Risk of Incident Obstructive Sleep Apnea Among Patients With Type 2 Diabetes

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OBJECTIVE

This study compared the incidence of obstructive sleep apnea (OSA) in patients with and without type 2 diabetes and investigated risk factors for OSA in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A retrospective cohort study was performed to compare OSA incidence between adult patients with and without type 2 diabetes matched for age, sex, and BMI. Patients with a prevalent OSA diagnosis were excluded. The study cohort was derived from The Health Improvement Network (THIN), a U.K. primary care database, from 1 January 2005 to 31 December 2017.

RESULTS

There were 3,110 (0.88%) and 5,968 (0.46%) incident OSA cases identified in the 360,250 exposed and 1,296,489 unexposed patient cohorts, respectively. Adjusted incidence rate ratio (aIRR) of OSA in patients with type 2 diabetes compared with those without was 1.48 (95% CI 1.42–1.55; $P < 0.001$). In a multivariate regression analysis of patients with type 2 diabetes, significant predictors of OSA were diabetes-related foot disease (1.23 [1.06–1.42]; $P = 0.005$), being prescribed insulin in the last 60 days (1.58 [1.42–1.75]; $P < 0.001$), male sex (2.27 [2.09–2.46]; $P < 0.001$), being overweight (2.02 [1.54–2.64]; $P < 0.001$) or obese (8.29 [6.42–10.69]; $P < 0.001$), heart failure (1.41 [1.18–1.70]; $P < 0.001$), ischemic heart disease (1.22 [1.11–1.34]; $P < 0.001$), atrial fibrillation (1.23 [1.04–1.46]; $P = 0.015$), hypertension (1.32 [1.23–1.43]; $P < 0.001$), and depression (1.75 [1.61–1.91]; $P < 0.001$).

CONCLUSIONS

When considered alongside previous evidence, this study indicates that the association between type 2 diabetes and OSA is bidirectional. In addition to known predictors of OSA, diabetes-related foot disease and insulin treatment were identified as risk factors in patients with type 2 diabetes.

Obstructive sleep apnea (OSA) is a common disorder characterized by repeated complete or partial upper airway obstructions during sleep, leading to recurrent oxygen desaturations, cyclical adverse changes in heart rate, blood pressure (BP), and sympathetic activity, and disruption to sleep architecture (1). As a result, OSA has been linked to multiple adverse outcomes, including road traffic accidents (2), reduced workplace productivity (3), cardiovascular disease (CVD) (4,5), hypertension (5,6), insulin resistance (7), increased mortality (8), and type 2 diabetes (9).

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Multiple epidemiological studies have indicated that OSA may be a risk factor for the development of type 2 diabetes independent of obesity and other confounders (9), possibly via the effect of recurrent hypoxemia, inflammation, sympathetic activation, and activation of the hypothalamic-adrenal axis on insulin resistance and β-cell function (10). In addition, multiple cross-sectional studies have shown a high prevalence of undiagnosed OSA in patients with type 2 diabetes (24–86%) (11,12). Furthermore, cross-sectional and cohort studies have shown that OSA is associated with worse glycemic control in patients with type 2 diabetes (11–13) and with diabetes-related vascular complications (14–17). Hence, understanding the complex relationships between OSA and type 2 diabetes is important, because OSA might be considered a modifiable risk factor for type 2 diabetes development and adverse outcomes in these patients (18).

However, the potential role for type 2 diabetes as a risk factor for OSA has been less well examined. The relationship between OSA and type 2 diabetes is plausibly bidirectional. Type 2 diabetes might lead to the development of OSA as a result of the effect of insulin resistance and autonomic dysfunction on upper airways stability (19–21) as well as the increase in weight associated with some type 2 diabetes treatments. Hence, there is a need to examine the effect of type 2 diabetes on incident OSA. Identifying predictors of OSA in patients with type 2 diabetes is also important to aid screening strategies.

The primary aim of our study was to evaluate the role of type 2 diabetes as a risk factor for incident OSA by using a matched controlled population-based retrospective cohort study. The secondary aim was to identify predictors of incident OSA in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

An age-, sex-, and BMI-matched controlled retrospective cohort study was conducted from 1 January 2005 to 31 December 2017.

Data Source

Data were extracted from The Health Improvement Network (THIN), an electronic primary care records database that contains anonymized medical records of more than 15 million patients from 787 practices in the U.K. The database is generalizable to the U.K. population. It consists of coded information on patient demographics, symptoms and diagnoses, drug prescriptions, consultations, and diagnostic tests and their results. THIN is particularly suitable for analyzing long-term health outcomes because general practitioners routinely collect and coordinate the patient's data (22). THIN has been extensively used previously to study cardiometabolic outcomes (23,24) and to study type 2 diabetes and OSA (25).

Ethics

The THIN data collection scheme and research performed using THIN data were approved by the National Health Service South-East Multicentre Research Ethics Committee in 2003. Under the terms of the approval, studies must undergo independent scientific review. The Scientific Review Committee approved the use of the use of THIN data for this study in July 2018 (SRC reference 18THIN062).

Population

To ensure high-quality data, general practices were eligible for inclusion in the study from the latest of 12 months after reporting acceptable mortality rates, 12 months after starting to use electronic medical records, and the study start date (1 January 2005). Adult patients aged 16 years and older registered for at least 12 months with any of the eligible general practices before study entry formed the source population.

Exposed Cohort

The exposed cohort consisted of adult patients with type 2 diabetes. Type 2 diabetes diagnosis was ascertained by the presence of any type 2 diabetes clinical (Read) code (Supplementary Table 1*A*) in the patient's medical record and the absence of any record of type 1 diabetes. The Read code list used to define exposure has previously been used to study type 2 diabetes (23). The primary analysis included all patients (prevalent and incident) with a type 2 diabetes diagnosis. A sensitivity analysis, including only patients with incident type 2 diabetes (newly diagnosed during the study period), was performed to explore any effect of survival bias.

Unexposed Cohort

For every exposed patient, up to four control subjects were randomly selected from an age-, sex-, and BMI-matched pool of eligible patients without a record of type 2 diabetes at any time before or during the study period. Age and BMI were matched to within 1 year and 2 kg/m^2 respectively.

Follow-up Period

A 15-month latency period was used for all patients. For patients with incident type 2 diabetes, the index date was 15 months after the date of diagnosis; for patients with prevalent type 2 diabetes, the index date was 15 months after the date the patient became eligible for inclusion. The 15-month interval was introduced to *1*) ensure that all predictors determining the risk of OSA in patients with diabetes were recorded at baseline, because the Quality and Outcomes Framework (QOF) ensures these are captured within a 15-month period; and *2*) limit the possibility of silent OSA preceding type 2 diabetes being misclassified as incident OSA. The unexposed patients were assigned the same index date as their corresponding exposed patient to avoid immortal time bias (26). Patients with type 2 diabetes and control subjects were monitored from the index date until the earliest of the following end points: outcome (OSA) date, death date, date patient left the practice, date the practice ceased contributing to the database, and study end date (31 December 2017).

Outcomes

OSA was identified by a record of any relevant clinical code (Supplementary Table 1*B*).

Analysis

Poisson regression was used to calculate crude incidence rate ratios (IRRs) and adjusted incidence rate ratios (aIRRs), together with their corresponding 95% CIs, *1*) comparing the incidence of OSA in patients with and without type 2 diabetes and *2*) in an analysis restricted to patients with type 2 diabetes to explore possible risk factors that may predict the incidence of OSA. These analyses excluded patients with a record of the outcome at baseline.

Further exploratory analysis comparing the incidence of OSA between patients with and without type 2 diabetes

was performed in subgroups of patients stratified by age, sex, BMI, and the presence or absence of comorbid conditions, including composite CVDs composed of heart failure, ischemic heart disease, stroke/transient ischemic attack (TIA), atrial fibrillation, and hypertension, and composite mental health conditions (anxiety and depression).

To evaluate any possible effect of surveillance bias and unobserved confounders on the outcome (OSA), in the same cohort we estimated the aIRR of chronic obstructive pulmonary disease (COPD), a negative control outcome that has symptoms that overlap with those of diabetes (sleep disturbance and fatigue).

A further sensitivity analysis was performed restricting outcomes to those specifically recorded as obstructive-type sleep apnea (Read code Fy03.11 or H5B0.00) to ensure the exclusion of central sleep apnea outcomes.

Study Variables

Covariates for the study were selected based on biological plausibility and previous literature. All regression models were adjusted for age, sex, BMI, Townsend deprivation quintile, smoking status, and ethnicity. BMI recorded closest to the index date was categorized as <25 kg/m^2, 25–30 kg/m^2 (overweight), and ≥ 30 kg/m^2 (obese). Implausible BMI values <14 and >75 were considered missing. Social deprivation was categorized as quintiles based on the Townsend score (27). Smoking status was categorized as nonsmoker, previous smoker, and smoker. Missing values for BMI, Townsend deprivation quintile, and smoking status were treated as a separate missing category.

In the model identifying risk factors for OSA among patients with type 2 diabetes, further diabetes-related covariates recorded before the index date were taken into consideration. These included HbA_{1c} category, estimated glomerular filtration rate (eGFR) category, record of hypoglycemic attack, diagnosis of foot disease, retinopathy, CVD (heart failure, ischemic heart disease, stroke/TIA, atrial fibrillation, and hypertension), mental health conditions, and prescription of lipid-lowering drugs and insulin within 60 days before the index date. Implausible HbA_{1c} values >200 mmol/mol and eGFR >200 mL/min/1.73 m^2 were considered missing. Lipid-lowering drugs were used as a proxy measure for hypercholesterolemia and insulin as an indicator of diabetes severity.

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation from the serum creatinine values and ethnicity data (where available). HbA_{1c} was categorized as $\leq 6.5\%$ (47.50 mmol/mol), 6.5–7.5% (47.51–58.50 mmol/mol), 7.5–8.5% (58.51–69.40 mmol/mol), and $>8.5\%$ (69.40 mmol/mol); calculated eGFR was categorized as ≥ 90 mL/min/1.73 m^2 (stage 1 chronic kidney disease), 60–89 mL/min/1.73 m^2 (stage 2), 30–59 mL/min/1.73 m^2 (stage 3), and <30 mL/min/1.73 m^2 (stage 4 and 5). Retinopathy was considered as a composite of sight-threatening retinopathy graded as R2 (preproliferative), R3 (proliferative), or M1 (maculopathy), vision loss, and use of medical procedures such as laser and vitreous injections. Diabetes-related foot disease was a composite of lower-limb amputation, gangrene, foot ulcer, Charcot foot, peripheral vascular disease, and peripheral neuropathy. The covariates were identified by clinical codes indicating the condition or treatments performed specific to the condition. Most covariates are included in disease registers that general practices are expected to maintain according to the QOF (28).

Analyses were performed in Stata IC 14 software. Two-sided P values were obtained, and a P value <0.05 was considered as statistically significant.

The results of this study are reported in line with RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines (Supplementary Table 2).

RESULTS

Baseline Characteristics

We identified 360,250 eligible patients with type 2 diabetes. These patients were matched for age, sex, and BMI to 1,296,489 patients without type 2 diabetes (unexposed/control cohort). Baseline characteristics are reported in Table 1. The matching parameters age and sex were similar between the exposed and unexposed groups (mean [SD] age, 64.9 [13.3] vs. 64.6 [13.6] years; male sex, 55.5% vs. 54.2%). Patients in the exposed cohort had a slightly higher mean BMI than control patients (31.0 [6.5] vs. 29.8 [5.8] kg/m^2), but the difference was within the matching range (± 2 kg/m^2). Compared with control patients, patients with diabetes were more deprived (13.7% vs. 9.9% were in the most deprived Townsend quintile) and more likely to be of south Asian ethnicity (3.8% vs. 0.9%). Patients with diabetes also had higher levels of CVDs, including heart failure (4.8% vs. 2.5%), ischemic heart disease (19.1% vs. 11.4%), and stroke/TIA (8.8% vs. 5.9%), and greater use of lipid-lowering drugs (63.7% vs. 23.6%). Prevalent OSA at baseline (recorded up to 15 months after the index date) was higher among exposed compared with unexposed patients (1.8% vs. 0.9%); these patients were excluded in subsequent analyses.

Type 2 Diabetes and Incidence of OSA

OSA developed in 3,110 patients (0.88%) with diabetes and in 5,968 control patients (0.46%) during the follow-up period (Table 2). The crude incidence rate of OSA among patients with and without diabetes was 1.76 and 1.00 per 1,000 person-years: IRR 1.76 (95% CI 1.69–1.84; $P < 0.001$). After adjustment for potential confounders, including age, sex, BMI, Townsend deprivation quintile, smoking status, and ethnicity, the association remained statistically significant: aIRR 1.48 (95% CI 1.42–1.55; $P < 0.001$). Further adjustment for composite CVD at baseline slightly attenuated the effect: aIRR 1.36 (95% CI 1.30–1.42; $P < 0.001$). The association remained similar in a further sensitivity analysis including only patients with incident type 2 diabetes and their corresponding control patients (Supplementary Table 3*A*): aIRR 1.41 (95% CI 1.32–1.51; $P < 0.001$) (Table 2).

Subgroup and Sensitivity Analyses

With the exception of patients aged 16–29 years, in all of the age- and BMI-stratified cohorts there was a significant increase in OSA incidence in patients with type 2 diabetes compared with patients without (Fig. 1). The risk of OSA was increased in both sexes, but the association between diabetes and OSA was stronger in women (aIRR 1.76 [95% CI 1.62–1.91]) than in men (1.39 [1.32–1.46]). Irrespective of the presence or absence of comorbid conditions, there was a statistically significant increase in OSA incidence in patients with type 2 diabetes.

In the analysis restricting outcomes to those explicitly coded as obstructive-type sleep apnea, there was an increase

Table 1—Baseline patient characteristics for type 2 diabetes–exposed and –unexposed patients

	Exposed (n = 360,250)	Unexposed (n = 1,296,489)
Age (years), mean (SD)	64.85 (13.28)	64.56 (13.63)
Age categories (years), *n* (%)		
16–29	2,117 (0.59)	8,373 (0.65)
30–39	11,095 (3.08)	43,951 (3.39)
40–49	38,704 (10.74)	149,940 (11.57)
50–59	74,341 (20.64)	271,837 (20.97)
60–69	99,805 (27.70)	346,252 (26.71)
≥70	134,188 (37.25)	476,136 (36.73)
Sex, *n* (%)		
Men	199,941 (55.50)	702,927 (54.22)
Women	160,309 (44.50)	593,562 (45.78)
BMI (kg/m^2), mean (SD)	31.00 (6.47)	29.83 (5.80)
BMI categories, *n* (%)		
Underweight/normal weight (<25 kg/m^2)	54,047 (15.00)	234,404 (18.08)
Overweight (25–30 kg/m^2)	118,393 (32.86)	489,719 (37.77)
Obese (≥30 kg/m^2)	179,959 (49.95)	542,588 (41.85)
Missing	7,851 (2.18)	29,778 (2.30)
Townsend deprivation quintile, *n* (%)		
1	64,764 (17.98)	299,727 (23.12)
2	64,862 (18.00)	270,123 (20.83)
3	68,180 (18.93)	241,708 (18.64)
4	65,566 (18.20)	197,086 (15.20)
5	49,372 (13.70)	128,651 (9.92)
Missing	47,506 (13.19)	159,194 (12.28)
Smoker categories, *n* (%)		
Nonsmoker	174,233 (48.36)	690,164 (53.23)
Previous smoker	129,534 (35.96)	405,090 (31.25)
Smoker	55,482 (15.40)	188,833 (14.56)
Missing	1,001 (0.28)	12,402 (0.96)
Ethnicity, *n* (%)		
Caucasian	151,519 (42.06)	533,954 (41.18)
Black Afro-Caribbean	5,858 (1.63)	10,272 (0.79)
Chinese	2,432 (0.68)	3,990 (0.31)
South Asian	13,663 (3.79)	11,351 (0.88)
Mixed race	1,199 (0.33)	2,432 (0.19)
Missing	185,579 (51.51)	734,490 (56.65)
eGFR (mL/min/1.73 m^2), median (IQR)	76.5 (60.6–91.3)	74.3 (61.2–87.2)
eGFR category, *n* (%)		
≥90 mL/min/1.73 m^2 (stage 1)	97,438 (27.05)	208,516 (16.08)
60–89 mL/min/1.73 m^2 (stage 2)	178,998 (49.69)	599,575 (46.25)
30–59 mL/min/1.73 m^2 (stage 3)	74,006 (20.54)	207,151 (15.98)
<30 mL/min/1.73 m^2 (stage 4+5)	7,384 (2.05)	13,083 (1.01)
Missing	2,424 (0.67)	268,164 (20.68)
Baseline comorbidities, *n* (%)		
CVDs		
Heart failure	17,304 (4.80)	32,924 (2.54)
Ischemic heart disease	68,908 (19.13)	147,418 (11.37)
Stroke/TIA	31,687 (8.80)	76,128 (5.87)
Atrial fibrillation	25,174 (6.99)	65,688 (5.07)
Hypertension	213,479 (59.26)	489,418 (37.75)
Mental health conditions		
Anxiety	57,756 (16.03)	200,706 (15.48)
Depression	75,642 (21.00)	241,215 (18.61)
Baseline drug use (within 60 days of index), *n* (%)		
Lipid-lowering drugs	229,287 (63.65)	305,443 (23.56)
Outcome at baseline, *n* (%)		
OSA*	6,567 (1.82)	11,682 (0.90)

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Table 1—Continued

	Exposed (n = 360,250)	Unexposed (n = 1,296,489)
Diabetes-related variables†		
HbA_{1c} (mmol/mol), median (IQR)	51.9 (45.0–60.6)	
HbA_{1c} category, *n* (%)		
≤6.5% (47.500 mmol/mol)	98,835 (27.44)	
6.5–7.5% (47.501–58.500 mmol/mol)	114,821 (31.87)	
7.5–8.5% (58.501–69.400 mmol/mol)	41,049 (11.39)	
≥8.5% (69.401 mmol/mol)	43,093 (11.96)	
Missing	62,452 (17.34)	
Concurrent diabetes-related conditions, *n* (%)		
Foot disease	22,305 (6.20)	
Retinopathy/low vision/blindness	16,911 (4.69)	
Hypoglycemic event	7,555 (2.10)	
Baseline drug use (within 60 days of index), *n* (%)		
Insulin	26,877 (7.46)	

*These patients were excluded from subsequent analysis. †Diabetes-related variables are reported only for the exposed cohort because they are not applicable to the unexposed cohort.

in the observed effect size: aIRR 1.62 (95% CI 1.52–1.73; $P < 0.001$) (Supplementary Table 3*B*).

Impact of Surveillance Bias

The analysis considering COPD as an outcome found no significant increase in the incidence of COPD in patients with type 2 diabetes compared with patients without type 2 diabetes after adjusting for age, sex, BMI, Townsend deprivation quintile, smoking status, and ethnicity: aIRR 1.03 (95% CI 0.99–1.08; $P = 0.112$).

Risk Factors for OSA Among Patients With Type 2 Diabetes

Among the 20 risk factors considered, male sex (aIRR 2.27 [95% CI 2.09–2.46]; $P < 0.001$), being overweight (2.02 [1.54–2.64]; $P < 0.001$) or obese (8.29 [6.42–10.69]; $P < 0.001$), being a previous smoker (1.13 [1.04–1.22]; $P = 0.004$), diabetes-related foot disease (1.23 [1.06–1.42]; $P = 0.005$), heart failure (1.41 [1.18–1.70]; $P < 0.001$), ischemic heart disease (1.22 [1.11–1.34]; $P < 0.001$), atrial fibrillation (1.23 [1.04–1.46]; $P = 0.015$), hypertension (1.32 [1.23–1.43]; $P < 0.001$), depression (1.75 [1.61–1.91]; $P < 0.001$), and insulin prescription (1.58 [1.42–1.75]; $P < 0.001$) were significantly predictive of incident OSA in patients with type 2 diabetes (Table 3).

In a sensitivity analysis including only patients with incident/newly diagnosed type 2 diabetes, the results remained similar except for four of the risk factors considered: hypoglycemic event became statistically significant as a predictor of OSA (aIRR 2.06 [95% CI 1.26–3.39]; $P = 0.004$), whereas being a previous smoker, atrial fibrillation, and prescription of insulin became nonsignificant as predictors in the model (Supplementary Table 3*C*).

CONCLUSIONS

This study showed that patients with type 2 diabetes have an almost 50% increase in risk of developing OSA compared with patients without type 2 diabetes, independent of potential confounders and traditional OSA risk factors. In addition, our study identified predictors of incident OSA in patients with type 2 diabetes, including male sex, obesity, CVDs, diabetes-related foot disease, insulin use, and depression. This is the first study to identify predictors of incident OSA in patients with type 2 diabetes and to examine the links between type 2 diabetes and incident OSA in a European population.

Previous literature has shown that OSA is an independent risk factor for the development of type 2 diabetes. Our results suggest that this relationship is bidirectional, because patients with

Table 2—Crude and aIRRs for OSA in patients with type 2 diabetes compared with those without type 2 diabetes

	Primary cohort		Incident cohort	
	Exposed	Unexposed	Exposed	Unexposed
Outcome events, *n* (%)	3,110 (0.88)	5,968 (0.46)	1,238 (0.82)	2,698 (0.48)
Person-years	1,763,982	5,963,919	646,356	2,245,189
Crude IR per 1,000 person-years	1.76	1.00	1.92	1.20
Follow-up years, median (IQR)	4.40 (2.06–7.60)	3.94 (1.80–7.07)	3.77 (1.84–6.39)	3.43 (1.62–5.94)
IRR (95% CI)				
Unadjusted	1.76 (1.69–1.84); $P < 0.001$		1.59 (1.47–1.72); $P < 0.001$	
Partially adjusted*	1.48 (1.42–1.55); $P < 0.001$		1.41 (1.32–1.51); $P < 0.001$	
Fully adjusted†	1.36 (1.30–1.42); $P < 0.001$		1.31 (1.22–1.40); $P < 0.001$	

*Adjusted for age category, sex, BMI category, Townsend deprivation quintile, smoking status, and ethnicity. †Adjusted for age category, sex, BMI category, Townsend deprivation quintile, smoking status, ethnicity, and baseline cardiovascular conditions (heart failure, ischemic heart disease, stroke/TIA, atrial fibrillation, and hypertension).

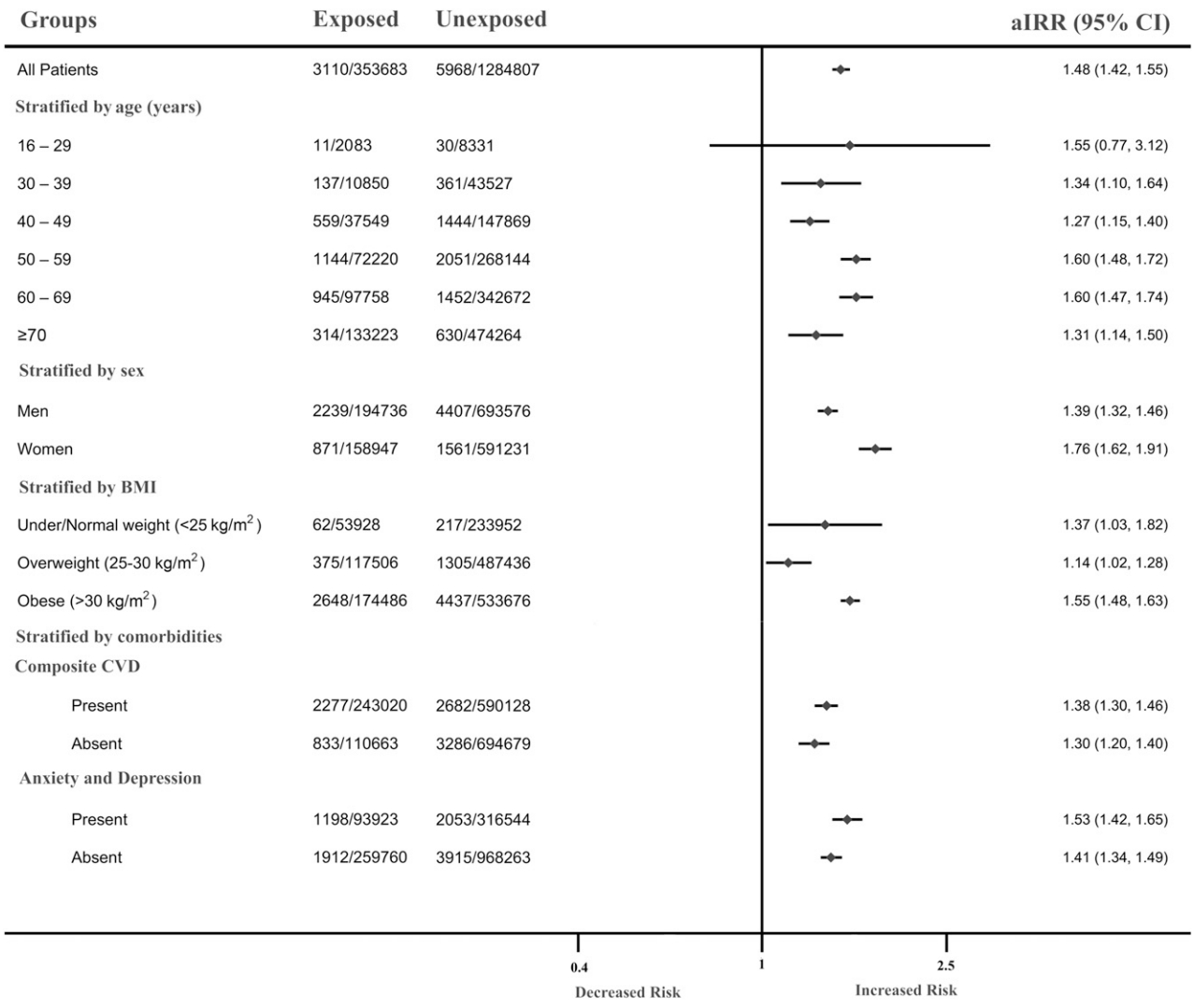

Figure 1—Forest plot showing aIRRs for OSA in patients with type 2 diabetes compared with patients without diabetes in patient subgroups stratified by age, sex, BMI, and comorbidity.

type 2 diabetes were also at increased risk of developing OSA, despite excluding patients in whom OSA was diagnosed up to 15 months after the type 2 diabetes diagnosis. Although many studies have examined the effect of OSA on type 2 diabetes, there is little evidence regarding the effect of type 2 diabetes on OSA. One longitudinal cohort study of 1,780 men and 1,785 women, the Data from an Epidemiologic Study on the Insulin Resistance Syndrome (D.E.S.I.R.) study, found that fasting insulin (odds ratio 1.31; 95% CI 1.13–1.51) and HOMA of insulin resistance (odds ratio 1.24; 95% CI 1.09–1.4) were predictors of incident "witnessed apnea" over a 6-year period independent of obesity (19). This result suggests that dysglycemia and insulin resistance might lead to the development of OSA, but there was no formal assessment of OSA in that study because the diagnosis was based on self-reported witnessed apneas during sleep.

A more recent analysis of the combined population of 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) by Huang et al. (29) showed that patients with type 2 diabetes were at increased risk of developing OSA compared with patients without diabetes (hazard ratio [HR] 1.53; 95% CI 1.32–1.77) which was attenuated after adjustment for obesity (HR 1.08; 95% CI 1.00–1.16). Consistent with our findings, Huang et al. also found that insulin-treated patients with type 2 diabetes were at increased risk of OSA compared with patients without diabetes after adjustment for obesity (HR 1.43; 95% CI 1.11–1.83), particularly among women (HR 1.60; 95% CI 1.34–1.89).

Our study differs from the Huang et al. (29) study in multiple aspects. The Huang et al. study included patients who were free of CVD at baseline, whereas CVD was common in our study population, suggesting that we have a population with more advanced disease. The diagnosis of OSA in the Huang et al. study was based on self-reporting, whereas the OSA diagnosis in our study was based on clinical codes indicating physician diagnosis. The design of the two studies also differed, because our study matched for major OSA risk factors between patients with and without type 2 diabetes. Finally, the relationship between type 2 diabetes and incident OSA became nonsignificant when adjusting for obesity in the Huang

Table 3—Predictors of OSA incidence in patients with type 2 diabetes (n = 353,683)

Risk factors	aIRR (95% CI)*	P value
Age categories, years		
16–29	Ref	
30–39	1.70 (0.92–3.14)	0.092
40–49	1.71 (0.94–3.11)	0.080
50–59	1.72 (0.95–3.13)	0.075
60–69	1.13 (0.62–2.05)	0.700
≥70	0.44 (0.24–0.81)	0.009
Sex		
Women	Ref	
Men	2.27 (2.09–2.46)	<0.001
BMI categories		
Underweight/normal weight (<25 kg/m^2)	Ref	
Overweight (25–30 kg/m^2)	2.02 (1.54–2.64)	<0.001
Obese (≥30 kg/m^2)	8.29 (6.42–10.69)	<0.001
Missing	3.68 (2.31–5.86)	<0.001
Townsend deprivation quintile		
1	Ref	
2	0.92 (0.82–1.04)	0.202
3	0.91 (0.81–1.03)	0.129
4	0.94 (0.84–1.06)	0.303
5	0.91 (0.80–1.03)	0.152
Missing	0.97 (0.86–1.11)	0.681
Smoker categories		
Nonsmoker	Ref	
Previous smoker	1.13 (1.04–1.22)	0.004
Smoker	1.11 (1.00–1.22)	0.051
Missing	0.89 (0.40–1.99)	0.775
Ethnicity		
Caucasian	Ref	
Black Afro-Caribbean	0.81 (0.57–1.16)	0.252
Chinese	0.67 (0.35–1.30)	0.238
South Asian	1.21 (0.98–1.49)	0.080
Mixed race	0.98 (0.49–1.97)	0.965
Missing	1.01 (0.93–1.08)	0.874
eGFR category		
>90 mL/min/1.73 m^2 (stage 1)	Ref	
60–90 mL/min/1.73 m^2 (stage 2)	0.95 (0.87–1.03)	0.223
30–59 mL/min/1.73 m^2 (stage 3)	1.00 (0.88–1.14)	0.987
<30 mL/min/1.73 m^2 (stage 4+5)	0.93 (0.64–1.36)	0.726
Missing	0.51 (0.26–0.99)	0.046
Concurrent conditions within 15 months of cohort entry		
CVDs		
Heart failure	1.41 (1.18–1.70)	<0.001
Ischemic heart disease	1.22 (1.11–1.34)	<0.001
Stroke/TIA	0.92 (0.78–1.07)	0.284
Atrial fibrillation	1.23 (1.04–1.46)	0.015
Hypertension	1.32 (1.23–1.43)	<0.001
Mental health conditions		
Anxiety	1.07 (0.97–1.18)	0.179
Depression	1.75 (1.61–1.91)	<0.001
Baseline drug use (within 60 days of index)		
Lipid-lowering drugs	1.05 (0.96–1.15)	0.296
Diabetes-related variables		
HbA_{1c} category		
≤6.5% (47.500 mmol/mol)	Ref	
6.5–7.5% (47.501–58.500 mmol/mol)	0.90 (0.82–1.00)	0.043
7.5–8.5% (58.501–69.400 mmol/mol)	1.00 (0.88–1.13)	0.977
≥8.5% (69.401 mmol/mol)	0.98 (0.87–1.10)	0.742
Missing	0.88 (0.78–0.98)	0.025

Continued on p. 961

et al. study, whereas our study showed that type 2 diabetes predicted incident OSA independent of obesity and despite adjustment for a wider range of potential confounders than those considered in the study by Huang et al. Despite these differences, our findings, together with those of the above-mentioned studies, strongly suggest that the relationship between type 2 diabetes and OSA is bidirectional.

The lack of a linear relationship between age and OSA incidence in patients with type 2 diabetes in this study is interesting and possibly explained by the fact that the average age of our study patients with type 2 diabetes was ~65 years old, and several previous studies have shown that the age-related increase in prevalence occurred before age 65 years (30), a finding that is reflected in our analysis.

In age-, sex-, and BMI-stratified subgroup analyses, increased incidence of OSA was observed in patients with type 2 diabetes in all of the subgroups except among patients aged 16–29 years. There was a greater effect size in women compared with men, which concurs with previous evidence suggesting an increased susceptibility of women with type 2 diabetes to adverse health outcomes (31). The observed effect sizes were slightly higher in patients with comorbid conditions, but this was not statistically significant. In a sensitivity analysis including baseline cardiovascular conditions as a covariate, there was a slight reduction in the effect size, indicating that CVD may be a potential effect modifier in the association between type 2 diabetes and incident OSA.

To explore any effect of surveillance bias, we performed an exploratory analysis considering COPD as the outcome instead of OSA. COPD was used because increased screening rates and surveillance, and therefore detection, might occur in patients with type 2 diabetes because the two conditions have common symptoms, including sleep disturbance and fatigue. However, there was no statistically significant increase in incident COPD in patients with type 2 diabetes, suggesting that the observed increase in incident OSA reflects a true difference.

Although the effect of OSA on incident type 2 diabetes is probably related to increased oxidative stress, inflammation, sympathetic activation, and hypothalamic-pituitary-adrenal activation (32), type 2

Table 3—Continued

Risk factors	aIRR (95% CI)*	*P* value
Concurrent diabetes-related conditions		
Foot disease	1.23 (1.06–1.42)	0.005
Retinopathy/low vision/blindness	0.95 (0.79–1.13)	0.556
Hypoglycemic event	1.06 (0.83–1.35)	0.656
Baseline drug use (within 60 days of index)		
Insulin	1.58 (1.42–1.75)	<0.001

*Adjusted for age, sex, BMI category, Townsend deprivation quintile, smoking status, ethnicity, HbA_{1c} category, eGFR category, record of hypoglycemic attack, diagnosis of foot disease, retinopathy, CVD (heart failure, ischemic heart disease, stroke/TIA, atrial fibrillation, and hypertension), mental health conditions (anxiety and depression), and prescription of lipid-lowering drugs and insulin within 60 days of the index date.

diabetes might lead to the development of OSA via multiple mechanisms, including weight gain mediated by medications, such as sulfonylureas, glitazones, and insulin, or by hypoglycemia-decreased physical activity, by comorbidities such as diabetic neuropathy, or by changes related to lung volumes (10). Our study supports some of these plausible mechanisms by showing obesity, diabetes-related foot disease (which encompasses neuropathy), and insulin treatment were predictors of incident OSA in patients with type 2 diabetes. However, the relationship between type 2 diabetes and OSA persisted after adjustment for a wide range of potential confounders. Interestingly, depression and CVD were predictors of incident OSA in our study, which aligns with previous studies showing high prevalence of OSA in these conditions (33,34). However, some traditional OSA risk factors, such as age, ethnicity, and smoking, were not identified as predictors of OSA in our study. This could potentially be due to the multiple risk factors considered in the model, where weak effects were obscured, or because our study population included only patients with type 2 diabetes rather than the general population.

Because of the high prevalence of OSA in patients with type 2 diabetes, the International Diabetes Federation (IDF) issued a statement suggesting that all patients with type 2 diabetes should be screened for OSA (35). However, owing to the large number of patients with type 2 diabetes and the lack of easily available screening methods beyond questionnaires, this IDF statement has not been widely followed (36). Our study supports the IDF statement by identifying high-risk groups within patients with type 2 diabetes who are at particularly high risk of developing OSA, including men and patients with CVD, depression, diabetes-related foot disease, patients experiencing hypoglycemia, and those treated with insulin. However, we note that despite the IDF statement, the proportion of patients with type 2 diabetes who are willing to be tested for OSA might be low (37) and that the effect of continuous positive airway pressure treatment on diabetes-related outcomes from randomized controlled trials remains uncertain or lacking (except with regard to BP) (38–40). Nonetheless, in general population studies, continuous positive airway pressure has been shown to improve quality of life and sleepiness in patients with and without diabetes (38,41).

OSA in patients with type 2 diabetes has been linked to worse glycemic control, higher BP, CVD, and microvascular complications (11,16,17,42,43). In all of these studies, whether the diagnosis of OSA preceded or followed the diagnosis of type 2 diabetes was not clear. In view of our data showing that patients with type 2 diabetes are at increased risk of developing OSA, it would be of interest to examine whether the effect of OSA in these patients differs depending on whether OSA developed before or after the diagnosis of type 2 diabetes.

Strengths and Limitations

This study included a large sample size from the THIN database, which is generalizable to the U.K. population. Routinely collected data may be subject to potential biases resulting from incorrect, inconsistent, or incomplete coding of conditions. However, the conditions considered in this study are mostly part of the QOF, and recording quality is therefore expected to be high. The prevalence of major conditions and death rates in THIN, adjusted for patient demographics, are similar to national rates (44).

Ethnicity is not well recorded in THIN; as a result, ethnicity data were not available for all patients in the sample. In addition, adiposity measures such as neck and waist circumference are poorly recorded in primary care and, hence, were not included as covariates in our analysis. It is possible that the observed association between diabetes and OSA was driven by these measures of central obesity, which are common to both diabetes and OSA. Nonetheless, our findings were independent of BMI, which is commonly used in large epidemiological studies and usually correlates with these measures of adiposity.

The prevalence of OSA observed in patients at baseline was lower than the prevalence reported in other studies (12,13,45) because the routinely collected primary care–based OSA diagnosis is subject to underdiagnosis, underrecording, and differences in temporal and interclinic diagnostic criteria. We introduced a 15-month latency period at the start of the study to limit the possibility of silent OSA preceding the diabetes diagnosis being classified as incident OSA. However, we cannot completely rule out the possibility that patients with undiagnosed OSA were included in the study because it was not possible to investigate patients for OSA at baseline. It is also possible that the effect of increased surveillance might have had an effect on the OSA detection rate in patients with diabetes, particularly because symptoms of OSA and diabetes, such as fatigue and sleep disturbance, might overlap. The exploratory analysis for COPD reported above suggests the effect of surveillance bias resulting from increased contact with health care practitioners is likely to be small; however, surveillance bias resulting from differential screening and detection rates in the exposed/unexposed groups cannot be completely ruled out.

Although we cannot determine the methods used to diagnose OSA in our study, patients in the U.K. are usually diagnosed with OSA after an assessment in a sleep clinic/center as described in the National Institute of Clinical Excellence and the British Lung Foundation guidance (46). Nonetheless, the methods (for example, oximetry vs. polygraphy vs. polysomnography) and criteria (oxygen desaturation index vs. apnea-hypopnea index and different cutoffs of

the apnea-hypopnea index or oxygen desaturation index) used to diagnose OSA could vary between different sleep centers.

Conclusion

Patients with type 2 diabetes are at increased risk of developing OSA, and the association remained significant after adjusting for potential confounders. In addition to known predictors of OSA, diabetes-related foot disease and insulin treatment were identified as risk factors for OSA in patients with type 2 diabetes. Clinicians should consider testing for OSA in patients with type 2 diabetes, particularly in men, and patients with high BMI, diabetes-related foot disease, CVD, hypertension, depression, and those prescribed insulin because these were shown to be independent risk factors for incident OSA. When taken together with previous evidence, this study indicates that the association between type 2 diabetes and OSA is bidirectional. Further research is required to investigate whether the sequence in which the two diseases develop has an effect on outcomes in patients with type 2 diabetes and OSA.

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References

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014;383:736–747
2. Basoglu OK, Tasbakan MS. Elevated risk of sleepiness-related motor vehicle accidents in patients with obstructive sleep apnea syndrome: a case-control study. Traffic Inj Prev 2014;15:470–476
3. Jurado-Gámez B, Guglielmi O, Gude F, Buela-Casal G. Workplace accidents, absenteeism and productivity in patients with sleep apnea. Arch Bronconeumol 2015;51:213–218 [in English, Spanish]
4. Grunstein RR, Stenlöf K, Hedner JA, Sjöström L. Impact of obstructive sleep apnea and sleepiness on metabolic and cardiovascular risk factors in the Swedish Obese Subjects (SOS) study. Int J Obes Relat Metab Disord 1995;19:410–418
5. Tkacova R, Dorkova Z, Molcanyiova A, Radikova Z, Klimes I, Tkac I. Cardiovascular risk and insulin resistance in patients with obstructive sleep apnea. Med Sci Monit 2008;14:CR438–CR444
6. Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol 2006;5:22
7. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 2002;165:670–676
8. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. Sleep Breath 2017;21:181–189
9. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Respirology 2013;18:140–146
10. Lecube A, Simó R, Pallayova M, et al. Pulmonary function and sleep breathing: two new targets for type 2 diabetes care. Endocr Rev 2017;38:550–573
11. Tahrani A. Obstructive sleep apnoea and vascular disease in patients with type 2 diabetes. Eur Endocrinol 2015;11:81–89
12. Tahrani AA. Obstructive sleep apnoea in diabetes: does it matter? Diab Vasc Dis Res 2017;14:454–462
13. Tahrani AA, Ali A, Stevens MJ. Obstructive sleep apnoea and diabetes: an update. Curr Opin Pulm Med 2013;19:631–638
14. Leong WB, Jadhakhan F, Taheri S, Thomas GN, Adab P. The association between obstructive sleep apnea on diabetic kidney disease: a systematic review and meta-analysis. Sleep (Basel) 2016;39:301–308
15. Leong WB, Jadhakhan F, Taheri S, Chen YF, Adab P, Thomas GN. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. Diabet Med 2016;33:158–168
16. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. Am J Respir Crit Care Med 2012;186:434–441
17. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. Diabetes Care 2013;36:3718–3725
18. Araghi MH, Chen YF, Jagielski A, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. Sleep (Basel) 2013;36:1553–1562, 1562A–1562E
19. Balkau B, Vol S, Loko S, et al.; Epidemiologic Study on the Insulin Resistance Syndrome Study Group. High baseline insulin levels associated with 6-year incident observed sleep apnea. Diabetes Care 2010;33:1044–1049
20. Horner RL. Neural control of the upper airway: integrative physiological mechanisms and relevance for sleep disordered breathing. Compr Physiol 2012;2:479–535
21. Bottini P, Dottorini ML, Cristina Cordoni M, Casucci G, Tantucci C. Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy. Eur Respir J 2003;22:654–660
22. Sanderson AA. Pay-for-performance programs in the United Kingdom. N Engl J Med 2006;355:1832; author reply 1833
23. Daly B, Toulis KA, Thomas N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: a population-based cohort study. PLoS Med 2018;15:e1002488
24. Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ 2018;361:k1717
25. Guest JF, Panca M, Sladkevicius E, Taheri S, Stradling J. Clinical outcomes and cost-effectiveness of continuous positive airway pressure to manage obstructive sleep apnea in patients with type 2 diabetes in the U.K. Diabetes Care 2014;37:1263–1271
26. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010;340:b5087
27. Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. J Public Health (Oxf) 2005;27:101–106
28. General Practitioners Committee (British Medical Association), NHS Employers, NHS England. 2016/17 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF): Guidance for GMS contract 2016/17 [Internet], 2016. Available from https://www.nhsemployers.org/-/media/Employers/Documents/Primary-care-contracts/QOF/2016-17/2016-17-QOF-guidance-documents.pdf. Accessed 10 July 2018
29. Huang T, Lin BM, Stampfer MJ, Tworoger SS, Hu FB, Redline S. A population-based study of the bidirectional association between obstructive sleep apnea and type 2 diabetes in three prospective U.S. cohorts. Diabetes Care 2018;41:2111–2119
30. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–1239
31. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocr Rev 2016;37:278–316
32. Rajan P, Greenberg H. Obstructive sleep apnea as a risk factor for type 2 diabetes mellitus. Nat Sci Sleep 2015;7:113–125
33. Jehan S, Auguste E, Pandi-Perumal SR, et al. Depression, obstructive sleep apnea and psychosocial health. Sleep Med Disord 2017;1

34. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 2008;52:686–717
35. International Diabetes Federation. *The IDF Consensus Statement on Sleep Apnoea and Type 2 Diabetes*. Brussels, International Diabetes Federation. 2008
36. Seetho IW, O'Brien SV, Hardy KJ, Wilding JP. Obstructive sleep apnoea in diabetes - assessment and awareness. Br J Diabetes Vasc Dis 2014; 14:105–108
37. Donovan LM, Rueschman M, Weng J, et al. The effectiveness of an obstructive sleep apnea screening and treatment program in patients with type 2 diabetes. Diabetes Res Clin Pract 2017;134:145–152
38. 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
39. 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
40. Myhill PC, Davis WA, Peters KE, Chubb SAP, Hillman D, Davis TME. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. J Clin Endocrinol Metab 2012;97:4212–4218
41. Schwartz M, Acosta L, Hung Y-L, Padilla M, Enciso R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. Sleep Breath 2018;22: 555–568
42. Altaf QA, Dodson P, Ali A, et al. Obstructive sleep apnea and retinopathy in patients with type 2 diabetes. A longitudinal study. Am J Respir Crit Care Med 2017;196:892–900
43. Altaf QA, Ali A, Piya MK, Raymond NT, Tahrani AA. The relationship between obstructive sleep apnea and intra-epidermal nerve fiber density, PARP activation and foot ulceration in patients with type 2 diabetes. J Diabetes Complications 2016;30:1315–1320
44. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. Inform Prim Care 2011;19:251–255
45. 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
46. British Lung Foundation. Obstructive sleep apnoea (OSA). Toolkit for commissioning and planning local NHS services in the UK, 2015. Available from https://www.blf.org.uk/sites/default/files/OSA_Toolkit_2015_BLF_0.pdf. Accessed 20 November 2018