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DOI:
10.2337/dc19-2116

Document Version
Peer reviewed version

Citation for published version (Harvard):
Adderley, N, Subramanian, A, Toulis, K, Gokhale, K, Taverner, T, Hanif, W, Haroon, S, Thomas, GN, Sainsbury, C, Tahrani, A & Nirantharakumar, K 2020, 'Obstructive sleep apnoea, a risk factor for cardiovascular and microvascular disease in patients with type 2 diabetes mellitus: findings from a population-based cohort study', *Diabetes Care*. https://doi.org/10.2337/dc19-2116

Obstructive sleep apnoea, a risk factor for cardiovascular and microvascular disease in patients with type 2 diabetes mellitus: findings from a population-based cohort study

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Running title:

OSA and cardio/microvascular disease in T2DM

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Abstract:	249
Word count:	4135
Tables:	1 + 5 supplementary
Figures:	3
References:	39

Abstract

Objective

To determine risk of cardiovascular diseases (CVD), microvascular complications and mortality in patients with type 2 diabetes who subsequently develop obstructive sleep apnoea(OSA) compared to patients with type 2 diabetes without a diagnosis of OSA.

Research Design and Methods

An age-, sex-, body mass index- and diabetes duration-matched cohort study using data from a UK primary care database from 01/01/2005 to 17/01/2018. Participants aged ≥16 years with type 2 diabetes were included. Exposed participants were those who developed OSA after their diabetes diagnosis; unexposed participants were those without diagnosed OSA. Outcomes were composite CVD (ischaemic heart disease(IHD), stroke/transient ischaemic attack(TIA), heart failure(HF)); peripheral vascular disease(PVD); atrial fibrillation(AF); peripheral neuropathy(PN); diabetes-related foot disease(DFD); referable retinopathy; chronic kidney disease(CKD); all-cause mortality. The same outcomes were explored in patients with pre-existing OSA before a diagnosis of type 2 diabetes versus diabetes without diagnosed OSA.

Results

3,667 exposed participants and 10,450 matched controls were included. Adjusted hazard ratios for the outcomes were: composite CVD 1.54(95%CI 1.32,1.79); IHD 1.55(1.26,1.90); HF 1.67(1.35,2.06); stroke/TIA 1.57(1.27,1.94); PVD 1.10(0.91,1.32); AF 1.53(1.28,1.83); PN 1.32(1.14,1.51); DFD 1.42(1.16,1.74); retinopathy 0.99(0.82,1.21); CKD (stage 3-5) 1.18(1.02,1.36); albuminuria 1.11(1.01,1.22); all-cause mortality 1.24(1.10,1.40). In the prevalent OSA cohort the results were similar but some associations not observed.

Conclusions

Patients with type 2 diabetes who develop OSA are at increased risk of CVD, AF, PN, DFD, CKD, and all-cause mortality compared to patients without diagnosed OSA. Patients with type 2 diabetes who develop OSA are a high-risk population and strategies to detect OSA and prevent cardiovascular and microvascular complications should be implemented.

Introduction

Diabetes-related microvascular complications and cardiovascular disease (CVD) are major causes of morbidity, mortality and worsening quality of life in patients with type 2 diabetes.[1,2,3] CVD prevention is one of the main aims of type 2 diabetes treatment.[4] Improved health care delivery, including the use of lipid-lowering treatments, antiplatelets (for secondary prevention) and antihypertensives, has resulted in reduced mortality, CVD and vascular complications in patients with type 2 diabetes; however, the burden of these complications remains large due to the increasing prevalence of type 2 diabetes.[4,5] Therefore, identifying risk factors and preventative strategies for the development of vascular disease and mortality in patients with type 2 diabetes are still needed.[6]

Obstructive sleep apnoea (OSA) is common in patients with type 2 diabetes (24-86%) and patients with type 2 diabetes are at increased risk of developing OSA compared to patients without diabetes.[7,8,9] Epidemiological studies in patients without diabetes showed that OSA was associated with increased risk of mortality and CVD (including stroke) which was improved with continuous positive airway pressure (CPAP) in non-randomised studies.[10,11,12,13,14,15] Our group has previously shown a cross-sectional association between OSA and peripheral neuropathy (PN), sight threatening retinopathy, and chronic kidney disease (CKD) in patients with type 2 diabetes.[8,16] We have also shown that OSA was associated with increased risk of renal function decline and development of CKD, and pre-proliferative/proliferative retinopathy in patients with type 2 diabetes in longitudinal studies.[17,18,19] However, these studies were in a relatively small and were from secondary/tertiary care centres. The longitudinal associations between OSA and PN and diabetes-related foot disease (DFD) have not been explored previously. In addition, the relationship between OSA and incident CVD and mortality in patients with type 2 diabetes is largely unknown.

We hypothesised that in patients with type 2 diabetes, the development of OSA increases the risk of CVD, microvascular complications and mortality.

The primary aims of this study were to determine risk of incident CVD (ischaemic heart disease, stroke/transient ischaemic attack, or heart failure), PN, DFD, referable retinopathy, and CKD in patients with type 2 diabetes who go on to develop OSA compared to patients with type 2 diabetes but without diagnosed OSA. Secondary outcomes included the individual components of the composite CVD outcome; peripheral vascular disease (PVD); atrial fibrillation (AF); micro- and macroalbuminuria; and all-cause mortality. Additionally, in order to explore whether the sequence in which type 2 diabetes and OSA are diagnosed has any impact on observed outcomes, we conducted a second cohort study to determine risk of each of the outcomes in patients with type 2 diabetes and pre-existing OSA compared to patients with type 2 diabetes but without diagnosed OSA.

Methods

Study Design

Age-, sex-, body mass index (BMI)- and diabetes duration-matched retrospective cohort study from 1st January 2005 to 17th January 2018.

Data Source

The study dataset was extracted from The Health Improvement Network (THIN), a database comprising anonymised electronic primary care records for more than 15 million patients from 787

general practices across the UK. It contains coded information on patient demographics, symptoms, diagnoses, medication prescriptions, consultations, and diagnostic tests. The dataset is derived from routinely collected patient records and is generalizable to the UK population. THIN data has been used in numerous studies in the contexts of type 2 diabetes, OSA and cardiovascular disease.[7,20,21,22]

Population

General practices were included in the study from the latest of the following dates: 12 months after reporting acceptable mortality rates (a measure of data recording quality),[23] 12 months after starting to use electronic medical records, and study start date (1st January 2005). This was to maximise data and recording quality.

Adults aged ≥16 years, registered with an eligible general practice for a minimum of 12 months, and with a record of type 2 diabetes were eligible for inclusion. Patients who underwent bariatric surgery or had a record of HIV at any time point were excluded.

Primary Analysis: Incident OSA Exposure

The exposed cohort comprised participants with type 2 diabetes and a subsequent, incident diagnosis of OSA (occurring after the diagnosis of type 2 diabetes and during the study period). Index (study entry) date for exposed patients was the date of OSA diagnosis.

Each person in the exposed group was matched on index date to up to 4 randomly selected individuals with type 2 diabetes but without diagnosed OSA by age, sex, BMI and diabetes duration. Age and diabetes duration were matched to within ±1 year; BMI was matched to within ±2 kg/m^2. Unexposed participants were assigned the same index date as their corresponding exposed participants in order to mitigate immortal time bias.[24] The study design was an open cohort, therefore any individual with type 2 diabetes who developed incident OSA during the study period was included in the exposed cohort; as a result, no individuals in the unexposed population developed OSA during follow-up.

Secondary Analysis: Prevalent OSA Exposure

The exposed cohort comprised participants with incident type 2 diabetes (diagnosed during the study period) and prevalent OSA (occurring before the diagnosis of type 2 diabetes). Each exposed participant was matched to up to 4 randomly selected individuals with incident type 2 diabetes and no existing or subsequent diagnosis of OSA by age, sex, BMI (±2 kg/m^2) and index year. Index date was the date of type 2 diabetes diagnosis for both exposed and unexposed participants.

Follow-up Period

Participants were followed up from the index date until the earliest of the following dates: outcome diagnosis, death, participant left the practice, the practice ceased contributing to the database, and study end (17th January 2018).

Outcomes

Primary outcomes were composite CVD (ischaemic heart disease (IHD), stroke or transient ischaemic attack (TIA) and heart failure (HF)); PN; DFD (defined as foot ulcer, lower limb amputation or gangrene of the foot); referable retinopathy (pre-proliferative (R2), proliferative (R3), maculopathy (M1), low vision/blindness, or corrective procedures for retinopathy such as laser and vitreous injections), and CKD stages 3-5. Secondary outcomes included each of the three composite CVD outcomes separately (IHD, stroke/TIA, HF); PVD; AF; albuminuria (albumin-creatinine ratio (ACR) >3

mg/mmol), macroalbuminuiria (ACR >30 mg/mmol), and severe macroalbuminuria (ACR >300 mg/mmol); and all-cause mortality.

Participants with a record of the outcome of interest at index date were excluded from the corresponding analysis, for example, for the composite CVD outcome, patients with a record of IHD, stroke/TIA or HF at baseline were excluded. In the analysis for PN as the outcome, participants with folate or B12 deficiency were excluded, as these deficiencies are associated with development of the outcome.

Definitions of variables

Type 2 diabetes was defined as a record of any diabetes clinical (Read) code and no record of type 1 diabetes. Individuals with prevalent or incident (first recorded during the study period) diabetes were included.

OSA, IHD, stroke/TIA, HF, PVD, AF, PN, DFD, referable retinopathy, hypertension and conditions contributing to the Charlson comorbidity index[25] were defined by a record of a relevant diagnostic clinical (Read) code indicating presence of the condition. CKD stage 3-5 was defined by the presence of a relevant clinical code or by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 in two records separated by at least 90 days (the latter aligns with the definition used in clinical guidelines).[26] All cardiovascular outcomes are included in the Quality and Outcomes Framework (QOF), a payment system which incentivises general practices in the UK to maintain disease registers;[27] these outcomes are therefore well recorded in primary care.

Covariates that might impact the outcomes were selected on the basis of biological plausibility and previous literature. Covariates included age; sex; BMI; Townsend deprivation quintile; smoking status; current prescription of lipid-lowering drugs, antihypertensives, antiplatelets, and insulin; ethnicity; diabetes duration; HbA1c; eGFR; ACR; hypertension; Charlson comorbidity index (CCI; mortality outcome only).

Covariates were measured at baseline. Physiological measures were taken as the latest value recorded prior to index date. Current medication prescriptions were defined as those issued within 60 days prior to the index date. Insulin prescription was used as an indication of disease severity.

BMI was categorised as <25 kg/m^2 (normal or underweight), 25-30 kg/m^2 (overweight), and ≥30 kg/m^2 (obesity). Smoking was categorised as current smoker, ex-smoker and non-smoker. HbA1c was categorised as ≤47.5, 47.5-58.5, 58.5-69.4 and >69.4 mmol/mol. eGFR was calculated from serum creatinine values and ethnicity data (where available) using the CKD-EPI equation,[28] and categorised as >60, 30-59 and <30 ml/min/1.73 m^2. ACR was categorised as <3, 3-30 and >30 mg/mmol.[26]

Missing data

Missing categories were used where values for BMI, smoking status, Townsend quintile, ethnicity, HbA1c, eGFR and ACR were not recorded. Implausible measurements of BMI, HbA1c, eGFR and ACR were considered data entry errors and were treated as missing. In a sensitivity analysis, missing values of BMI, HbA1c, eGFR and ACR were replaced using multiple imputation, using chained equations with predictive mean matching. The absence of a diagnostic code or medication code was taken to indicate absence of the condition or prescription, respectively.

Analysis

Crude incidence rates (IR) were calculated for each outcome. Crude and adjusted hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazards models. The proportional hazards assumption was checked using log-log plots and the Schoenfeld residuals test. Adjusted models for all cardiovascular outcomes (composite CVD, IHD, stroke/TIA, HF, PVD, AF) and microvascular diabetes complications (PN, DFD, referable retinopathy) included the following covariates measured at baseline: age category, sex, BMI category, smoking category, Townsend deprivation quintile, hypertension, prescription of lipid-lowering drugs, antihypertensives, antiplatelets and insulin, ethnicity, diabetes duration, HbA1c category, eGFR category, and ACR category. For renal outcomes (CKD, albuminuria), covariates were as above with the exclusion of eGFR and ACR, and with the addition of baseline cardiovascular disease (ischaemic heart disease, heart failure, stroke/transient ischaemic attack). The adjusted model for all-cause mortality outcome included: age, sex, BMI, smoking status, Townsend quintile, lipid-lowering drug prescription, antiplatelet prescription, antihypertensive prescription, insulin prescription, ethnicity, diabetes duration, HbA1c category, and CCI.

In primary analysis, all identified exposed patients and their corresponding controls were included. It was not possible to identify matched controls for a small proportion of patients with OSA; therefore, sensitivity analyses were performed restricting to those exposed patients for whom one or more control was identified, together with the corresponding controls.

All analyses were performed in Stata IC version 14. Two-sided p-values were obtained and $p<0.05$ was considered statistically significant.

Results

Primary Analysis: Incident OSA Exposure

In the primary analysis, we compared participants with type 2 diabetes and a subsequent diagnosis of OSA with participants with type 2 diabetes and no OSA. 3,667 adults with type 2 diabetes and a subsequent diagnosis of OSA and 10,450 controls with type 2 diabetes but no diagnosis of OSA were included in the analysis (Figure 1). Baseline characteristics are summarised in Table 1. The overall study population was middle age, mostly male, with a high prevalence of IHD (approximately one fifth) and hypertension (almost two thirds) at baseline, with the majority prescribed antihypertensives and lipid-lowering medications, and an average HbA1c of 7.5% (59 mmol/mol). Approximately 15% of the study population were current smokers. Age, sex, BMI and diabetes duration (matching parameters) were broadly similar between exposed and unexposed participants (Table 1). Compared to controls without diagnosed OSA, patients with type 2 diabetes who went on to develop OSA had marginally higher deprivation scores; were slightly more likely to be of South Asian ethnicity (3.0% compared to 2.2%); had a higher prevalence of hypertension and IHD; had a slightly higher mean HbA1c; and were more likely to be prescribed medications, particularly insulin (19.3% compared to 8.9%) at baseline (Table 1).

Cardiovascular outcomes

250 (10.1%) participants with type 2 diabetes and incident OSA and 564 (7.0%) controls with type 2 diabetes and without diagnosed OSA developed composite CVD (IHD, stroke/TIA and HF) during follow-up (Supplementary Table 1). Median (IQR) follow-up was 3.1 (1.6-5.5) and 3.5 (1.7-5.9) years in exposed and unexposed patients. Crude IRs were 26.6 and 17.4 per 1000 person-years in exposed and unexposed participants, respectively. Crude and adjusted hazard ratios were 1.54 (95% CI 1.32,

1.78) and 1.54 (1.32, 1.79) respectively (Supplementary Table 1, Figure 2). These results suggest that incident OSA in patients with type 2 diabetes was associated with increased risk of incident composite CVD compared to patients with type 2 diabetes but without diagnosed OSA.

Adjusted HRs for each of the component cardiovascular diseases were: IHD 1.55 (95% CI 1.26, 1.90); stroke/TIA 1.57 (1.27, 1.94); and HF 1.67 (1.35, 2.06) showing similar associations to those between OSA and composite CVD.

For AF, adjusted HR was 1.53 (95% CI 1.28, 1.83). There was no statistically significant difference in hazard of PVD: adjusted HR 1.10 (0.91, 1.32; p=0.319).

Diabetes-related microvascular outcomes

For each of the microvascular outcomes, median follow-up period was approximately 3 years for exposed participants with type 2 diabetes and comorbid OSA and approximately 3.5 years for unexposed participants with type 2 diabetes but without diagnosed OSA.

288 (10.5%) exposed participants and 697 (8.2%) unexposed participants developed peripheral neuropathy during follow-up (Supplementary Table 2). Hazard of peripheral neuropathy was significantly higher in participants with OSA compared to those without diagnosed OSA: crude hazard ratio was 1.37 (95% CI 1.19, 1.57); adjusted HR was 1.32 (1.14, 1.51) (Supplementary Table 2, Figure 3).

161 (4.7%) and 289 (2.9%) exposed and unexposed participants, respectively, developed DFD. Hazard of DFD was significantly higher in participants with OSA compared to those without diagnosed OSA: crude and adjusted HRs were 1.76 (95% CI 1.45, 2.13) and 1.42 (1.16, 1.74), respectively.

156 (4.7%) and 395 (4.0%) exposed and unexposed participants, respectively, developed diabetes-related referable retinopathy. Crude HR was 1.22 (95% CI 1.01, 1.47); after adjustment for potential confounders, the result was not statistically significant: adjusted HR was 0.99 (0.82, 1.21; p=0.952).

Renal outcomes

276 (9.7%) exposed and 740 (8.6%) exposed and unexposed participants, respectively, developed CKD stage 3-5. There was a significant increase in hazard of CKD in the exposed group compared to the unexposed group: crude and adjusted HRs were 1.20 (95% CI 1.05, 1.38) and 1.18 (1.02, 1.36), respectively (Supplementary Table 2, Figure 3).

Hazard of albuminuria was higher in participants with type 2 diabetes and incident OSA compared to those without diagnosed OSA, although this did not reach statistical significance for severe macroalbuminuria: adjusted HRs for micro/macroalbuminuria (ACR >3 mg/mmol), macroalbuminuria (ACR >30 mg/mmol) and severe macroalbuminuria (ACR >300 mg/mmol) were 1.11 (95% CI 1.01, 1.22), 1.33 (1.13, 1.55) and 1.33 (0.92, 1.93), respectively.

All-cause mortality

434 (11.8%) exposed and 891 (8.5%) unexposed participants died during follow-up. Median (IQR) follow-up was 3.2 (1.7-5.8) and 3.6 (1.8-6.1) years in the exposed and comparator groups, respectively. Crude mortality rates were 29.9 and 20.3 per 1000 person-years in exposed and unexposed patients, respectively. Adjusted HR was 1.24 (95% CI 1.10, 1.40) (Supplementary Table 1, Figure 2), showing that OSA was associated with increased all-cause mortality in patents with type 2 diabetes.

Sensitivity analysis

A sensitivity analysis was performed excluding exposed participants with no matched controls; this made no difference to the observed findings (Supplementary Tables 1-3). A further supplementary analysis was performed replacing missing values by multiple imputation; this did not affect the results (Supplementary Tables 1-2).

Prevalent OSA Exposure

In secondary analysis, we explored outcomes in participants with incident type 2 diabetes and pre-existing OSA (prevalent at the time of the type 2 diabetes diagnosis) compared to participants with type 2 diabetes and no OSA. 4,564 participants with type 2 diabetes and prevalent OSA and 15,589 controls with diabetes and without diagnosed OSA were included in the analysis. Baseline characteristics are presented in Table 1.

Cardiovascular outcomes

Adjusted HRs for composite CVD, IHD, stroke/TIA and HF were 1.23 (95% CI 1.05, 1.43), 1.14 (0.95, 1.38), 1.20 (0.94, 1.52), and 1.26 (0.98, 1.63), respectively (Supplementary Table 4, Figure 2). Adjusted HR for AF was 1.11 (0.91, 1.34) and for PVD 1.27 (1.17, 1.47).

Microvascular outcomes

Adjusted HRs for peripheral neuropathy, DFD and referable retinopathy were 1.22 (95% CI 1.11, 1.34), 1.36 (1.08, 1.71), and 0.93 (0.75, 1.16), respectively (Supplementary Table 5, Figure 3).Adjusted HRs for CKD (stage 3-5), micro/macroalbuminuria, macroalbuminuria and severe macroalbuminuria were 1.01 (95% CI 0.89, 1.15), 1.16 (1.09, 1.24), 1.21 (1.04, 1.41) and 1.37 (0.78, 2.41), respectively (Supplementary Table 5, Figure 3).

All-cause mortality

Adjusted HR for all-cause mortality was 1.00 (95% CI 0.88-1.14) (Supplementary Table 4, Figure 2)

Discussion

In this cohort study, participants who developed OSA after their diagnosis of type 2 diabetes had a more than 50% increase in risk of composite CVD, IHD, HF and stroke/TIA, a 53% greater risk of developing AF, a 32% increase in risk of peripheral neuropathy, a 42% increase in risk of DFD, an 18% increase in risk of CKD stages 3-5, an 11% increased risk of albuminuria, and a 24% increase in risk of all-cause mortality compared to participants with type 2 diabetes and no OSA. These results were observed after matching for age, sex, BMI and diabetes duration, and adjusting for a range of potential confounders. There were no significant associations between OSA and the risk of PVD or referable retinopathy in this study.

This study adds novel insights and findings to the limited published literature describing the impact of OSA on cardiovascular outcomes in patients with type 2 diabetes. A previous study showed an association between OSA and stroke; however, this was cross-sectional, relied on self-reported outcomes and was of small sample size.[29]. Two previously published cohort studies showed an association between OSA and CVD/mortality,[30,31,32] but these studies were in highly selected populations (patients with type 2 diabetes referred to cardiology units for the investigation of coronary artery disease in one study, and patients referred for percutaneous coronary intervention in the other). In addition, these studies were of smaller sample size, the analysis adjusted for a

limited number of variables, and one of the studies included people at high risk of OSA rather than diagnosed OSA.

Hence, our study provides significant findings and adds methodological rigour compared to the limited published literature in that it was a population-based study of large sample size, allowing for adjustment for a large number of potential confounders, and examined the association between OSA and multiple individual CVD outcomes, as well as all-cause mortality and microvascular complications, in patients with type 2 diabetes.

The association of OSA with incident AF in our study was mirrored by a similar association with incident stroke. Hence, our data suggest that identifying patients with type 2 diabetes who have OSA might provide an opportunity to examine for AF and implement appropriate stroke prevention strategies. There is interest in the impact of OSA in AF patients on the risk of stroke and AF recurrence following ablation.[33,34]

Our study also shows that having OSA identifies a high-risk population with type 2 diabetes in which CVD-prevention measures should be maximised. To our knowledge, our study is the first to report the association between OSA and mortality in patients with type 2 diabetes, which is similar to that observed in general population studies without diabetes.[12,13,15]

Our study is the first to show the relationship between OSA and PN and DFD in patients with type 2 diabetes in a longitudinal, population-based study. We have previously shown an association between OSA and PN in a cross-sectional study.[16] We have also previously shown OSA to be associated with CKD in a cross-sectional analysis, and with eGFR decline in a longitudinal study, in secondary/tertiary care centres in the UK.[19,35] The current study allowed us to expand our findings to a more representative population and to examine the impact of OSA on albuminuria. Unlike our previous longitudinal study that showed an association between OSA and increased risk of pre-proliferative and proliferative retinopathy,[17] this study showed no significant association between OSA and referable retinopathy after adjustment. This difference may be explained by the different study populations – secondary/tertiary vs primary care – and the use of a broader outcome measure (referable retinopathy) compared to our previous study, which was based only on the development of R2 or R3.

There are multiple mechanisms that link OSA to CVD and microvascular complications including insulin resistance, hypertension, increased oxidative and nitrosative stress, sympathetic activation, increased inflammation and endothelial dysfunction, which can improve with CPAP.[35,36] Our findings pose the question whether CPAP should form part of CVD and mortality prevention in patients with type 2 diabetes and comorbid OSA. Our study does not address this question, but despite observational studies showing an association between use of CPAP and vascular benefits in patients with OSA, data from RCTs remains lacking,[37,38] with the exception of one RCT that showed CPAP reduced cardiovascular events and mortality after first ischaemic stroke.[11] However, CPAP trials are always challenging due to the lack of adherence to treatment. Nonetheless, the impact of CPAP on cardiovascular disease in patients with type 2 diabetes needs to be assessed in well-designed RCTs.

In the secondary analysis exploring outcomes in participants with type 2 diabetes and prevalent OSA compared to type 2 diabetes only, participants with OSA continued to be at increased risk of composite CVD, peripheral neuropathy, DFD and albuminuria. The association between OSA and increased risk of individual components of the composite CVD outcome, AF, CKD, and all-cause mortality was no longer significant. This secondary analysis included participants with incident/newly diagnosed type 2 diabetes; the difference in findings is therefore likely to be driven by the fact that these individuals had had type 2 diabetes for a shorter period of time at the end of

follow-up compared to the primary analysis cohort (which included participants with prevalent diabetes). Another possible reason is that patients in the prevalent OSA group might have received better vascular prevention compared to the control group prior to the incident diagnosis of type 2 diabetes.

Strengths and Limitations

Routinely collected data may be subject to incorrect, inconsistent or incomplete recording. However, type 2 diabetes, cardiovascular diseases and CKD are part of the UK QOF which is linked to practice funding, and recording quality is therefore expected to be high. The QOF indicator set for diabetes includes requirements to measure and record smoking status, BMI, blood pressure, HbA1c, ACR and serum creatinine, as well as to perform and record annual foot assessments and retinal screening; this information is therefore likely to be well recorded for patients included in the cohort. After adjusting for patient demographics, the prevalence of major chronic diseases and death rates in THIN are similar to national rates.[39]

Ethnicity is poorly recorded in THIN and was therefore not available for all patients in the cohort. Previous analysis has shown that the prevalence of OSA in THIN may be lower than expected rates based on existing literature, suggesting that OSA may be underdiagnosed or underreported in UK primary care data;[7] it is possible, therefore, that patients diagnosed with OSA in routine care represent a more severe or symptomatic phenotype and hence our results may not be representative of all patients with type 2 diabetes and OSA. Underdiagnosis of OSA in primary care may have resulted in patients with undiagnosed OSA being included in the unexposed group, leading to an underestimation of the strength of the observed associations.

The presence of detection bias cannot be completely ruled out; however, we think it is unlikely to have had a major impact. All patients with type 2 diabetes are reviewed at least annually in England and assessed for vascular complications as part of the QOF; therefore, surveillance bias is unlikely to have had a major impact on our results. This is supported by the lack of increased risk of retinopathy, and by evidence from previous studies in which screen-detected OSA was associated with vascular complications in patients with type 2 diabetes.

The study included a large sample size from a dataset which is generalizable to the UK population. This is the first population-based cohort study to assess the association of OSA diagnosed after type 2 diabetes with cardiovascular endpoints, including composite CVD, AF, IHD, stroke/TIA and heart failure, and with microvascular and renal outcomes. The large sample size and characterisation of the study population allowed us to adjust for a large number of variables that might affect the associations between OSA and CVD in patients with type 2 diabetes. In addition, the matching design further strengthened the methodology of our study.

Conclusion

Patients with type 2 diabetes who go on to develop comorbid OSA are at increased risk of incident CVD, including IHD, stroke/TIA and heart failure, and AF, as well as increased risk of PN, DFD, CKD, albuminuria and all-cause mortality. Physicians need to recognise that patients with type 2 diabetes who develop OSA are a high-risk population and strategies to detect OSA and prevent vascular complications should be implemented. RCTs examining the impact of CPAP on cardiovascular and microvascular outcomes in patients with OSA and type 2 diabetes are needed.

Table 1. Baseline characteristics of study participants

Participant characteristic	Primary analysis: Incident OSA		Secondary analysis: Prevalent OSA	
	Exposed	Unexposed	Exposed	Unexposed
Population, n	3,667	10,450	4,564	15,589
Age (years), mean (SD)†	60.07 (10.56)	60.99 (9.08)	57.14 (11.04)	57.60 (10.89)
Age at diagnosis of T2DM (years), mean (SD)	53.12 (10.33)	54.95 (8.71)	57.14 (11.04)	57.60 (10.89)
Age at diagnosis of OSA (years), mean (SD)	60.07 (10.56)	-	51.51 (11.12)	-
T2DM to OSA development time (years), mean (SD)	6.95 (6.18)	-	-	-
OSA to T2DM development time (years), mean (SD)	-	-	5.63 (4.80)	-
T2DM duration (years), mean (SD)†	6.95 (6.18)	6.04 (4.94)		
Sex, n (%)†				
Male	2679 (73.06)	7914 (75.73)	3558 (77.96)	12062 (77.38)
Female	988 (26.94)	2536 (24.27)	1006 (22.04)	3527 (22.62)
BMI (kg/m^2), mean (SD)†	37.68 (7.65)	35.70 (6.00)	38.27 (7.94)	36.89 (6.95)
BMI categories, n (%)				
Underweight (< 25 kg/m^2)	56 (1.53)	183 (1.75)	60 (1.31)	243 (1.56)
Overweight (25 - 30 kg/m^2)	356 (9.71)	1431 (13.69)	494 (10.82)	2050 (13.15)
Obese (> 30 kg/m^2)	3216 (87.70)	8828 (84.48)	3898 (85.41)	12871 (82.56)
Missing	39 (1.06)	8 (0.08)	112 (2.45)	425 (2.73)
Smoking status, n (%)				
Non-smoker	1489 (40.61)	4548 (43.52)	1815 (39.77)	6846 (43.92)
Ex-smoker	1588 (43.31)	4284 (41.00)	1835 (40.21)	5690 (36.50)
Smoker	589 (16.06)	1608 (15.39)	903 (19.79)	2988 (19.17)
Missing	1 (0.03)	10 (0.10)	11 (0.24)	65 (0.42)
Ethnicity, n (%)				
White	1774 (48.38)	4939 (47.26)	2215 (48.53)	7473 (47.94)
Black Afro-Caribbean	39 (1.06)	154 (1.47)	59 (1.29)	213 (1.37)
Chinese	10 (0.27)	25 (0.24)	8 (0.18)	29 (0.19)
South Asian	109 (2.97)	230 (2.20)	91 (1.99)	344 (2.21)
Mixed race	15 (0.41)	42 (0.40)	31 (0.68)	82 (0.53)
Missing	1720 (46.90)	5060 (48.42)	2160 (47.33)	7448 (47.78)
Townsend deprivation quintile, n (%)				
1 (least deprived)	637 (17.37)	1868 (17.88)	768 (16.83)	2651 (17.01)
2	606 (16.53)	1854 (17.74)	818 (17.92)	2698 (17.31)
3	696 (18.98)	2003 (19.17)	896 (19.63)	2987 (19.16)
4	692 (18.87)	1857 (17.77)	816 (17.88)	2823 (18.11)
5 (most deprived)	555 (15.13)	1452 (13.89)	633 (13.87)	2265 (14.53)
Missing	481 (13.12)	1416 (13.55)	633 (13.87)	2165 (13.89)
HbA1c (mmol/mol), mean (SD)	59.82 (17.03)	58.37 (16.78)	62.39 (21.13)	63.98 (21.76)
HbA1c category, n (%)				
≤ 47.5 mmol/mol	699 (19.06)	2169 (20.76)	398 (8.72)	1303 (8.36)
47.5 - 58.5 mmol/mol	1123 (30.62)	3321 (31.78)	1268 (27.78)	3744 (24.02)
58.5 - 69.4 mmol/mol	598 (16.31)	1462 (13.99)	366 (8.02)	1235 (7.92)
> 69.4 mmol/mol	680 (18.54)	1681 (16.09)	659 (14.44)	2498 (16.02)

Missing	567 (15.46)	1817 (17.39)	1873 (41.04)	6809 (43.68)
eGFR (ml/min per 1.73 m^2), mean (SD)	79.33 (22.57)	81.42 (19.10)	85.40 (18.26)	85.03 (18.18)
eGFR category, n (%)				
> 60 ml/min per 1.73 m^2 (stage 2 and below)	2913 (79.44)	8808 (84.29)	3997 (87.58)	13393 (85.91)
30-59 ml/min per 1.73 m^2 (stage 3)	568 (15.49)	1223 (11.70)	350 (7.67)	1175 (7.54)
< 30 ml/min per 1.73 m^2 (stage 4-5)	99 (2.70)	101 (0.97)	12 (0.26)	57 (0.37)
Missing	87 (2.37)	318 (3.04)	205 (4.49)	964 (6.18)
Albumin creatinine ratio (mg/mmol), mean (SD)	11.47 (48.72)	6.16 (26.04)	6.99 (20.24)	7.47 (29.75)
Albumin creatinine ratio category, n (%)				
< 3 mg/mmol	1479 (40.33)	4791 (45.85)	388 (8.50)	1366 (8.76)
3.0 - 30.0 mg/mmol	582 (15.87)	1293 (12.37)	172 (3.77)	507 (3.25)
> 30 mg/mmol	166 (4.53)	243 (2.33)	32 (0.70)	87 (0.56)
Missing	1440 (39.27)	4123 (39.45)	3972 (87.03)	13629 (87.43)
Baseline cardiovascular conditions, n (%)				
Heart failure	336 (9.16)	377 (3.61)	226 (4.95)	437 (2.80)
Ischaemic heart disease	867 (23.64)	1836 (17.57)	765 (16.76)	2037 (13.07)
Stroke/TIA	307 (8.37)	665 (6.36)	257 (5.63)	729 (4.68)
Peripheral vascular disease	607 (16.55)	1189 (11.38)	106 (2.32)	366 (2.35)
Atrial fibrillation	375 (10.23)	623 (5.96)	339 (7.43)	780 (5.00)
Hypertension	2451 (66.84)	6615 (63.30)	2376 (52.06)	7699 (49.39)
Baseline microvascular conditions, n (%)				
Peripheral neuropathy	921 (25.12)	1997 (19.11)	81 (1.77)	161 (1.03)
Diabetes-related foot disease	247 (6.74)	427 (4.09)	147 (3.22)	349 (2.24)
Referable retinopathy	320 (8.73)	699 (6.69)	91 (1.99)	194 (1.24)
CKD stage 3-5	828 (22.58)	1856 (17.76)	551 (12.07)	1645 (10.55)
Micro-macroalbuminuria	1391 (37.93)	3209 (30.71)	296 (6.49)	823 (5.28)
Macroalbuminuria	347 (9.46)	555 (5.31)	66 (1.45)	148 (0.95)
Sever macroalbuminuria	26 (0.71)	33 (0.32)	5 (0.11)	17 (0.11)
Baseline drug use (within 60 days of index), n (%)				
Lipid-lowering drugs	2628 (71.67)	7267 (69.54)	1963 (43.01)	6381 (40.93)
Antihypertensives	2911 (79.38)	7600 (72.73)	2808 (61.52)	8941 (57.35)
Antiplatelets	1439 (39.24)	3616 (34.60)	1040 (22.79)	2953 (18.94)
Insulin	708 (19.31)	930 (8.90)	16 (0.35)	42 (0.27)
Charlson comorbidity index, n (%)				
1	1184 (32.29)	4511 (43.17)	2202 (48.25)	9234 (59.23)
2	1199 (32.70)	3330 (31.87)	1448 (31.73)	4004 (25.68)
3	664 (18.11)	1481 (14.17)	543 (11.90)	1463 (9.38)
≥4	620 (16.91)	1128 (10.79)	371 (8.13)	888 (5.70)

[†]Matching parameters. T2DM = type 2 diabetes; BMI = body mass index; eGFR = estimated glomerular filtration rate.

Figures

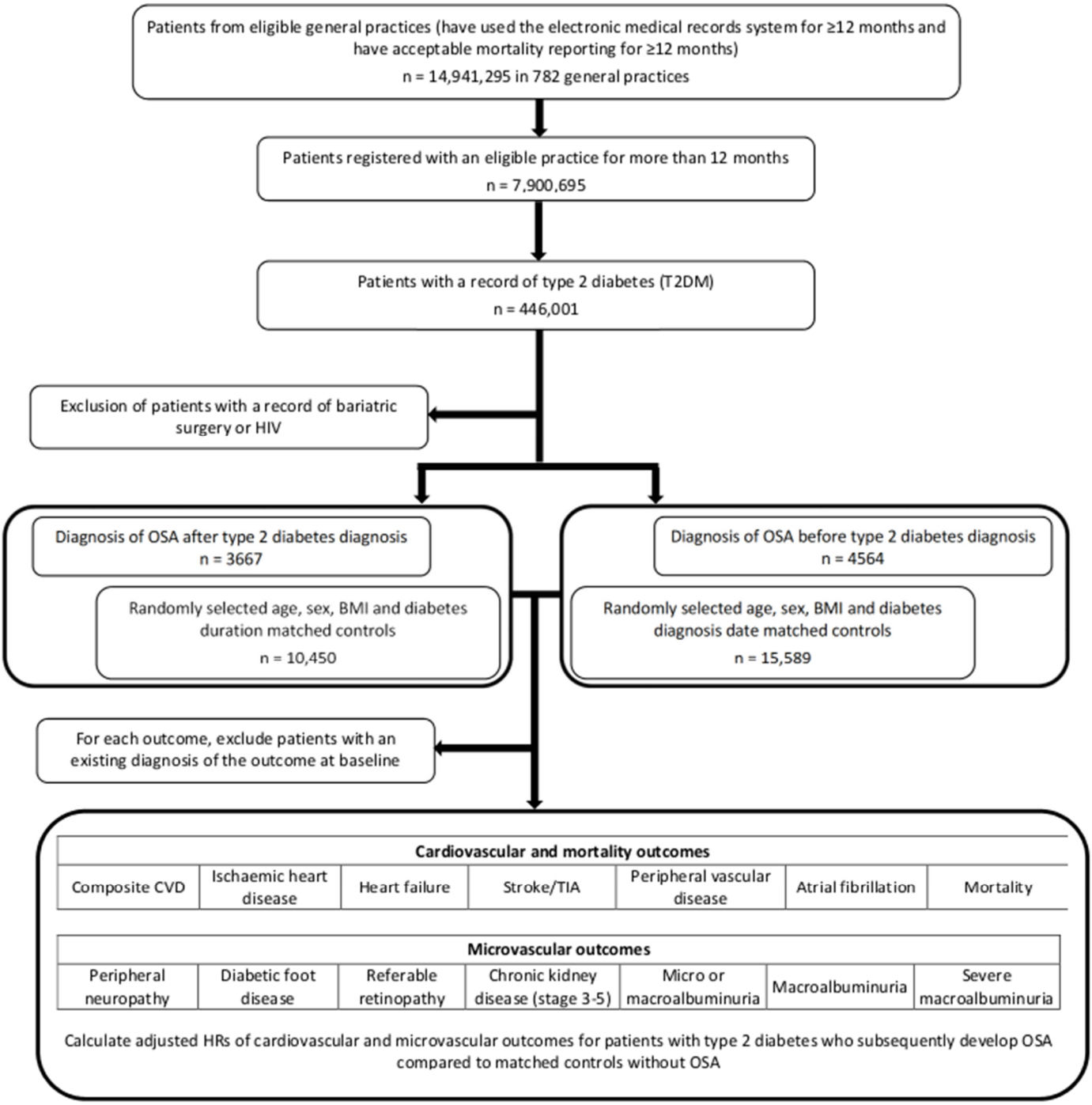

Figure 1. Flow diagram summarising numbers of included participants in the incident OSA analysis.

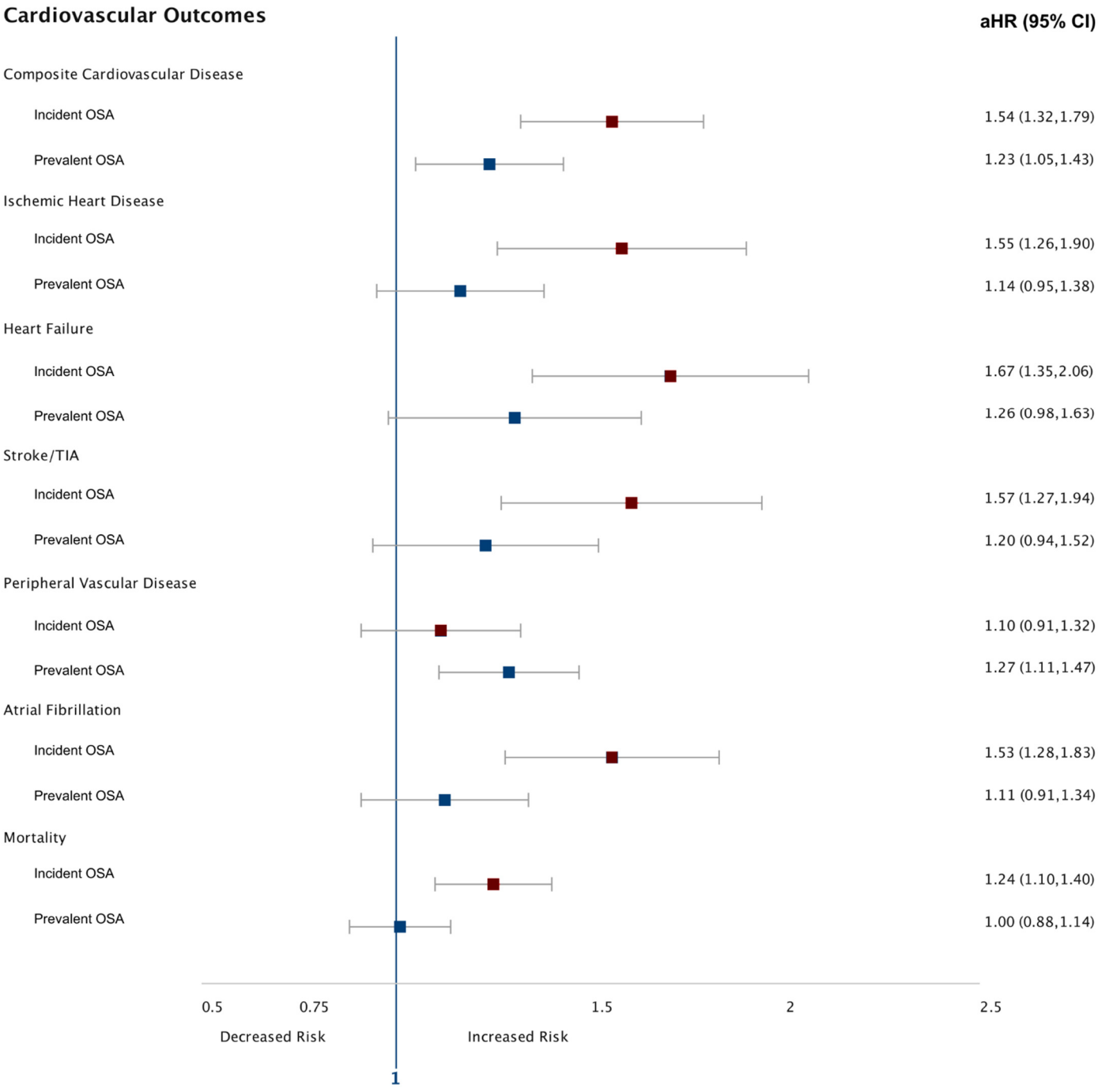

Figure 2. Forest plot showing adjusted hazard ratios for each of the cardiovascular and mortality outcomes assessed, for both incident and prevalent OSA exposure.

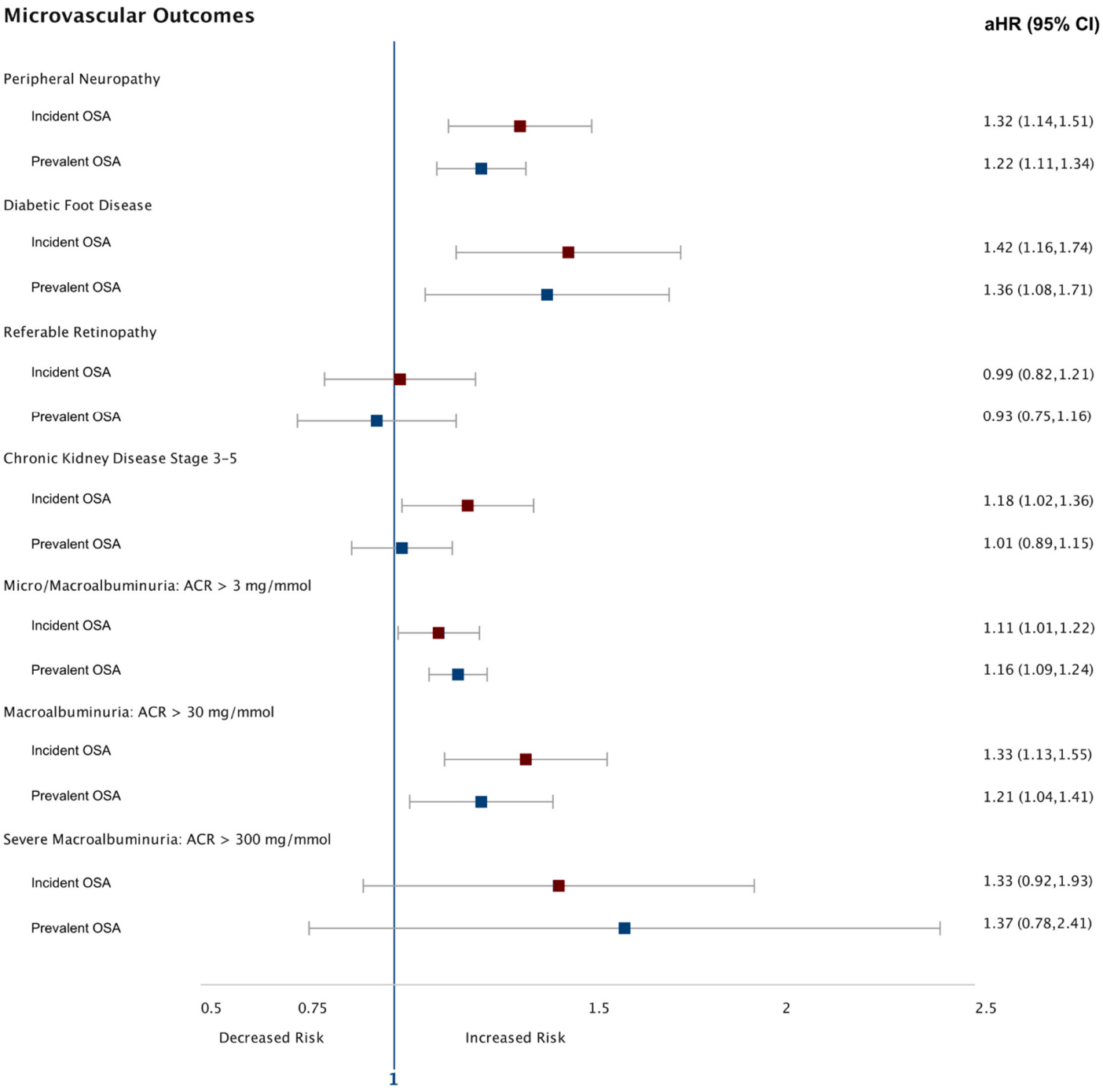

Figure 3. Forest plot showing adjusted hazard ratios for each of the microvascular outcomes assessed, for both incident and prevalent OSA exposure.

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).

Copyright Statement

Funding

AAT is a clinician scientist supported by the National Institute for Health Research in the UK (CS-2013-13-029). 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.

Conflicts of interest

AS, NT and KN received funding from AstraZeneca (RSBD20464). KN reports fees from Sanofi and Boehringer Ingelheim outside the submitted work. AAT reports personal fees and non-financial support from Novo Nordisk, Eli Lilly, AstraZeneca, and Boehringer Ingleheim, personal fees from Janssen, and non-financial support from Impeto Medical, Resmed, and Aptiva. AAT is a clinician scientist supported by the National Institute for Health Research (NIHR) in the UK (CS-2013-13-029). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health. WH reports personal fees and non-financial support from Novo Nordisk, Eli Lilly, AstraZeneca, Boehringer Ingleheim, and NAPP. No other potential conflicts of interest relevant to this article were reported.

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions

AAT, KN and NJA conceived the idea for the study. AS, NJA and KN designed and performed the analysis. NJA and AAT wrote the initial draft of the manuscript. All authors reviewed and revised the manuscript and agreed to submission of the final manuscript.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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