

# UNIVERSITY OF BIRMINGHAM

## Research at Birmingham

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

Subramanian, Anuradhaa; Adderley, Nicola J; Tracy, Alexander; Taverner, Tom; Hanif, Wasim; Toulis, Konstantinos A; Thomas, G Neil; Tahrani, Abd A; Nirantharakumar, Krishnarajah

DOI:  
[10.2337/dc18-2004](https://doi.org/10.2337/dc18-2004)

License:  
None: All rights reserved

*Document Version*  
Peer reviewed version

*Citation for published version (Harvard):*  
Subramanian, A, Adderley, NJ, Tracy, A, Taverner, T, Hanif, W, Toulis, KA, Thomas, GN, Tahrani, AA & Nirantharakumar, K 2019, 'Risk of incident obstructive sleep apnea among patients with type 2 diabetes' *Diabetes Care*, vol. 42, no. 5, pp. 954-963. <https://doi.org/10.2337/dc18-2004>

[Link to publication on Research at Birmingham portal](#)

**Publisher Rights Statement:**  
Checked for eligibility 06/02/2019

This is an author-produced, peer-reviewed version of an article forthcoming in *Diabetes Care*  
<http://care.diabetesjournals.org/>

<https://doi.org/10.2337/dc18-2004>

#### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

#### **Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

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

Short Running Title: Type 2 Diabetes and Risk of OSA

Anuradhaa Subramanian MSc\*<sup>1</sup>, Nicola J Adderley PhD\*<sup>1</sup>, Alexander Tracy BM BCh<sup>2</sup>, Tom Taverner PhD<sup>1</sup>, Wasim Hanif PhD<sup>3</sup>, Konstantinos A. Toulis PhD<sup>1</sup>, Neil Thomas PhD†<sup>1</sup>, Abd A Tahrani PhD†<sup>4,5</sup>, Krishnarajah Nirantharakumar MD†<sup>1,4,5</sup>

### Author Information

1. Institute of Applied Health Research, University of Birmingham, Birmingham, UK.
2. Institute of Clinical Sciences, Centre for Translational Inflammation Research, University of Birmingham, UK.
3. University Hospital Birmingham, Birmingham, UK
4. Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK.
5. Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK

\* Contributed equally

†Joint Senior Authors

### Corresponding author

Prof Neil Thomas

Institute of Applied Health Research, Birmingham B15 2TT

Email: [gneilthomas@yahoo.co.uk](mailto:gneilthomas@yahoo.co.uk) / [G.N.Thomas@bham.ac.uk](mailto:G.N.Thomas@bham.ac.uk); Tel: +44 121 414 8696

**Word count:** 4000; **Tables:** 3; **Figures:** 1

## 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);  $p < 0.001$ ), 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<sup>(1)</sup>. As a result, OSA has been linked to multiple adverse outcomes including: road traffic accidents<sup>(2)</sup>, reduced workplace productivity<sup>(3)</sup>, cardiovascular disease<sup>(4,5)</sup>, hypertension<sup>(5,6)</sup>, insulin resistance<sup>(7)</sup>, increased mortality<sup>(8)</sup>, and type 2 diabetes mellitus<sup>(9)</sup>.

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<sup>(9)</sup>, possibly via the impact of recurrent hypoxaemia, inflammation, sympathetic activation and activation of the hypothalamic adrenal axis on insulin resistance and beta cell function<sup>(10)</sup>. In addition, multiple cross-sectional studies have shown a high prevalence of undiagnosed OSA in patients with type 2 diabetes (24-86%)<sup>(11,12)</sup>. Furthermore, cross-sectional and cohort studies have shown that OSA is associated with worse glycaemic control in patients with type 2 diabetes<sup>(11-13)</sup> and with diabetes-related vascular complications<sup>(14-17)</sup>. 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<sup>(18)</sup>.

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<sup>(19-21)</sup>, 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<sup>(22)</sup>.

THIN has been extensively used previously to study metabolic outcomes<sup>(23,24)</sup> and to study type 2 diabetes and OSA<sup>(25)</sup>.

### 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<sup>(26)</sup>. 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/m<sup>2</sup> 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<sup>(27)</sup>. 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  $<25 \text{ kg/m}^2$ ,  $25\text{-}30 \text{ kg/m}^2$  (overweight) and  $\geq 30 \text{ kg/m}^2$  (obese). Implausible BMI values below 14 and above 75 were considered missing. Social deprivation was categorized as quintiles based on Townsend score<sup>(28)</sup>. 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<sup>2</sup> 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  $\leq 6.5\%$  (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  $\geq 90 \text{ mL/min/1.73m}^2$  (stage 1 chronic kidney disease), 60-89 mL/min/1.73m<sup>2</sup> (stage 2), 30-59 mL/min/1.73m<sup>2</sup> (stage 3) and  $<30 \text{ mL/min/1.73m}^2$  (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<sup>(29)</sup>.

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 ( $\pm 2$  kg/m<sup>2</sup>). 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<sup>(19)</sup>. 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)<sup>(30)</sup>. 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,<sup>(31)</sup> 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<sup>(32)</sup>. 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<sup>(33)</sup>, 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<sup>(10)</sup>. 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<sup>(34,35)</sup>. 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<sup>(36)</sup>. 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<sup>(37)</sup>. 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<sup>(38)</sup> and the impact of CPAP treatment on diabetes-related outcomes from RCTs remains uncertain or lacking (except with regard to blood pressure)<sup>(39-41)</sup>. Nonetheless, in general population studies, CPAP has been shown to improve quality of life and sleepiness in patients with and without diabetes<sup>(42,43)</sup>.

OSA in patients with type 2 diabetes has been linked to worse glycaemic control, higher BP, CVD and microvascular complications<sup>(11,16,17,44,45)</sup>. 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<sup>(46)</sup>.



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<sup>(12,13,47)</sup> 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<sup>(48)</sup>. 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 comorbidity-stratified patient subgroups.

## Acknowledgements

**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).

**Funding.** A. T. is a clinician scientist supported by the National Institute for Health Research in the UK. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health. K.N. and A.S. received funding from AstraZeneca; K.N. reports fees from Sanofi and Boehringer Ingelheim outside the submitted work. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Duality of interest.** No potential conflicts of interest relevant to this article

**Author contributions.** K.N. and A.A.T conceived the idea for the study. K.N, A.S and N.A designed and performed the analysis. A.S, A.T, A.A.T and N.A wrote the initial draft of the manuscript. All authors reviewed and revised the manuscript and agreed to submission of the final manuscript.

**Statement of guarantor.** Dr. Krishnarajah Nirantharakumar is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## References

- (1) Jordan, Amy S, Dr|McSharry, David G, MB|Malhotra, Atul, Prof. Adult obstructive sleep apnoea. *Lancet*, The 2014;383(9918):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 injury prevention* 2014;15(5):470-476.
- (3) Jurado-Gámez, Bernabé|Guglielmi, Ottavia|Gude, Francisco|Buela-Casal, Gualberto. Workplace Accidents, Absenteeism and Productivity in Patients With Sleep Apnea. *Archives of Bronchology (Archivos de Bronconeumología, English Edition)* 2014;51(5):213-218.
- (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. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 1995;19(6):410.

- (5) Tkacova R, Dorkova Z, Molcanyiova A, Radikova Z, Klimes I, Tkac I. Cardiovascular risk and insulin resistance in patients with obstructive sleep apnea. *Medical science monitor : international medical journal of experimental and clinical research* 2008 Sep;14(9):CR438.
- (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. *Cardiovascular diabetology* 2006 Nov 1;5(1):22.
- (7) IP MSM, LAM B, NG MMT, LAM WK, TSANG KWT, LAM KSL. Obstructive Sleep Apnea Is Independently Associated with Insulin Resistance. *American Journal of Respiratory and Critical Care Medicine* 2002 Mar 1;165(5):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 Mar;21(1):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 Respiratory 2013 Jan;18(1):140-146.
- (10) Lecube A, Simó R, Pallayova M, Punjabi NM, López-Cano C, Turino C, et al. Pulmonary Function and Sleep Breathing: Two New Targets for Type 2 Diabetes Care. *Endocrine Reviews* 2017 Dec 1;38(6):550-573.
- (11) A Tahrani A. Obstructive Sleep Apnoea and Vascular Disease in Patients with Type 2 Diabetes. *European endocrinology* 2015 Aug;11(2):81.
- (12) Tahrani AA. Obstructive sleep apnoea in diabetes: Does it matter? *Diabetes & Vascular Disease Research* 2017 Sep;14(5):454-462.
- (13) Tahrani A, Ali A, Stevens M. Obstructive sleep apnoea and diabetes: an update. *Current Opinion in Pulmonary Medicine* 2013 Nov;19(6):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* 2016 Feb 1;39(2):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. *Diabetic Medicine* 2016 Feb;33(2):158-168.
- (16) Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Mughal S, et al. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. *American journal of respiratory and critical care medicine* 2012 Sep 1;186(5):434-441.
- (17) Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Altaf Q, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. *Diabetes care* 2013 Nov;36(11):3718-3725.

- (18) Araghi MH, Chen Y, Jagielski A, Choudhury S, Banerjee D, Hussain S, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. *Sleep* 2013 Oct 1;36(10):1553-1562.
- (19) Balkau B, Vol S, Loko S, Andriamboavonjy T, Lantieri O, Gusto G, et al. High baseline insulin levels associated with 6-year incident observed sleep apnea. *Diabetes care* 2010 May;33(5):1044-1049.
- (20) Horner RL. Neural control of the upper airway: integrative physiological mechanisms and relevance for sleep disordered breathing. *Comprehensive Physiology* 2012 Jan;2(1):479.
- (21) Bottini P, Dottorini ML, Cristina Cordoni M, Casucci G, Tantucci C. Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy. *European Respiratory Journal* 2003 Oct 1;22(4):654-660.
- (22) Sanderson AAF, Tahrani AA, Varughese GI, Macleod AF, Epstein AM. Pay-for-Performance Programs in the United Kingdom. *The New England Journal of Medicine* 2006 Oct 26;355(17):1832-1833.
- (23) Daly B, Toulis KA, Thomas N, Gokhale K, Martin J, Webber J, 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 Medicine* 2018 Jan 16;15(1):e1002488.
- (24) Nicola J Adderley, Krishnarajah Nirantharakumar, Tom Marshall. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. *BMJ : British Medical Journal (Online)* 2018 May 9;361.
- (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(5):1263-1271.
- (26) Daly B, Toulis KA, Thomas N, Gokhale K, Martin J, Webber J, 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 medicine* 2018 Jan;15(1):e1002488.
- (27) 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(7752):907-911.
- (28) Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *Journal of public health (Oxford, England)* 2005 Mar;27(1):101-106.
- (29) General Medical Services (GMS) contract Quality and Outcomes Framework (QOF) Guidance for GMS contract; General Practitioners Committee, NHS Employers and NHS England 2016.

- (30) 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 Aug 2;:dc180675.
- (31) Young T, Peppard PE, Gottlieb DJ. Epidemiology of Obstructive Sleep Apnea: A Population Health Perspective. *American Journal of Respiratory and Critical Care Medicine* 2002 May 1;:165(9):1217-1239.
- (32) Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. *Endocrine Reviews* 2016 Jun;:37(3):278-316.
- (33) Rajan P, Greenberg H. Obstructive sleep apnea as a risk factor for type 2 diabetes mellitus. *Nature and science of sleep* 2015;7:113-125.
- (34) Jehan S, Auguste E, Pandi-Perumal SR, Kalinowski J, Myers AK, Zizi F, et al. Depression, Obstructive Sleep Apnea and Psychosocial Health. *Sleep medicine and disorders : international journal* 2017;1(3).
- (35) Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, 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. *Journal of the American College of Cardiology* 2008 Aug 19;:52(8):686.
- (36) The IDF Consensus Statement on Sleep Apnoea and Type 2 Diabetes. *International Diabetes Federation* 2008.
- (37) Seetho IW, O'Brien SV, Hardy KJ, Wilding JP. Obstructive sleep apnoea in diabetes - assessment and awareness. *British Journal of Diabetes* 2014 Sep 12;:14(3):105.
- (38) Donovan LM, Rueschman M, Weng J, Basu N, Dudley KA, Bakker JP, et al. The effectiveness of an obstructive sleep apnea screening and treatment program in patients with type 2 diabetes. *Diabetes Research and Clinical Practice* 2017 Dec;:134:145-152.
- (39) Martínez-Cerón E, Barquiel B, Bezos A, Casitas R, Galera R, García-Benito C, 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. *American journal of respiratory and critical care medicine* 2016 Aug 15;:194(4):476-485.
- (40) Jamie Chung Mei Lam, Agnes Yuen Kwan Lai, Terence Chi Chun Tam, Michele Mae Ann Yuen, Karen Siu Ling Lam, Mary Sau Man Ip. CPAP therapy for patients with sleep apnea and type 2 diabetes mellitus improves control of blood pressure. *Sleep and Breathing* 2017 May 1;:21(2):377-386.
- (41) 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. *The Journal of Clinical Endocrinology & Metabolism* 2012 Nov;:97(11):4212-4218.

- (42) Martha Schwartz, Luis Acosta, Yuan-Lung Hung, Mariela Padilla, Reyes Enciso. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: a systematic review and meta-analysis. *Sleep and Breathing* 2018 Sep 1;22(3):555-568.
- (43) Donovan LM, Rueschman M, Weng J, Basu N, Dudley KA, Bakker JP, et al. The effectiveness of an obstructive sleep apnea screening and treatment program in patients with type 2 diabetes. *Diabetes Research and Clinical Practice* 2017 Dec;134:145-152.
- (44) Altaf QA, Dodson P, Ali A, Raymond NT, Wharton H, Fellows H, et al. Obstructive Sleep Apnea and Retinopathy in Patients with Type 2 Diabetes. A Longitudinal Study. *American journal of respiratory and critical care medicine* 2017 Oct 1;196(7):892-900.
- (45) 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. *Journal of Diabetes and Its Complications* 2016 Sep;30(7):1315-1320.
- (46) Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics in primary care* 2011;19(4):251.
- (47) Heinzer, R, Dr|Vat, S, MD|Marques-Vidal, P, MD|Marti-Soler, H, PhD|Andries, D, RPSGT|Toback, N, RPSGT|Mooser, V, MD|Preisig, M, MD|Malhotra, A, MD|Waeber, G, MD|Vollenweider, P, MD|Tafti, M, PhD|Haba-Rubio, J, MD. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respiratory Medicine*, The 2015;3(4):310-318.
- (48) Obstructive sleep apnoea syndrome. National Institute for Health and Care Excellence 2015 Apr.





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

	<b>Exposed</b>	<b>Unexposed</b>
<b>Population, n</b>	360250	1296489
<b>Age years, mean (SD)</b>	64.85 (13.28)	64.56 (13.63)
<b>Age categories, years, n (%)</b>		
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)
<b>Sex, n (%)</b>		
Men	199941 (55.50)	702927 (54.22)
Women	160309 (44.50)	593562 (45.78)
<b>BMI (kg/m<sup>2</sup>), mean (SD)</b>	31.00 (6.47)	29.83 (5.80)
<b>BMI categories, n (%)</b>		
Under/Normal weight (<25 kg/m <sup>2</sup> )	54047 (15.00)	234404 (18.08)
Overweight (25-30 kg/m <sup>2</sup> )	118393 (32.86)	489719 (37.77)
Obese (≥30 kg/m <sup>2</sup> )	179959 (49.95)	542588 (41.85)
Missing	7851 (2.18)	29778 (2.30)
<b>Townsend, n (%)</b>		
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)
<b>Smoker categories, n (%)</b>		
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)
<b>Ethnicity, n (%)</b>		
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)
<b>eGFR, median (IQR)</b>	76.5 (60.6-91.3)	74.3 (61.2-87.2)
<b>eGFR category</b>		
>90 mL/min/1.73m <sup>2</sup> (Stage 1)	97438 (27.05)	208516 (16.08)
60-90 mL/min/1.73m <sup>2</sup> (Stage 2)	178998 (49.69)	599575 (46.25)
30-59 mL/min/1.73m <sup>2</sup> (Stage 3)	74006 (20.54)	207151 (15.98)
<30 mL/min/1.73m <sup>2</sup> (Stage 4+5)	7384 (2.05)	13083 (1.01)
Missing	2424 (0.67)	268164 (20.68)
<b>Baseline comorbidities, n (%)</b>		
<b>Cardiovascular diseases</b>		
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)

<b>Mental health conditions</b>		
Anxiety	57756 (16.03)	200706 (15.48)
Depression	75642 (21.00)	241215 (18.61)
<b>Baseline drug use (within 60 days of index), n (%)</b>		
Lipid-lowering drugs	229287 (63.65)	305443 (23.56)
<b>Outcome at baseline</b>		
OSA*	6567 (1.82)	11682 (0.90)
<b>Diabetes-related variables†</b>		
<b>HbA1c (mmol/mol), median (IQR)</b>	51.9 (45.0-60.6)	
<b>HbA1c category †</b>		
≤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)	
<b>Concurrent conditions within 15 months of diabetes diagnosis</b>		
Foot Disease	22305 (6.20)	
Retinopathy/Low vision/Blindness	16911 (4.69)	
Hypoglycaemic event	7555 (2.10)	
<b>Baseline drug use(within 60 days of index), n (%)</b>		
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
<b>Outcome events, n (%)</b>	3110 (0.88)	5968 (0.46)	1238 (0.82)	2698 (0.48)
<b>Person-years</b>	1763982	5963919	646356	2245189
<b>Crude IR per 1000 person-years</b>	1.76	1.00	1.92	1.20
<b>Follow-up years, median (IQR)</b>	4.40 (2.06-7.60)	3.94 (1.80-7.07)	3.77 (1.84-6.39)	3.43 (1.62-5.94)
<b>Unadjusted IRR (95% CI)</b>	1.76 (1.69-1.84); p<0.001		1.59 (1.47-1.72); p<0.001	
<b>Partially adjusted IRR* (95% CI)</b>	1.48 (1.42-1.55); p<0.001		1.41 (1.32-1.51); p<0.001	
<b>Fully adjusted IRR* (95% CI)</b>	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)**

<b>Risk factors</b>	<b>aIRR (95% CI); p value*</b>
<b>Age categories, years</b>	
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
<b>Sex</b>	
Women	Ref
Men	2.27 (2.09-2.46); <0.001
<b>BMI categories</b>	
Underweight/normal weight (<25 kg/m <sup>2</sup> )	Ref
Overweight (25-30 kg/m <sup>2</sup> )	2.02 (1.54-2.64); <0.001
Obese (≥30 kg/m <sup>2</sup> )	8.29 (6.42-10.69); <0.001
Missing	3.68 (2.31-5.86); <0.001
<b>Townsend</b>	
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
<b>Smoker categories</b>	
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
<b>Ethnicity</b>	
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
<b>eGFR category</b>	
>90 mL/min/1.73m <sup>2</sup> (Stage 1)	Ref
60-90 mL/min/1.73m <sup>2</sup> (Stage 2)	0.95 (0.87-1.03); 0.223
30-59 mL/min/1.73m <sup>2</sup> (Stage 3)	1.00 (0.88-1.14); 0.987
<30 mL/min/1.73m <sup>2</sup> (Stage 4+5)	0.93 (0.64-1.36); 0.726
Missing	0.51 (0.26-0.99); 0.046
<b>Concurrent conditions within 15 months of diabetes diagnosis</b>	
<b>Cardiovascular diseases</b>	
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
<b>Mental health conditions</b>	
Anxiety	1.07 (0.97-1.18); 0.179
Depression	1.75 (1.61-1.91); <0.001
<b>Baseline drug use (within 60 days of index), n (%)</b>	

Lipid-lowering drugs	1.05 (0.96-1.15); 0.296
<b>Diabetes-related variables</b>	
<b>HbA1c category</b>	Ref
≤6.5% (47.500 mmol/mol)	
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
<b>Concurrent conditions within 15 months of diabetes diagnosis</b>	
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
<b>Baseline drug use (within 60 days of index), n (%)</b>	
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.