Risk of incident obstructive sleep apnea among patients with type 2 diabetes

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Full Title: Risk of incident obstructive sleep apnoea among patients with type 2 diabetes

Short Running Title: Type 2 Diabetes and Risk of OSA

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Abstract

Aims

To compare incidence of OSA in patients with and without type 2 diabetes and to investigate risk factors for OSA in patients with type 2 diabetes.

Methods

A retrospective cohort study was carried out to compare OSA incidence between adult patients with and without type 2 diabetes matched for age, sex and body mass index (BMI). Patients with a prevalent OSA diagnosis were excluded. The study cohort was derived from The Health Improvement Network (THIN), a UK primary care database, from 01/01/2005 to 31/12/2017

Results

3110 (0.88%) and 5968 (0.46%) incident OSA cases were 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 to 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, 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); <0.001), male sex (aIRR 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), ischaemic 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) were significant predictors of OSA.

Conclusions

When considered alongside previous evidence, this study indicates that the association between type 2 diabetes and OSA is bi-directional. 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.

Introduction

Obstructive sleep apnoea (OSA) is a common disorder characterised 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[4,5], hypertension[5,6], insulin resistance[7], increased mortality[8], and type 2 diabetes mellitus[9].

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 impact of recurrent hypoxaemia, inflammation, sympathetic activation and activation of the hypothalamic adrenal axis on insulin resistance and beta 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 glycaemic control in patients with type 2 diabetes[11-13] and with diabetes-related vascular complications[14-17]. Hence, it is important to understand the complex relationships between OSA and type 2 diabetes, as 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 bi-directional. Type 2 diabetes might lead to the development of OSA due to the impact 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 impact

of type 2 diabetes on incident OSA. In addition, it is important to identify predictors of OSA in patients with type 2 diabetes 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 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.

Methods

Study design

An age-, sex- and body mass index (BMI)-matched controlled retrospective cohort study from 01/01/2005 to 31/12/2017.

Data source

Data was extracted from The Health Improvement Network (THIN), an electronic primary care records database that contains anonymised medical records of over 15 million patients from 787 practices in the UK. The database is generalizable to the UK population. It consists of coded information on patient demographics, symptoms and diagnoses, drug prescriptions, consultations, diagnostic tests and their results. THIN is particularly suitable for analysing long-term health outcomes as GPs routinely collect and coordinate the patient's data[22]. THIN has been extensively used previously to study metabolic outcomes[23,24] and to study type 2 diabetes and OSA[25].

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 (01/01/2005). Adult patients aged 16 years and above registered for at least 12 months with any of the eligible general practices prior to 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 1A) 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[26]. In the primary analysis, all patients (prevalent and incident) with a type 2 diabetes diagnosis were included. A sensitivity analysis including only patients with incident type 2 diabetes (newly diagnosed during the study period) was carried out to explore any effect of survival bias.

Unexposed cohort

For every exposed patient, up to 4 controls were randomly selected from an age-, sex- and BMI-matched pool of eligible patients without a record of type 2 diabetes at any time point before or during the study period. Age and BMI were matched to within 1 year and 2 kg/m2 respectively.

Follow-up period

A 15-month latency period was used for all patients. For patients with incident type 2 diabetes, index date was 15 months after the date of diagnosis; for patients with prevalent type 2 diabetes, index date was 15 months after the date the patient became eligible for inclusion. The 15-month interval was introduced to: 1) ensure that at baseline all predictors determining the risk of OSA in patients with diabetes were recorded, as the Quality and Outcomes Framework (QOF) ensures these are captured within a 15-month period; 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[27]. Patients with type 2 diabetes and controls were followed from the index date until the earliest of the following end points: outcome (OSA)

date, death date, date patient left practice, date the practice ceased contributing to the database, and study end date (31/12/2017).

Outcomes

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

Analysis

Poisson regression was used to calculate crude incidence rate ratios (IRR) and adjusted incidence rate ratios (aIRR), together with their corresponding 95%CIs, 1) comparing 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 incidence of OSA. Patients with a record of the outcome at baseline were excluded for these analyses.

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 cardiovascular diseases (CVD) composed of heart failure, ischaemic heart disease, stroke/TIA, atrial fibrillation and hypertension, and composite mental health conditions (anxiety and depression).

To evaluate any possible impact of surveillance bias and unobserved confounders on the outcome (OSA), in the same cohort we estimated the adjusted IRR 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 carried out restricting outcomes to those specifically recorded as obstructive-type sleep apnoea (Read code Fy03.11 or H5B0.00) to ensure the exclusion of central sleep apnoea 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, 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 below 14 and above 75 were considered missing. Social deprivation was categorized as quintiles based on Townsend score[28]. Smoking status was categorised as non-smoker, ex-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 within the 15-month period prior to index date were taken into consideration; these included: ethnicity, HbA1c category, eGFR category, record of hypoglycaemic attack, diagnosis of foot disease, retinopathy, cardiovascular disease (heart failure, ischaemic heart disease, stroke/TIA, atrial fibrillation and hypertension), mental health conditions, and prescription of lipid-lowering drugs and insulin within 60 days prior to the index date. Implausible HbA1c values above 20 mmol/mol and eGFR above 200 mL/min/1.73m^2 were considered missing. Lipid-lowering drugs were used as a proxy measure for hypercholesterolaemia, and insulin as an indicator of diabetes severity.

eGFR was calculated using the CKD-EPI equation from the serum creatinine values and ethnicity data (where available). HbA1c was categorized as ≤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/1.73m^2 (stage 1 chronic kidney disease), 60-89 mL/min/1.73m^2 (stage 2), 30-59 mL/min/1.73m^2 (stage 3) and <30 mL/min/1.73m^2 (stage 4 and 5). Retinopathy was considered as a composite of sight-threatening retinopathy graded as R2 (pre-proliferative), R3 (proliferative) or M1

(maculopathy), vision loss and utilization 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. All covariates are included in disease registers which general practices are expected to maintain as per the QOF[29].

Analyses were performed in Stata IC version 14. Two-sided p-values were obtained and p-value <0.05 was considered as statistically significant.

The results of this study are reported in line with RECORD guidelines (Supplementary Table 2).

Results

Baseline characteristics

360,250 eligible patients with type 2 diabetes were identified; 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 compared to controls (31.0 (6.5) vs 29.8 (5.8)), but the difference was within the matching range (±2 kg/m^2). Compared to controls, patients with diabetes were more deprived (13.7% vs 9.9% were in the most deprived Townsend quintile), and were more likely to be of south Asian ethnicity (3.8% vs 0.9%). Patients with diabetes also had higher levels of cardiovascular diseases, including heart failure (4.8% vs 2.5%), ischaemic heart disease (19.1% vs 11.4%) and stroke/TIA (8.8% vs 5.9%) and greater usage of lipid-lowering drugs (63.7% vs 23.6%). Prevalent OSA at baseline (recorded up to 15 months after index date)

was higher among exposed compared to unexposed patients (1.8% vs 0.9%); these patients were excluded in subsequent analyses.

Type 2 diabetes and incidence of OSA

3110 (0.88%) patients with diabetes and 5968 (0.46%) controls developed OSA during the follow-up period (Table 2). Crude incidence rate of OSA among patients with and without diabetes was 1.76 and 1.00 per 1000 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 controls (Supplementary table 3A): aIRR 1.41 (95%CI 1.30-1.51; 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 to patients without (Figure 1). Risk of OSA was increased in both sexes but the association between diabetes and OSA was stronger in women (aIRR: 1.39 (95%CI 1.32-1.46) and 1.76 (95%CI 1.62-1.91); in men and women respectively). 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 apnoea, there was an increase in the observed effect size: (aIRR 1.62 (95%CI 1.52-1.73); p<0.001) (Supplementary Table 3B).

Impact of surveillance bias

In the analysis considering COPD as an outcome, there was no significant increase in the incidence of COPD in patients with type 2 diabetes compared to 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), ischaemic 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 incident/newly diagnosed patients with type 2 diabetes, the results remained similar except for four of the risk factors considered: hypoglycaemic event became statistically significant as a predictor of OSA (aIRR 2.06 (95%CI 1.26-3.39); p=0.004), while being a previous smoker, atrial fibrillation and prescription of insulin became non-significant as predictors in the model (Supplementary Table 3C).

Discussion

This study showed that patients with type 2 diabetes have an almost 50% increase in risk of developing OSA compared to 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, CVD, diabetes-related foot disease, 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 bi-directional, as patients with type 2 diabetes were also at increased risk of developing OSA, despite excluding patients in whom OSA was diagnosed up to 15 months after type 2 diabetes diagnosis. While many studies have examined the impact of OSA on type 2 diabetes, there is little evidence regarding the impact of type 2 diabetes on OSA. One longitudinal cohort study of 1780 men and 1785 women, the Data from an Epidemiologic Study on the Insulin Resistance Syndrome (D.E.S.I.R.) study, found that fasting insulin (OR 1.31, 95%CI 1.13-1.51) and homeostasis model assessment of insulin resistance (HOMA-IR) (OR 1.24, 95%CI 1.09-1.4) were predictors of incident "witnessed apnoea" over a 6-year period independent of obesity [(19)]. This result suggests that dysglycaemia and insulin resistance might lead to the development of OSA, but there was no formal assessment of OSA in this study as the diagnosis was based on self-reported witnessed apnoeas 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 showed that patients with type 2 diabetes were at increased risk of developing OSA compared to patients without diabetes (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)[(30)]. Consistent with our findings, Huang et al also found that insulin-treated patients with type 2 diabetes were at increased risk of OSA compared to 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 study in multiple aspects. The study of Huang et al included patients who were free of CVD at baseline while CVD was common in our study population, suggesting that we have a population with more advanced disease. The diagnosis of OSA in the study by Huang et al was based on self-reporting while in our study the OSA diagnosis was based on clinical codes indicating physician diagnosis. The design of the two studies also differed as 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 non-significant when adjusting for obesity in the Huang et al study, while 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 bi-directional.

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 approximately 65 years old, and several previous studies have shown that the age-related increase in prevalence occurred before age 65,[31] 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. There was a greater effect size in women compared to men, which concurs with previous evidence suggesting an increased susceptibility of women with type 2 diabetes to adverse health outcomes[32]. 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 impact of surveillance bias, we performed an exploratory analysis considering COPD as the outcome instead of OSA. COPD was used as increased screening rates and surveillance, and therefore detection, might occur in patients with type 2 diabetes as 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. While the impact of OSA on incident type 2 diabetes is probably related to increased oxidative stress, inflammation, sympathetic activation and HPA activation[33], type 2 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 hypoglycaemia decreased physical activity; co-morbidities like diabetic neuropathy; or 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, in our study depression and CVD were predictors of incident OSA, which aligns with previous studies showing high prevalence of OSA in these conditions[34,35]. On the other hand, 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 the fact that our study population included only patients with type 2 diabetes rather than the general population.

Due to 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[36]. However, due 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[37]. 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 hypoglycaemia, and those treated with insulin. However, it must be noted that despite the IDF statement, the proportion of patients with type 2 diabetes who are willing to be tested for OSA might be low[38] and the impact of CPAP treatment on diabetes-related outcomes from RCTs remains uncertain or lacking (except with regard to blood pressure)[39-41]. Nonetheless, in general population studies, CPAP has been shown to improve quality of life and sleepiness in patients with and without diabetes[42,43].

OSA in patients with type 2 diabetes has been linked to worse glycaemic control, higher BP, CVD and microvascular complications[11,16,17,44,45]. In all these studies, it was not clear whether the diagnosis of OSA preceded or followed the diagnosis of type 2 diabetes. 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 impact 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 UK 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 part of the Quality and Outcomes Framework and recording quality is therefore expected to be high. The prevalence of major conditions and death rates, adjusted for patient demographics, in THIN are similar to national rates[46].

Ethnicity is not well recorded in THIN; as a result, ethnicity data was 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 what has been reported in other studies[12,13,47] as routinely collected primary care-based OSA diagnosis is subject to under-diagnosis, under-recording and differences in temporal and inter-clinic diagnostic criteria. We introduced a 15-month latency period at the start of the study in order 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, as 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 impact on the OSA detection rate in patients with diabetes, particularly since symptoms of OSA and diabetes might overlap (such as fatigue and sleep disturbance). The exploratory analysis for COPD reported above suggests the impact of surveillance bias due to increased contact with health care practitioners is likely to be small, however, surveillance bias due to 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 UK are usually diagnosed with OSA following an assessment in a sleep clinic/centre as described in the National Institute of Clinical Excellence and the British Lung Foundation guidance[48]. Nonetheless, the methods (for example, oximetry vs polygraphy vs

polysomnography) and criteria (ODI vs AHI and different cut offs of AHI or ODI) used to diagnose OSA could vary between different sleep centres.

Conclusions

Patients with type 2 diabetes are at increased risk of developing OSA; 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 and depression, and those prescribed insulin, as 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 bi-directional. Further research is required to investigate whether the sequence in which the two diseases develop has an impact on outcomes in patients with type 2 diabetes and OSA.

Figure legend

Figure 1. Forest plot showing adjusted incidence rate ratios (aIRR) for OSA in patients with type 2 diabetes compared to patients without diabetes in age-, sex-, BMI- and comborbidity-stratified patient subgroups.

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

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

	Exposed	Unexposed
Population, n	360250	1296489
Age years, mean (SD)	64.85 (13.28)	64.56 (13.63)
Age categories, years, n (%)		
16 – 29	2117 (0.59)	8373 (0.65)
30 – 39	11095 (3.08)	43951 (3.39)
40 – 49	38704 (10.74)	149940 (11.57)
50 – 59	74341 (20.64)	271837 (20.97)
60 – 69	99805 (27.70)	346252 (26.71)
70 – max	134188 (37.25)	476136 (36.73)
Sex, n (%)		
Men	199941 (55.50)	702927 (54.22)
Women	160309 (44.50)	593562 (45.78)
BMI (kg/m^2), mean (SD)	31.00 (6.47)	29.83 (5.80)
BMI categories, n (%)		
Under/Normal weight (<25 kg/m^2)	54047 (15.00)	234404 (18.08)
Overweight (25-30 kg/m^2)	118393 (32.86)	489719 (37.77)
Obese (≥30 kg/m^2)	179959 (49.95)	542588 (41.85)
Missing	7851 (2.18)	29778 (2.30)
Townsend, n (%)		
1	64764 (17.98)	299727 (23.12)
2	64862 (18.00)	270123 (20.83)
3	68180 (18.93)	241708 (18.64)
4	65566 (18.20)	197086 (15.20)
5	49372 (13.70)	128651 (9.92)
Missing	47506 (13.19)	159194 (12.28)
Smoker categories, n (%)		
Non-smoker	174233 (48.36)	690164 (53.23)
Previous smoker	129534 (35.96)	405090 (31.25)
Smoker	55482 (15.40)	188833 (14.56)
Missing	1001 (0.28)	12402 (0.96)
Ethnicity, n (%)		
Caucasian	151519 (42.06)	533954 (41.18)
Black Afro-Caribbean	5858 (1.63)	10272 (0.79)
Chinese	2432 (0.68)	3990 (0.31)
South Asian	13663 (3.79)	11351 (0.88)
Mixed Race	1199 (0.33)	2432 (0.19)
Missing	185579 (51.51)	734490 (56.65)
eGFR, median (IQR)	76.5 (60.6-91.3)	74.3 (61.2-87.2)
eGFR category		
>90 mL/min/1.73m^2 (Stage 1)	97438 (27.05)	208516 (16.08)
60-90 mL/min/1.73m^2 (Stage 2)	178998 (49.69)	599575 (46.25)
30-59 mL/min/1.73m^2 (Stage 3)	74006 (20.54)	207151 (15.98)
<30 mL/min/1.73m^2 (Stage 4+5)	7384 (2.05)	13083 (1.01)
Missing	2424 (0.67)	268164 (20.68)
Baseline comorbidities, n (%)		
Cardiovascular diseases		
Heart failure	17304 (4.80)	32924 (2.54)
Ischaemic heart disease	68908 (19.13)	147418 (11.37)
Stroke/TIA	31687 (8.80)	76128 (5.87)
Atrial fibrillation	25174 (6.99)	65688 (5.07)
Hypertension	213479 (59.26)	489418 (37.75)

Mental health conditions		
Anxiety	57756 (16.03)	200706 (15.48)
Depression	75642 (21.00)	241215 (18.61)
Baseline drug use (within 60 days of index), n (%)		
Lipid-lowering drugs	229287 (63.65)	305443 (23.56)
Outcome at baseline		
OSA*	6567 (1.82)	11682 (0.90)
Diabetes-related variables†		
HbA1c (mmol/mol), median (IQR)	51.9 (45.0-60.6)	
HbA1c category †		
≤6.5% (47.500 mmol/mol)	98835 (27.44)	
6.5-7.5% (47.501-58.500 mmol/mol)	114821 (31.87)	
7.5-8.5% (58.501-69.400 mmol/mol)	41049 (11.39)	
≥ 8.5% (69.401 mmol/mol)	43093 (11.96)	
Missing	62452 (17.34)	
Concurrent conditions within 15 months of diabetes diagnosis		
Foot Disease	22305 (6.20)	
Retinopathy/Low vision/Blindness	16911 (4.69)	
Hypoglycaemic event	7555 (2.10)	
Baseline drug use(within 60 days of index), n (%)		
Insulin	26877 (7.46)	

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

Table 2. Crude and adjusted incidence rate ratios for OSA in patients with type 2 diabetes compared to those without type 2 diabetes

	Primary Cohort		**Incident Cohort**	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Outcome events, n (%)	3110 (0.88)	5968 (0.46)	1238 (0.82)	2698 (0.48)
Person-years	1763982	5963919	646356	2245189
Crude IR per 1000 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)
Unadjusted IRR (95% CI)	1.76 (1.69-1.84); p<0.001		1.59 (1.47-1.72); p<0.001	
Partially adjusted IRR* (95% CI)	1.48 (1.42-1.55); p<0.001		1.41 (1.32-1.51); p<0.001	
Fully adjusted IRR* (95% CI)	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).

Table 3. Predictors of OSA incidence in patients with type 2 diabetes (n=353683)

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	
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	
Non-smoker	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/1.73m^2 (Stage 1)	Ref
60-90 mL/min/1.73m^2 (Stage 2)	0.95 (0.87-1.03); 0.223
30-59 mL/min/1.73m^2 (Stage 3)	1.00 (0.88-1.14); 0.987
<30 mL/min/1.73m^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 diabetes diagnosis	
Cardiovascular diseases	
Heart failure	1.41 (1.18-1.70); <0.001
Ischaemic 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), n (%)	

Lipid-lowering drugs	1.05 (0.96-1.15); 0.296
Diabetes-related variables	
HbA1c 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
Concurrent conditions within 15 months of diabetes diagnosis	
Foot Disease	1.23 (1.06-1.42); 0.005
Retinopathy/Low vision/Blindness	0.95 (0.79-1.13); 0.556
Hypoglycaemic event	1.06 (0.83-1.35); 0.656
Baseline drug use (within 60 days of index), n (%)	
Insulin	1.58 (1.42-1.75); <0.001

*Adjusted for age, sex, BMI category, Townsend deprivation quintile, smoking status, ethnicity, HbA1c category, eGFR category, record of hypoglycaemic attack, diagnosis of foot disease, retinopathy, cardiovascular disease (heart failure, ischaemic 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.