete (apneas) or partial (hypopneas) obstruction of the upper airway that lead to intermittent hypoxemia and hypercapnia, microarousals, sleep fragmentation, increased oxidative stress, and inflammation. Epidemiologic studies have reported an independent association between OSA and type 2 diabetes. A meta-analysis of 65,100 participants revealed that OSA is associated with incident type 2 diabetes (4).

The exact mechanisms by which chronic short sleep duration and OSA increase the risk for developing type 2 diabetes have not been fully elucidated. A growing body of sleep laboratory–derived evidence implicates insufficient sleep and several cardinal features of OSA, such as sleep fragmentation and intermittent hypoxemia, as risk factors for metabolic dysfunction and as likely to be in the causal pathway leading to the development of type 2 diabetes (4). However, these studies were limited by their short-term nature and performance in healthy, nonobese participants only (5–8). Existing studies have relied primarily on indirect measures of insulin sensitivity and islet β-cell responses derived from fasting glucose and insulin levels or from glucose tolerance testing after an oral or intravenous challenge (4). Given that progressive β-cell dysfunction in the face of increasing severity of insulin resistance is critical for the development of type 2 diabetes (9), there is a need to investigate the association among OSA, insufficient sleep, and glucose metabolism using direct measures of β-cell response and insulin sensitivity in individuals across a wide range of β-cell function, particularly in obese adults with insulin resistance. We hypothesized that in participants with prediabetes or recently diagnosed, treatment-naive type 2 diabetes, short sleep duration and OSA severity are independently associated with decreased insulin sensitivity and reduced β-cell responses to glucose. To examine these hypotheses, we analyzed state-of-the-art measures of insulin sensitivity and β-cell responses in the Restoring Insulin Secretion (RISE) study to identify components of the glucose regulatory pathway related to OSA and sleep duration.

RESEARCH DESIGN AND METHODS

Participants

We performed a cross-sectional analysis of data obtained during the run-in and baseline phases of the RISE Adult Medication Study (10). Between 2013 and 2017, participants were recruited from the patient populations and communities at three centers: *1*) the University of Chicago Medical Center together with the Jesse Brown Chicago Veterans Administration Medical Center, *2*) Indiana University, and *3*) Veterans Administration Puget Sound Health Care System. Individuals at risk for impaired glucose tolerance (IGT) and type 2 diabetes who met other study inclusion/exclusion criteria were screened with a 2-h oral glucose tolerance test (OGTT) and HbA_{1c}. Preliminary screening was performed to identify adults who were highly predisposed to the development of type 2 diabetes. High risk was defined as *1*) impaired fasting glucose or IGT, *2*) overweight or obesity (BMI $\geq$25 kg/m^2 but $\leq$50 kg/m^2 [$\geq$23 kg/m^2 in Asian Americans]), *3*) first-degree relative with type 2 diabetes, *4*) sedentary lifestyle, *5*) presence of components of the metabolic syndrome (low HDL cholesterol, high triglycerides, hypertension), *6*) member of a high-risk racial and/or ethnic group, *7*) women who had gestational diabetes mellitus or who have had a baby weighing $\geq$9 lb at birth, *8*) offspring of mothers who had any form of diabetes while pregnant, and/or *9*) women with polycystic ovarian syndrome.

Recruitment techniques included notices placed on bulletin boards at the medical centers, newspaper and radio advertisements and public service announcements, social media, and primarily referral from colleagues and screening from the investigators' clinics. Prescreening of electronic and clinical medical records was used when possible. The inclusion criteria were *1*) 20–65 years of age, *2*) BMI of 25–50 kg/m^2 (23–50 kg/m^2 in Asians), *3*) fasting plasma glucose of 5.3–6.9 mmol/L (95–125 mg/dL) plus 2-h glucose $\geq$7.8 mmol/L (140 mg/dL) (11) and HbA_{1c} $\leq$7.0% (53 mmol/mol), *4*) diabetes duration <1 year, and *5*) naive for medications known to affect glucose metabolism. Detailed participant recruitment and eligibility criteria have been described (11) and are available on the RISE website (https://rise.bsc.gwu.edu/web/rise/collaborators). The study was approved by the institutional review boards of all centers, and all participants provided written informed consent before initiation of study-related activities.

Sleep Assessments

Before randomization, eligible participants completed a 3-week run-in period to further assess eligibility for participation in the RISE Adult Medication Study. The quantitative measures of sleep were performed during the run-in period.

Sleep Questionnaires

All participants completed a questionnaire before randomization to ascertain whether they had been clinically diagnosed with OSA and whether they were being treated with continuous positive airway pressure (CPAP). Participants previously prescribed treatment were asked to estimate their CPAP usage (nights per week and number of hours per night). CPAP adherence on the basis of self-report was defined as use of CPAP for $\geq$5 nights/week plus $\geq$4 h/night. The Epworth Sleepiness Scale (ESS) (scores 0–24) assessed subjective daytime sleepiness; scores of >10 define daytime sleepiness.

Polysomnography

In-laboratory polysomnograms (PSGs) were performed by the study site sleep laboratory during the run-in period, with a median (25th, 75th percentile) of 15 days (9, 21 days) before the hyperglycemic clamp and 12 days (7, 17 days) before the 3-h OGTT. All laboratories were accredited by the American Academy of Sleep Medicine. Bedtimes were based on participants' habitual bedtimes. Deidentified PSG data were uploaded to the University of Chicago Sleep Center for central analysis (Neurofax EEG 1100 system; Nihon Kohden, Foothill Ranch, CA). PSGs were staged and scored according to established criteria by the American Academy of Sleep Medicine. CPAP use was not permitted during PSGs. Apneas were defined as total cessation of airflow for $\geq$10 s (obstructive if

respiratory effort was present, central if respiratory effort was absent). Hypopneas were scored if the ventilation signal magnitude decreased by ≥30% of the baseline nasal pressure transducer amplitude for ≥10 s and were associated with either a ≥3% drop in oxygen saturation or a microarousal. Total apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Hypoxemia during sleep was assessed using the oxygen desaturation index defined as either ≥3% or ≥4% oxygen desaturation events per hour of sleep and total sleep time <90% oxygen saturation (T90). OSA was graded as absent, mild, moderate, or severe if AHI was <5, 5–14, 15–29, or ≥30 events per hour, respectively. Participants were categorized into four groups: no OSA/untreated mild OSA ($n = 61$), untreated moderate OSA ($n = 47$), untreated severe OSA ($n = 72$), and CPAP-treated OSA ($n = 41$).

Wrist Actigraphy Measurements

Participants wore the Actiwatch Spectrum (Philips Respironics, Murrysville, PA) on their nondominant wrist for 7 consecutive days without removal except for lengthy water activities (e.g., swimming, bathing) and pressed the event marker upon getting into or out of bed. Participants were instructed to continue their usual sleep and activities while wearing the device and to complete a sleep diary upon awakening each morning to document time to bed, latency to sleep, time awake, time out of bed, and naps. Actigraphy was performed during the run-in period, with a median (25th, 75th percentile) of 29 days (22, 36 days) before the hyperglycemic clamp and 25 days (21, 30 days) before the 3-h OGTT.

Actigraphs were preprogrammed centrally at the University of Chicago Sleep Center to collect physical activity and light intensity in 30-s epochs. Rest and wake intervals were determined using a standardized scoring algorithm (12). Physical activity was derived as previously described (13).

OGTT and Hyperglycemic Clamp Procedures

Following a 10-h overnight fast, a 75-g OGTT was performed. Blood samples were collected through an indwelling intravenous catheter 10 and 5 min before and 10, 20, 30, 60, 90, 120, 150, and 180 min after glucose ingestion (11,14). A two-stage hyperglycemic clamp was performed on a different day following a 10-h overnight fast with goal glucose levels of 11.1 and >25 mmol/L (200 and >450 mg/dL), respectively, followed by administration of the nonglucose secretagogue arginine (11,14,15). Neither procedure was performed after the in-laboratory PSG.

Laboratory assays were performed by the study's central biochemistry laboratory (11). All measures are presented in International System of Units. Standard conversion factors to conventional units can be used except for insulin, which is 0.134.

Calculations for OGTT-Derived Measurements

Individuals were classified as having IGT or type 2 diabetes using the screening 2-h glucose on the basis of American Diabetes Association OGTT criteria (16). C-peptide index ($\Delta C_{0–30}/\Delta G_{0–30}$) and insulinogenic index ($\Delta I_{0–30}/\Delta G_{0–30}$) were calculated using the 0- and 30-min OGTT samples (17,18). Incremental glucose area under the curve (G-iAUC) over the 3-h sampling period was calculated using the trapezoidal method. Insulin resistance during the fasting state was measured using HOMA for insulin resistance (HOMA-IR): (fasting glucose [mmol/L] · fasting insulin [mIU/L]) / 22.5 (19).

Calculations for Clamp-Derived Measurements

Insulin sensitivity (M/I) was quantified as mean glucose infusion rate (M) at 100, 110, and 120 min of the clamp, corrected for urinary glucose loss, divided by mean steady-state plasma insulin concentration at these same time points (I) (20). Acute (first phase) C-peptide response to glucose ($ACPR_g$) was calculated as mean incremental response above baseline at 2, 4, 6, 8, and 10 min after intravenous dextrose administration (21). Steady-state (second phase) C-peptide was calculated as the mean of the measurements at 100, 110, and 120 min of the clamp (20). Acute C-peptide response to arginine at maximal (>25 mmol/L [>450 mg/dL]) glycemic potentiation ($ACPR_{max}$) was calculated as mean incremental response at 2, 3, 4, and 5 min after arginine injection minus the prearginine baseline.

Statistical Analysis

Descriptive statistics are presented as percentages, mean ± SD, or geometric means and 95% CIs for nonnormally distributed data; for geometric means, *P* values from log-transformed data were calculated. Comparisons between groups (categories of OSA severity: no OSA/untreated mild OSA, untreated moderate OSA, untreated severe OSA, CPAP-treated OSA) were computed using ANOVA for continuous variables and χ^2 test for categorical variables. $P < 0.05$ was considered statistically significant, without adjustments made for multiple tests.

Linear regression models were used to explore relationships between continuous measures of OSA severity (AHI, 3% and 4% oxygen desaturation indices, T90) and measures of glycemia, insulin sensitivity, and β-cell response. Models were adjusted for age, sex, race/ethnicity, BMI, waist-to-hip ratio (WHR), actigraphically measured physical activity and sleep duration, and self-reported CPAP adherence. Measures of β-cell response were also adjusted for M/I. Models used natural logarithmically transformed M/I and β-cell response variables because of their skewed distribution. Additional linear regression models were used to explore the relationship between categories of OSA severity and the same measures of glycemia, insulin sensitivity, and β-cell response. Models were adjusted for age, sex, race/ethnicity, BMI, WHR, actigraphically measured physical activity, and sleep duration as well as for M/I for measures of β-cell responses. Before log transformation, a constant of 1.06 was added to the $ACPR_g$ because of negative values in this β-cell response variable. Analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Of the 267 participants who completed baseline procedures for the RISE Adult Medication Study, 221 also completed a PSG and 1 week of actigraphy (Supplementary Fig. 1). The participants were 57.5% male, aged 54.5 ± 8.7 years, with a BMI 35.1 ± 5.5 kg/m^2. Seventy-three percent had prediabetes, and 27% had recently diagnosed, treatment-naive type 2 diabetes. Objective sleep duration by actigraphy was 6.6 ± 1.0 h/night; 22% had mean sleep duration <6 h/night. Mean ESS score was 8.5 ± 4.6; 37.1% had a score indicating excessive daytime sleepiness. There were no significant differences between participants with prediabetes or type 2 diabetes in demographic or sleep variables (Supplementary Table 1).

OSA was present in 89% of the participants: 20% mild, 28% moderate, and 41% severe. Sixty-five (29%) participants reported having a CPAP device at home, but 16 of these participants never used their CPAP. Of the 49 participants using CPAP, 41 self-reported adherence to CPAP (≥4 h; ≥5 nights/week). Baseline demographics and sleep data on the basis of categories of OSA severity are summarized in Table 1. Severe OSA was more prevalent in men. Waist circumference and WHR were greater in participants with untreated severe OSA compared with those with no OSA/mild untreated OSA. In unadjusted analyses, there were no differences in hyperglycemic clamp–derived variables across the OSA categories. Compared with no OSA/untreated mild OSA, participants with moderate and severe untreated OSA had a trend toward lower insulin sensitivity as quantified by M/I ($P = 0.051$). Similarly, participants with untreated moderate and severe OSA had higher levels of insulin resistance measured by HOMA-IR ($P = 0.003$). However, there was no evidence of lower insulin resistance in the subgroup of participants who self-reported being adherent to CPAP therapy (Table 2).

In multiple regression analyses using continuous variables, higher AHI and higher 3% and 4% oxygen desaturation indices were associated with higher HbA_{1c} ($P = 0.007$, $P = 0.007$, $P = 0.009$, respectively). The slope of the AHI relationship was such that a 40-unit higher AHI was associated with a 0.12% higher HbA_{1c} absolute value. Similarly, higher AHI, 4% oxygen desaturation index, and microarousal index were each associated with increased G-iAUC ($P = 0.0223$, $P = 0.0267$, $P = 0.043$, respectively), which remained significant after excluding CPAP-adherent participants. However, categories of OSA severity were not associated with HbA_{1c} or G-iAUC. Moreover, OSA severity, using either continuous variables (AHI, 3% and 4% oxygen desaturation indices, T90) or categories of severity, was not associated with fasting or 2-h glucose, HOMA-IR, insulin sensitivity, or β-cell response (Figs. 1 and 2), irrespective of exclusion of all 49 CPAP users (Supplementary Table 2 and Supplementary Figs. 2 and 3). Similarly, objectively measured sleep duration by actigraphy, either expressed as a continuous variable or categorized as <6 or >6 h/night, was not associated with any of the metabolic outcomes. There were no sex differences in the association of OSA and sleep duration with any outcomes. Presence of daytime sleepiness did not alter any of the associations (data not shown). In participants with a BMI <30 kg/m^2 ($n = 44$), AHI was inversely associated with $ACPR_g$ (interaction $P = 0.0044$) but not with fasting and 2-h glucose, HbA_{1c}, insulin sensitivity, HOMA-IR, or other β-cell responses.

CONCLUSIONS

Growing evidence has implicated OSA and short sleep duration as modifiable risk factors that can adversely affect insulin sensitivity and glucose metabolism (4). However, it remains unclear whether OSA and short sleep remain important risk factors for progression of prediabetes to type 2 diabetes or increasing severity of diabetes. Moreover, whether OSA and short sleep adversely impact β-cell function remains to be elucidated. To shed some light on these questions, we performed a baseline cross-sectional analysis of the RISE clinical trial that included a racially/ethnically diverse group of overweight/obese adults with IGT or recently diagnosed, treatment-naive type 2 diabetes. Prevalence of OSA in the RISE adult participants was extremely high, with 89% having OSA and 41% exhibiting severe OSA. Moreover, 22% of the participants had habitual sleep duration <6 h/night. However, using gold standard assessments of insulin sensitivity and β-cell responses, we found no associations between severity of OSA and sleep duration with insulin sensitivity, β-cell responses, or most measures of glycemia. The clinical significance of the association between AHI and HbA_{1c} remains unclear given that a 40-unit higher AHI was associated with only a 0.12% higher HbA_{1c}. Our study represents the largest group of overweight and obese participants with IGT or recently diagnosed type 2 diabetes undergoing objective assessments of sleep combined with an assessment of insulin sensitivity and β-cell responses using hyperglycemic clamps.

Mechanistic evidence linking insufficient sleep to reduced insulin sensitivity (assessed mostly through a frequently sampled intravenous glucose tolerance test) has been obtained in several well-controlled laboratory studies (5–8). In these studies, sleep restriction led to a consistent marked (25–30%) reduction in insulin sensitivity with inadequate acute insulin response. However, these experimental studies were limited by their short-term nature and included only healthy participants. Cross-sectional studies have provided evidence consistent with the laboratory studies (22). A meta-analysis of 10 longitudinal studies reported a significantly increased risk of incident type 2 diabetes for those reporting sleeping ≤5–6 h per night (relative risk 1.28 [95% CI 1.03, 1.60]) (23). These studies did not enroll exclusively overweight and obese individuals with established prediabetes, did not obtain objective measures of habitual sleep duration or sleep-disordered breathing, and did not use gold standard measures of insulin sensitivity and β-cell responses. Moreover, none took physical activity into account as an important confounder. Our study overcomes some of these limitations by using objective measures of sleep and physical activity combined with robust measures of insulin sensitivity and β-cell responses.

Numerous population and clinic-based studies have revealed a robust relationship between the presence and severity of OSA with both insulin resistance and glucose intolerance, independent of adiposity (4). In a cross-sectional analysis of >2,500 individuals without type 2 diabetes (24), the presence of OSA was associated with higher odds of impaired fasting glucose and IGT after adjusting for age, sex, BMI, waist circumference, and race. Consistent findings were recently reported in a study focused on Blacks (25). A cross-sectional study using frequently sampled intravenous glucose tolerance testing in 118 individuals without type 2 diabetes found that compared with participants without OSA, those with mild, moderate, or severe OSA had a 26.7, 36.5, and 43.7% decrease in insulin sensitivity, respectively, after adjusting for age, sex, race, and percent body fat (26). Prospective longitudinal studies have also observed a higher incidence of type 2 diabetes in people with OSA (27–29). Although associations among OSA, glucose intolerance, and insulin sensitivity are well documented, these associations were never examined in predominantly obese people with established prediabetes and lacked a robust measure of the β-cell response. Moreover, previous studies did not adjust for habitual sleep duration and physical activity. This is relevant since

Table 1—Participant characteristics on the basis of OSA severity categories

	No OSA/untreated mild OSA (n = 61)	Untreated moderate OSA (n = 47)	Untreated severe OSA (n = 72)	Treated OSA (n = 41)	Pvalue*
Demographics					
Age (years)	53.0 ± 10.2	55.8 ± 8.3	55.3 ± 7.8	53.9 ± 8.1	0.306
Men	16 (26.2)	26 (55.3)	58 (80.6)	27 (65.9)	<0.001
Race/ethnicity					0.593
White	28 (45.9)	28 (59.6)	39 (54.2)	27 (65.9)	
Black	23 (37.7)	16 (34.0)	22 (30.6)	11 (26.8)	
Hispanic (any)	2 (3.3)	2 (4.3)	6 (8.3)	1 (2.4)	
Asian	4 (6.6)	1 (2.1)	4 (5.6)	1 (2.4)	
American Indian	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Mixed	3 (4.9)	0 (0.0)	1 (1.4)	1 (2.4)	
Diabetes at screening	14 (23.0)	10 (21.3)	25 (34.7)	10 (24.4)	0.305
Weight (kg)	94.8 ± 16.6	101.5 ± 16.9	106.9 ± 18.5	108.6 ± 19.3	<0.001
Waist (cm)	106.7 ± 12.7	112.7 ± 12.2	114.7 ± 12.9	117.3 ± 13.1	<0.001
WHR	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	<0.001
BMI (kg/m^2)	34.0 ± 5.3	34.7 ± 5.4	35.3 ± 5.5	36.6 ± 5.9	0.130
Obese (BMI ≥30 kg/m^2)	47 (77.0)	37 (78.7)	56 (78.9)	36 (87.8)	0.573
Systolic BP (mmHg)	121.8 ± 13.9	128.7 ± 13.6	128.4 ± 12.4	128.1 ± 12.3	0.012
Diastolic BP (mmHg)	74.5 ± 11.0	77.7 ± 12.0	78.6 ± 9.8	77.1 ± 9.3	0.158
HbA_{1c} (%)	5.8 ± 0.4	5.7 ± 0.4	5.8 ± 0.5	5.8 ± 0.3	0.326
ESS score	8.8 ± 5.3	7.7 ± 3.7	8.6 ± 4.7	8.6 ± 4.3	0.628
Sleepy (Epworth >10)	23 (37.7)	17 (36.2)	27 (37.5)	15 (36.6)	0.998
CPAP adherent†	0 (0.0)	0 (0.0)	0 (0.0)	41 (100.0)	<0.001
CPAP use in subset adherent to CPAP (h/night) (n = 41)	—	—	—	6.2 ± 1.1	NA
Actigraphy measurements					
Sleep time (h)	6.83 ± 0.82	6.59 ± 0.88	6.26 ± 1.12	6.70 ± 0.74	0.004
Activity duration (min)	974 ± 55	1,041 ± 208	991 ± 69	986 ± 49	0.015
Percent immobility	20.2 ± 8.6	19.1 ± 9.1	21.9 ± 8.9	19.1 ± 8.6	0.254
Total activity count	227,485 ± 76,012	247,953 ± 78,135	225,467 ± 78,741	231,039 ± 70,177	0.426
Activity (counts/min)	233 ± 77	244 ± 78	226 ± 79	234 ± 68	0.673
PSG measurements					
Total recording time (min)	449.0 ± 39.9	463.1 ± 35.2	458.8 ± 37.4	439.1 ± 66.9	0.048
Total sleep time (min)	370.3 ± 62.0	361.3 ± 68.1	361.0 ± 67.2	344.1 ± 96.9	0.362
Sleep efficiency (%)	85.0 (76.7, 91.0)	84.7 (70.0, 87.9)	82.1 (73.9, 89.1)	82.9 (70.7, 90.4)	0.356
REM sleep (%)	19.2 (15.8, 23.7)	19.3 (15.7, 25.1)	16.5 (11.0, 20.0)	12.1 (5.0, 19.2)	<0.001
N3 sleep (%)	17.6 (10.1, 24.0)	14.1 (11.1, 22.2)	6.6 (1.0, 13.9)	9.3 (2.0, 17.0)	<0.001
AHI (events/h)	8.6 (3.7, 12.5)	22.0 (16.9, 26.6)	50.9 (37.2, 71.8)	29.1 (18.5, 59.2)	<0.001
REM AHI (events/h)	16.5 (5.8, 31.9)	34.9 (17.3, 52.0)	60.0 (38.6, 74.7)	30.0 (15.8, 54.7)	<0.001
Non-REM AHI (events/h)	4.1 (2.5, 8.0)	18.8 (11.6, 24.0)	50.8 (34.8, 76.5)	27.7 (15.1, 61.1)	<0.001
3% ODI (events/h)	5.5 (2.8, 8.6)	15.4 (11.5, 18.8)	38.4 (26.8, 56.0)	20.6 (9.7, 36.7)	<0.001
4% ODI (events/h)	3.0 (1.6, 6.1)	10.0 (7.7, 13.2)	27.9 (14.9, 50.0)	11.7 (6.6, 26.9)	<0.001
Microarousal index (events/h)	12.9 (9.3, 19.6)	20.6 (16.1, 27.4)	34.5 (27.3, 51.3)	26.9 (16.7, 52.6)	<0.001
T90 (%)	0.8 (0.1, 3.4)	5.0 (1.2, 13.4)	15.4 (4.8, 41.4)	4.7 (1.7, 17.8)	<0.001

Data are n (%), mean ± SD, or median (25th, 75th percentile). BP, blood pressure; N3, stage 3 of non–rapid eye movement sleep; NA, not applicable; ODI, oxygen desaturation index; REM, rapid eye movement. *ANOVA for continuous variables and χ^2 test for categorical variables. †CPAP adherence defined as self-report of using CPAP ≥4 h on ≥5 nights per week.

we previously reported that physical activity is associated with insulin sensitivity in prediabetes (13).

In addition to insulin resistance, β-cell dysfunction is pivotal in the pathogenesis of type 2 diabetes (9). Given that the incidence of prediabetes is increasing at an alarming rate (1), it is important to understand whether OSA and short sleep duration are associated with an additional risk of β-cell dysfunction, above and beyond excess adiposity, in people with prediabetes and IGT. To that end, our analysis shows that after adjusting for important confounders, neither objectively measured short sleep duration nor OSA severity was associated with robust measures of insulin sensitivity or β-cell responses. This lack of association was found across a range of insulin sensitivity, β-cell responses, sleep duration, OSA severity, and hypoxemia during sleep. One possible explanation for the lack of association is the high prevalence of obesity in our participants. It is possible that once obesity crosses a certain threshold, the contribution of OSA or short sleep to insulin resistance or β-cell dysfunction becomes less relevant. In one study using hyperinsulinemic-euglycemic clamps in 40 adults (mostly normoglycemic men) with moderate to severe OSA, short-term CPAP treatment

Table 2—Unadjusted metabolic outcomes on the basis of OSA severity categories

	All (N = 221)	No OSA/untreated mild OSA (n = 61)	Untreated moderate OSA (n = 47)	Untreated severe OSA (n = 72)	Treated OSA (n = 41)	P value
Hyperglycemic clamp variables						
Fasting glucose (mg/dL)	109.80 ± 9.94	107.74 ± 11.49	110.79 ± 9.02	110.67 ± 8.56	110.20 ± 10.58	0.295
Fasting C-peptide (ng/dL)	3.68 ± 1.43	3.29 ± 1.13	3.66 ± 1.10	3.89 ± 1.80	3.88 ± 1.31	0.071
Steady-state insulin (μU/mL)	85.63 (21.29, 344.33)	75.94 (18.52, 311.44)	88.23 (22.38, 347.93)	84.77 (20.67, 347.65)	99.48 (27.83, 355.67)	0.267
Steady-state C-peptide (ng/dL)	12.59 ± 4.88	11.81 ± 4.33	12.47 ± 3.51	12.80 ± 6.00	13.54 ± 4.74	0.350
M/I (mg/kg/min/pg/L)	40.45 (9.67, 169.15)	49.9 (12.9, 192.94)	38.09 (8.59, 168.95)	38.09 (8.76, 165.67)	34.81 (9.18, 132)	0.051
$ACPR_g$ (ng/dL)	2.86 (1.07, 7.61)	2.97 (1.23, 7.19)	2.97 (1.21, 7.33)	2.77 (0.89, 8.64)	2.72 (1.13, 6.57)	0.745
$ACPR_{max}$ (ng/dL)	14.44 (6.1, 34.21)	13.74 (5.58, 33.84)	14.01 (5.69, 34.52)	14.88 (6.28, 35.25)	15.49 (7.35, 32.62)	0.529
OGTT variables						
Fasting glucose (mg/dL)	111.05 ± 11.53	108.36 ± 12.26	114.00 ± 13.10	111.08 ± 10.74	111.62 ± 9.05	0.089
Fasting insulin (μU/mL)	14.44 (4.82, 43.28)	11.59 (4.35, 30.88)	15.49 (5.07, 47.33)	15.64 (4.92, 49.72)	15.96 (5.65, 45.1)	0.005
2-h glucose (mg/dL)	179.85 ± 39.41	179.48 ± 44.61	179.72 ± 34.03	180.25 ± 35.74	179.85 ± 44.24	1.000
G-iAUC (mg/dL)	10,670.3 ± 4,341.6	10,915.8 ± 4,540.4	9,637.8 ± 3,843.1	11,031.7 ± 4,139.8	10,818.4 ± 4,857.7	0.353
C-peptide index (ng/mg)	6.75 (2.34, 19.46)	6.36 (2.39, 16.95)	7.17 (2.91, 17.67)	6.75 (1.93, 23.67)	6.75 (2.49, 18.35)	0.745
Insulinogenic index (μU/mg)	85.63 (21.29, 344.33)	77.48 (22.54, 266.35)	91.84 (23.75, 355.1)	85.63 (17.16, 427.18)	91.84 (26.71, 315.7)	0.588
HOMA-IR (mIU/mmol)	3.94 (1.21, 12.76)	3.06 (1.04, 9.01)	4.31 (1.28, 14.52)	4.26 (1.29, 14.09)	4.39 (1.47, 13.17)	0.003

Data are mean ± SD or geometric mean (95% CI). P values represent comparisons across the four groups by ANOVA, using native scale data for normally distributed variables or log-transformed data otherwise.

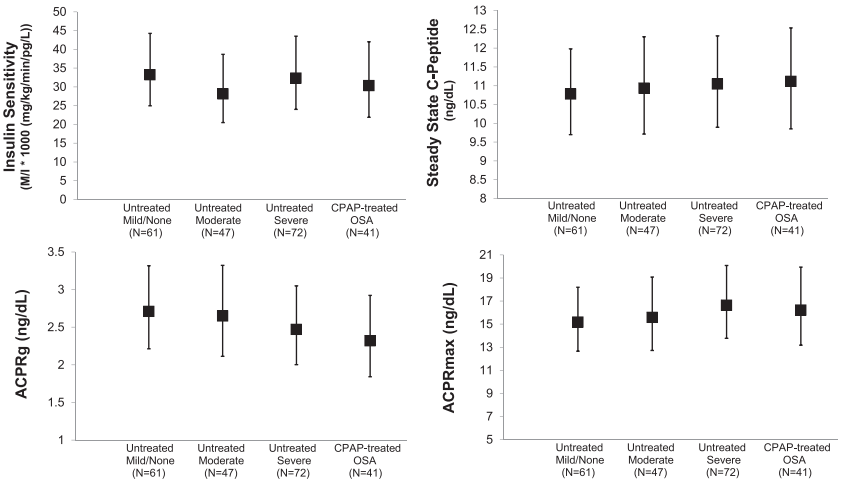

Figure 1—Effect of OSA on insulin sensitivity and β-cell function as assessed by the hyperglycemic clamp. Adjusted means from multiple linear regression models for the relationship of log-transformed dependent variables (insulin sensitivity and β-cell function as assessed by the hyperglycemic clamp) with categories of OSA severity and treatment adherence. Data are least square means and 95% CIs adjusted for age, sex, race/ethnicity, BMI, WHR, and actigraphically measured sleep duration and physical activity. Steady-state C-peptide, $ACPR_g$, and $ACPR_{max}$ are also adjusted for log insulin sensitivity (M/I).

of OSA resulted in improved insulin sensitivity only in the nonobese subgroup (30). This supports our supposition that with increasing obesity, excess adiposity becomes a major contributor to insulin resistance and β-cell dysfunction.

We did not find any evidence of improved insulin sensitivity or β-cell responses in participants who self-reported being adherent to CPAP therapy. In clinical trials of patients with type 2 diabetes and OSA, CPAP has not been consistently shown to improve glycemic control or reduce insulin resistance after 1–6 months of use (31–34). This heterogeneous response to CPAP may be a consequence of variation in levels of CPAP adherence, duration of type 2 diabetes, and background glycemic control. In short-term laboratory experiments, however, CPAP therapy with documented use for 8 h/night for 1 or 2 weeks resulted in improved glucose metabolism, including reduction in 24-h mean glucose levels in adults with type 2 diabetes (35,36), and reduction in glucose response to glucose challenge and improved insulin sensitivity in those with prediabetes (37). This night-long use of CPAP could be a significant factor because rapid eye movement–related obstructive apneas and hypopneas, generally occurring in the later part of the night, were found to be associated with glycemic control in type 2 diabetes (38). However, in the largest clinical trial with the longest duration of follow-up to date, there was no significant difference between CPAP and usual care in serum glucose, HbA_{1c}, or antidiabetic medication use in those with known type 2 diabetes (39). Moreover, no significant differences were found in glycemic measures in those with prediabetes or in incident type 2 diabetes. Although mean CPAP usage for the duration of the trial was 3.5 ± 2.3 h/night, there was no relationship between various metrics of OSA severity or levels of CPAP adherence and the outcomes. It is possible that this clinical trial lacked enough statistical power to adequately assess the impact of CPAP on the incidence of type 2 diabetes. Therefore, there is a need for well-designed clinical trials examining the role of CPAP therapy in slowing the progression from prediabetes to type 2 diabetes.

Our study has several noteworthy strengths in that it represents the largest group of overweight and obese adults with prediabetes/recently diagnosed, untreated type 2 diabetes to undergo simultaneous quantification of sleep, physical activity, insulin sensitivity, and β-cell responses using sophisticated methodologies. Our inclusion criteria allowed enrollment

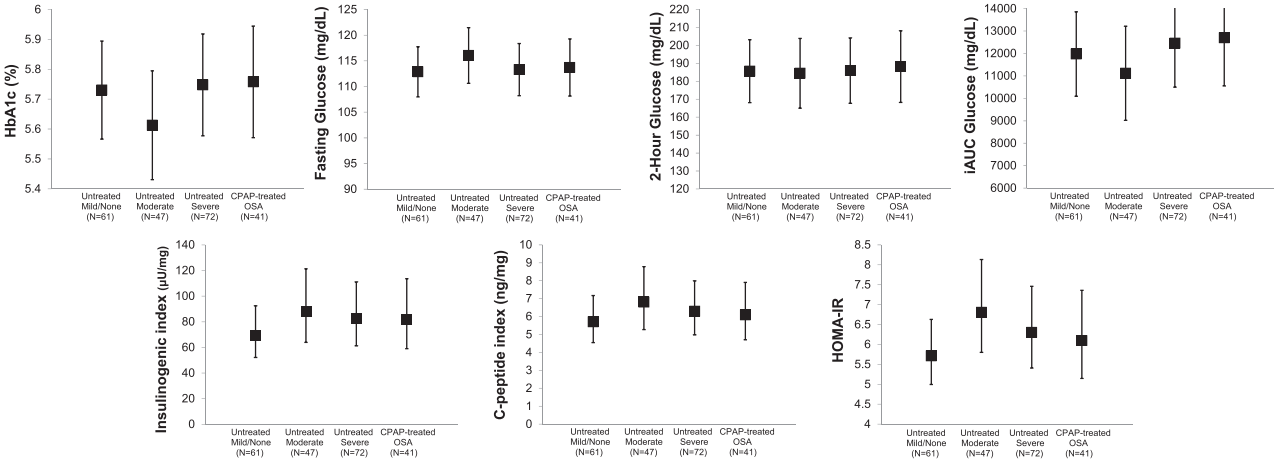

Figure 2—Effect of OSA on HbA_{1c} and measures of glycemia as assessed by the OGTT. Adjusted means from multiple linear regression models for the relationship of dependent variables (glycemia as assessed by the 3-h OGTT) with categories of OSA severity and treatment adherence. Data are least square means and 95% CIs adjusted for age, sex, race/ethnicity, BMI, WHR, and actigraphically measured sleep duration and physical activity. Insulinogenic index, C-peptide index, and HOMA-IR were log-transformed for analyses.

of participants with a wider range of fasting and 2-h glucose than what is used to define prediabetes, thereby allowing us to include participants with recently diagnosed, treatment-naive type 2 diabetes on the basis of 2-h glucose. As such, our inclusion criteria increase the generalizability of our findings. The participants were ethnically/racially diverse, and both sexes were well represented. Sleep and actigraphy data were scored centrally using standard recommended scoring criteria. Similarly, all assays were performed in a central laboratory.

Our study has several limitations. First, it represents the baseline analyses of the participants enrolled in a clinical trial, which can lead to some bias when compared with enrolling an unselected cohort. However, as stated above, our inclusion criteria allowed the enrollment of participants with a wider range of fasting and 2-h glucose than what is traditionally used to define prediabetes. Second, we did not directly quantify body fat. Our models were adjusted for BMI and WHR as an indirect measure of fat distribution. Moreover, we found no associations between sleep variables and most metabolic outcomes in the 20% (n = 44) of overweight, but nonobese individuals. Third, we did not have objective CPAP adherence data. However, our findings remained unchanged whether those self-reporting adherent CPAP use were included or all 49 participants who used CPAP were excluded (Supplementary Table 2 and Supplementary Figs. 2 and 3). Finally, the direction of causality cannot be ascertained because of the cross-sectional nature of the analysis of participants enrolled in a clinical trial.

In summary, OSA and short sleep duration are highly prevalent in obese adults with prediabetes and recently diagnosed untreated type 2 diabetes, but on the basis of detailed and intensive assessments of insulin sensitivity and β-cell responsiveness, there were no significant associations between OSA severity or short sleep duration with various components of the glucose regulatory pathway. Future studies should examine the association between sleep disturbances and β-cell responses in nonobese individuals. Finally, well-designed interventional studies are needed in patients with prediabetes, particularly in the nonobese group, to assess whether OSA therapy or sleep extension can lead to improved insulin sensitivity and β-cell function and thereby reduce the risk of developing type 2 diabetes. In obese individuals, treatment of OSA is important, but our results underscore the need for a comprehensive approach that includes additional interventions, particularly exercise and weight loss.

Acknowledgments. The RISE Consortium is grateful to Dr. David White and Philips Respironics for providing 40 Actiwatch Spectrum devices for the completion of the study. The RISE Consortium acknowledges the support and input of the RISE data and safety monitoring board and Barbara Linder, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Program Official for RISE; Ellen Leschek, the NIDDK scientific officer; and Peter Savage, who served as the scientific officer for RISE before his retirement. The consortium is also grateful to the participants who, by volunteering, are furthering the ability to reduce the burden of diabetes.

Funding. RISE is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (U01-DK-094406, U01-DK-094430, U01-DK-094431, U01-DK-094438, U01-DK-094467, P30-DK-017047, P30-DK-020595, P30-DK-045735, P30-DK-097512, UL1-TR-000430, UL1-TR-001082, UL1-TR-001108, UL1-TR-001855, UL1-TR-001857, UL1-TR-001858, and UL1-TR-001863), the Department of Veterans Affairs, and Kaiser Permanente Southern California. In addition, the National Heart, Lung, and Blood Institute provided support for the RISE Sleep Ancillary study to B.M. (R01-HL-119161). Additional financial and material support from the American Diabetes Association, Allergan, Apollo Endosurgery, Abbott Laboratories, and Novo Nordisk was received.

The funders had no role in the study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the article for publication.

Duality of Interest. K.J.M. holds an investigator-initiated research grant from Novo Nordisk. S.E.K. serves as a paid consultant on advisory boards for Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.M. interpreted the data and wrote the first draft, which was also reviewed and edited by all members of the writing group (A.H.T., K.A.T., S.L.E., S.S., K.J.N., T.S.H., S.M., K.J.M., S.E.K., D.A.E., and E.V.C.). B.M. and E.V.C. proposed the analysis. A.H.T. and S.L.E. performed the analysis. Members of the RISE Consortium recruited participants and collected study data. The RISE Steering Committee reviewed and edited the manuscript and approved its submission. B.M. and A.H.T. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Sharing. In accordance with the National Institutes of Health Public Access Policy, we provide all manuscripts to PubMed Central, including this manuscript. RISE has provided the protocols to the public through its public website (http://www.risestudy.org). The RISE study abides by the NIDDK data sharing policy and implementation guidance as required by the National Institutes of Health/NIDDK (https://www.niddkrepository.org/studies/rise).

References

1. U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2020 estimates of diabetes and its burden in the United States, 2020. Accessed 26 July 2020. Available from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
2. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. JAMA 2018;319:1723–1725
3. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 2015;3:310–318
4. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. Chest 2017;152:1070–1086
5. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435–1439
6. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. Ann Intern Med 2012;157:549–557
7. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A 2008;105:1044–1049
8. Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol (1985) 2009;106:1538–1544
9. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006;444:840–846
10. RISE Consortium. Lack of durable improvements in β-cell function following withdrawal of pharmacological interventions in adults with impaired glucose tolerance or recently diagnosed type 2 diabetes. Diabetes Care 2019;42:1742–1751
11. RISE Consortium. Restoring Insulin Secretion (RISE): design of studies of β-cell preservation in prediabetes and early type 2 diabetes across the life span. Diabetes Care 2014;37:780–788
12. Patel SR, Weng J, Rueschman M, et al. Reproducibility of a standardized actigraphy scoring algorithm for sleep in a US Hispanic/Latino population. Sleep (Basel) 2015;38:1497–1503
13. Temple KA, Tjaden AH, Atkinson KM, et al.; RISE Consortium. Association of habitual daily physical activity with glucose tolerance and β-cell function in adults with impaired glucose tolerance or recently diagnosed type 2 diabetes from the Restoring Insulin Secretion (RISE) Study. Diabetes Care 2019;42:1521–1529
14. Hannon TS, Kahn SE, Utzschneider KM, et al.; RISE Consortium. Review of methods for measuring β-cell function: design considerations from the Restoring Insulin Secretion (RISE) Consortium. Diabetes Obes Metab 2018;20:14–24
15. RISE Consortium. Metabolic contrasts between youth and adults with impaired glucose

tolerance or recently diagnosed type 2 diabetes: I. Observations using the hyperglycemic clamp. Diabetes Care 2018;41:1696–1706
16. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S13–S27
17. Phillips DI, Clark PM, Hales CN, Osmond C. Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. Diabet Med 1994;11:286–292
18. Seltzer HS, Allen EW, Herron AL Jr., Brennan MT. Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. J Clin Invest 1967;46:323–335
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
20. Elahi D. In praise of the hyperglycemic clamp. A method for assessment of beta-cell sensitivity and insulin resistance. Diabetes Care 1996;19:278–286
21. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42:1663–1672
22. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis. Sleep Med Rev 2016;30:11–24
23. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2010;33:414–420
24. Seicean S, Kirchner HL, Gottlieb DJ, et al. Sleep-disordered breathing and impaired glucose metabolism in normal-weight and overweight/obese individuals: the Sleep Heart Health Study. Diabetes Care 2008;31:1001–1006
25. Yano Y, Gao Y, Johnson DA, et al. Sleep characteristics and measures of glucose metabolism in blacks: The Jackson Heart Study. J Am Heart Assoc 2020;9:e013209
26. Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. Am J Respir Crit Care Med 2009;179:235–240
27. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HK. Obstructive sleep apnea as a risk factor for type 2 diabetes. Am J Med 2009;122:1122–1127
28. Marshall NS, Wong KK, Phillips CL, Liu PY, Knuiman MW, Grunstein RR. Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med 2009;5:15–20
29. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med 2005;172:1590–1595
30. Harsch IA, Schahin SP, Radespiel-Tröger M, et al. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2004;169:156–162
31. Martínez-Cerón E, Barquiel B, Bezos AM, et al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. Am J Respir Crit Care Med 2016;194:476–485
32. Shaw JE, Punjabi NM, Naughton MT, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. Am J Respir Crit Care Med 2016;194:486–492
33. Morariu EM, Chasens ER, Strollo PJ Jr., Korytkowski M. Effect of continuous positive airway pressure (CPAP) on glycemic control and variability in type 2 diabetes. Sleep Breath 2017;21:145–147
34. Lam JCM, Lai AYK, Tam TCC, Yuen MMA, Lam KSL, Ip MSM. CPAP therapy for patients with sleep apnea and type 2 diabetes mellitus improves control of blood pressure. Sleep Breath 2017;21:377–386
35. Mokhlesi B, Grimaldi D, Beccuti G, et al. Effect of one week of 8-hour nightly continuous positive airway pressure treatment of obstructive sleep apnea on glycemic control in type 2 diabetes: a proof-of-concept study. Am J Respir Crit Care Med 2016;194:516–519
36. Mokhlesi B, Grimaldi D, Beccuti G, Van Cauter E. Effect of one week of CPAP treatment of obstructive sleep apnoea on 24-hour profiles of glucose, insulin and counter-regulatory hormones in type 2 diabetes. Diabetes Obes Metab 2017;19:452–456
37. Pamidi S, Wroblewski K, Stepien M, et al. Eight hours of nightly continuous positive airway pressure treatment of obstructive sleep apnea improves glucose metabolism in patients with prediabetes. A randomized controlled trial. Am J Respir Crit Care Med 2015;192:96–105
38. Grimaldi D, Beccuti G, Touma C, Van Cauter E, Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. Diabetes Care 2014;37:355–363
39. Loffler KA, Heeley E, Freed R, et al.; SAVE Substudy Investigators. Continuous positive airway pressure treatment, glycemia, and diabetes risk in obstructive sleep apnea and comorbid cardiovascular disease. Diabetes Care 2020;43:1859–1867