Received: 1 May 2024 | Revised: 23 July 2024 | Accepted: 7 September 2024

DOI: 10.1111/jsr.14357

RESEARCH ARTICLE

Associations of polysomnographic measures of obstructive sleep apnea, and nocturnal oxygen saturation with incident type 2 diabetes mellitus in middle-aged and older men

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Funding information
National Heath and Medical Research Council of Australia, Grant/Award Numbers: 1122342, 627227; Hospital Research Foundation; Freemasons Centre for Male Health and Wellbeing

Summary

Obstructive sleep apnea (OSA) has been associated with incident type 2 diabetes mellitus (T2DM); however, few prospective epidemiological studies have accounted for important T2DM predictors including pre-diabetes status and testosterone. Participants in the longitudinal Men Androgens Inflammation Lifestyles Environment and Stress (MAILES) study, who underwent eight-channel home-based polysomnography (PSG) in 2010–2011 ($n = 824$) and were free of diabetes at baseline were included in the analysis ($n = 682$). From 2015 to 2021, 78.6% ($n = 536$) completed at least one follow-up assessment. Incident T2DM was determined by self-reported doctor diagnosis, diabetes medications, plasma glucose (fasting ≥7.0 mmol/L or random ≥11.0 mmol/L) or glycated haemoglobin ≥6.5%. Conservative hierarchical Poisson regression models adjusted associations of PSG metrics (categorical and continuous) for age, waist circumference, baseline fasting glucose and testosterone concentrations. In all, 52 men (9.7%) developed T2DM over a mean (range) of 8.3 (3.5–10.5) years. Significant age- and waist circumference-adjusted association of incident T2DM with rapid eye movement (REM) sleep apnea–hypopnea index (AHI) ≥20 events/h (incidence rate ratio [IRR] 1.5, 95% confidence interval [CI] 0.8–2.8; $p = 0.23$] and highest quartile of delta index (IRR 2.1, 95% CI 0.95–4.6; $p = 0.066$) were attenuated after adjustment for baseline glucose and testosterone, and the association with the lowest quartile of mean oxygen saturation persisted (IRR 4.2, 95% CI 1.7–10.3; $p = 0.029$). Categorical measures of AHI severity, oxygen desaturation index, and hypoxia burden index (HBI) were not independently associated with incident T2DM. Associations with T2DM were similar when continuous PSG variables were used; however, HBI was significant (IRR 1.015, 95% CI 1.006–1.024; $p = 0.007$). In a sub-sample with OSA treatment data ($n = 479$), these significant associations persisted after excluding adequately treated OSA ($n = 32$). Understanding

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underlying OSA endotypes generating hypoxaemia may identify opportunities for diabetes prevention.

KEYWORDS
diabetes mellitus; epidemiology; men; sleep apnea, obstructive

1 | INTRODUCTION

The increase in prevalence of overweight and obesity has been associated with a marked increase in prevalence of obstructive sleep apnea (OSA) and type 2 diabetes mellitus (T2DM), which are common comorbid conditions (Andayeshgar et al., 2022; Kent et al., 2014; Punjabi et al., 2004; Reutrakul & Mokhlesi, 2017). Moderate-to-severe OSA has been estimated to affect around one fifth to a half of adult males and females using contemporary scoring criteria (Cunningham et al., 2021; Heinzer et al., 2015). The International Diabetes Federation projects that the number of people with diabetes worldwide will reach 578 million by 2030, and 700 million by 2045 amounting to a 51% increase on 2019 estimates of 463 million (Saeedi et al., 2019). Although the pathophysiological mechanisms linking OSA and T2DM are not fully understood, chronic intermittent hypoxaemia, sleep fragmentation and increased sympathetic drive could lead to dysregulation of glucose metabolism (Almendros et al., 2022; Reutrakul & Mokhlesi, 2017).

A meta-analysis (Reutrakul & Mokhlesi, 2017) of nine prospective clinical and epidemiological studies published between 2005 and 2016 generated an adjusted relative risk of T2DM onset associated with OSA of 1.35 (95% confidence interval [CI] 1.24–1.47). However, this was not an individual participant level data analysis and was limited by minimal adjustment for confounding factors due to low numbers of incident cases (ranging from nine to 61) (Botros et al., 2009; Celen et al., 2010; Lindberg et al., 2012; Marshall et al., 2009; Reichmuth et al., 2005) in some of the included studies. A further meta-analysis of studies from 2011 to 2021 demonstrated similar findings (Wang et al., 2022). Other recent findings from a large clinical cohort (Xu et al., 2019) and population studies (Li et al., 2021; Siddiquee et al., 2023; Strausz et al., 2018) have found associations of varying strength between incident T2DM and OSA severity assessed by the apnea–hypopnea index (AHI).

More recently, findings from the Determining Risk of Vascular Events by Apnea Monitoring (DREAM) Study involving a cohort of mostly male United States veterans ($n = 650$) showed that metrics of oxygen saturation but not the AHI, were predictive of T2DM onset (Wojeck et al., 2023). Previous work in the DREAM Study suggested that among a group with severe OSA, a combination of hypoxia and cardiometabolic risk factors including obesity and elevated fasting glucose might drive the development of T2DM (Ding et al., 2021). However, the association of T2DM with nocturnal hypoxaemia metrics such as the total sleep time (TST) with oxygen saturation <90% (T90) has not been consistently demonstrated (Kendzerska et al., 2014; Muraki et al., 2010). A specific role for rapid eye movement (REM) sleep in the relationship between OSA and endocrine function is also supported by cross-sectional studies (Varga & Mokhlesi, 2019) and Kendzerska et al. (2014) demonstrated T2DM incidence over 5 years was associated with REM sleep OSA in addition to T90 and severe OSA (AHI >30 events/h) in a large clinical cohort.

However, only three studies have accounted for the influence of baseline glucose (Botros et al., 2009; Ding et al., 2021; Muraki et al., 2010), which is consistently the strongest predictor of incident T2DM (Balkau et al., 2008). Although each has found an association of OSA with incident T2DM, the metrics used to categorise OSA have varied between studies, making definitive conclusions difficult. Furthermore, none have accounted for the influence of testosterone, shown to be a strong predictor of T2DM onset in men (Wittert et al., 2021). Given the frequent co-occurrence of OSA and T2DM (Reichmuth et al., 2005), the potential for confounding in studies where these major predictors of incident T2DM are not included is significant. Therefore, in a population-based sample of community dwelling men free of T2DM at baseline, we aimed, firstly, to determine polysomnography (PSG) predictors of T2DM onset beyond the AHI, by considering for the first time, alternate measures of hypoxaemia, including a measure of hypoxic burden (Chen et al., 2018), which may capture some of the physiological impacts of OSA more accurately than the AHI (Kulkas et al., 2013; Martinez-Garcia et al., 2023; Muraja-Murro et al., 2013). Secondly, we accounted for the influence of baseline fasting glucose and serum testosterone concentrations on the incidence of T2DM.

2 | METHODS

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study is comprised of randomly selected community dwelling men aged ≥35 years at baseline who were recruited to the Florey Adelaide Male Ageing Study or the North West Adelaide Health Study, and has been described previously (Grant et al., 2014). Initial random recruitment occurred in 2000–2005 and biomedical assessment was conducted in two hospital-based clinics, using standardised and reproducible study protocols. Detailed demographic, biographical, self-reported co-morbidities, and risk factor information was collected via a self-completed questionnaire. Follow-up clinical assessments occurred in 2007–2010, and in 2010–2011 participants were recruited to a PSG sub-study (described below) by computer-assisted telephone interview (CATI).

Approval for the conduct of these MAILES study assessments was provided by Central Adelaide Local Health Network Human

Research Ethics Committee approval numbers (02305H, 2,010,054, HREC/17/TQEH/74, HREC/15/TQEH/127) and the University of Adelaide Human Research Ethics Committee (H-2020-109). All participants provided written informed consent for the conduct of biomedical measures, and self-completed surveys including postal and online surveys.

2.1 | Sleep and PSG data

In 2010, MAILES study participants completed a CATI ($n = 1629$). Of these, 184 reported 'yes' to 'Have you ever been diagnosed with obstructive sleep apnea with a sleep study?' and 1445 men reporting 'no' were invited to undergo a sleep study, with 75% agreeing. During 2010–2011, 837 men underwent eight-channel in-home unattended PSG (Embletta X100, Embla Systems, Broomfield, CO, USA) measuring electroencephalogram (EEG), electromyogram, electro-oculogram, nasal pressure, thoracic and abdominal effort, oximetry, body position, and limb movements. Trained staff visited study participants in their homes to set-up and attach the sleep study equipment. The Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) were administered and measurements of height, and weight, and a record of current medications were also taken.

A single experienced sleep technician performed manual scoring of all home PSGs according to 2007 American Academy of Sleep Medicine (AASM; alternate) criteria as recommended for epidemiological studies by the AASM and the Australasian Sleep Association (ASTA/ASA, 2010), with hypopneas defined as a >50% decrease in nasal flow (or in both thoracic and abdominal excursions) and associated ≥3% oxygen desaturation or an EEG arousal. OSA was defined as an AHI of ≥10 events/h, with further categorisation: mild, AHI of 10–19 events/h; moderate: 20–29 events/h; and severe: ≥30 events/h (ASTA/ASA, 2010). Ruehland et al. (2009) have shown that an AHI of 5 events/h of sleep scored by the 2007 'recommended' AASM criteria is equivalent to an AHI of 10 events/h of sleep using the alternate AASM definition, and 15 events/h using the older 1999 criteria. We used the percentage TST90, oxygen desaturations of ≥3%/h (ODI 3%), oxygen desaturations of ≥4%/h (ODI 4%), the hypoxic burden index (HBI) and the delta index (described below) as indicators of nocturnal hypoxaemia. AHI during REM sleep (AHI_{REM}) was also considered in participants with at least 20 min of REM sleep.

2.2 | The HBI

The HBI, was calculated using the method of Chen et al. (2018), by dividing the total desaturation area of oxygen saturation (SpO_2) <90% by the TST measured in seconds, as shown in the equation below. Oxygen saturation values <40% were excluded as artefacts (Chen et al., 2018). Higher HBI values represent a higher hypoxic burden.

$$HBI\,(\%) = \frac{\sum_{t=t_0}^{t_n}(90 - SpO_{2t})}{\mathrm{TST}},\ if\ SpO_{2t} < 90\%$$

2.3 | Delta index

The delta index measures variation between successive oxygen saturation data at constant (time) intervals. The method employs the average absolute difference of consecutive oxygen saturation measurements at regular intervals (12 s). The delta index relates to the sum of the absolute variations between two successive points divided by the number of intervals (Levy et al., 1996). The delta index is computed using the following equation:

$$Delta\ Index\,(\Delta) = 1/n \sum_{n}^{1} \left| \frac{\partial(SpO_2)}{\partial(t)} \right|, (12\,s\ Intervals)$$

where ∂ represents a change in *successive* values; n = number of intervals; t = time.

This technique focuses on the magnitude of change between adjacent oxygen saturation measurements, disregarding the direction of fluctuation (increase or decrease). Hence, if oxygen saturation is nearly constant during the recording, the delta index will have low values (Terrill, 2020). A high delta index reflects a pulse oximetry oxygen saturation signal with a higher overall variance.

Insomnia was estimated based on a report of difficulties initiating or maintaining sleep at least 3 times/week (PSQI items) and the presence of daytime dysfunction (fatigue identified as one standard deviation [SD] below the mean 36-item Short-Form Health Survey [SF-36] Vitality scale) (Lang et al., 2017).

3 | COVARIATES/PREDICTORS

The covariates considered were collected at the 2007–2010 face-to-face clinical assessment as previously described (Grant et al., 2014), including standard demographic (age, education) and biomedical factors known to predict T2DM onset. See the data supplement for more details of the data collection. These included self-reported measures of smoking status and physical activity. Clinical characteristics contemporaneous with the baseline measure used to exclude prevalent T2DM cases included hypertension (systolic pressure ≥140 mmHg and/or diastolic pressure ≥ 90 mmHg or medication use), waist circumference (cm, categorised as <95, 95–101, ≥102), and depression (score of >12 on the Beck Depression Inventory or ≥21 on the Center for Epidemiological Studies Depression Scale or treatment). Cardiovascular disease (CVD) was determined from self-reported records of myocardial infarction, angina, stroke, and transient ischaemic attack or public hospital administrative data (available from July 1, 2001 to June 30, 2014). A fasting blood sample was drawn for measures of plasma glucose, glycated haemoglobin (HbA1c), and lipids, and serum total testosterone. Body mass index (BMI, kg/m^2 (Andayeshgar et al., 2022) on the night of the PSG study was calculated from measured height

and weight. Alcohol use, marital status, and family financial strain were assessed during the 2010 CATI.

3.1 | Outcome – T2DM assessment

Participants with pre-existing diabetes were excluded from the present analyses, based upon a self-reported doctor diagnosed diabetes, or fasting plasma glucose ≥7.0 mmol/L, or HbA1c ≥6.5%, or use of diabetes medications as determined in the 2007–2010 clinical assessments. Participation in the three follow-up assessments after the PSG sub-study to ascertain incident T2DM is shown in Figure 1. Details of the data collection at these time points is provided in the data supplement. Incident cases were identified by the following measures:

1. Postal survey in 2015–2016: a questionnaire assessed doctor-diagnosed chronic conditions, and medication use. T2DM was determined from a self-report of doctor-diagnosed diabetes, and/or use of diabetes medication(s).
2. Clinical follow-up from June 2018–March 2020: participants were posted a blood test request form for basic biochemistry (including glucose), and HbA1c, and a questionnaire assessing doctor-diagnosed chronic conditions, and medication use. T2DM was determined from a self-report of doctor-diagnosed diabetes, diabetes medication use, fasting plasma glucose ≥7.0 mmol/L or non-fasting (random) plasma glucose ≥11.0 mmol/L, HbA1c ≥6.5%.
3. Postal survey in October 2020–January 2021: this questionnaire assessed health and sleep and broad impacts of COVID-19 restrictions. Questionnaire items included doctor-diagnosed chronic conditions, and medication use. T2DM was determined from a self-report of doctor-diagnosed diabetes or diabetes medication use.

Mortality in the cohort after the PSG was identified through data linkage via SA-NT Datalink with data available until December 2018.

Treatment of OSA diagnosed in the MAILES PSG or subsequently, was identified in self-completed follow-up questionnaires in 2015–2016 and 2018–2020 with data available from 479 participants. Participants were asked 'Have you been diagnosed with sleep apnoea with an overnight sleep study?' and 'Do you use treatment for your sleep apnea?'. Treatment was categorised based on presence or absence of diagnosed OSA as: (i) no OSA diagnosis ($n = 332$); (ii) untreated OSA or continuous positive airway pressure (CPAP) <4 h/night ($n = 115$); and (iii) adequately treated OSA ($n = 32$, CPAP average use of ≥4 h/night, mandibular advancement splint [MAS] use or surgery for OSA).

3.2 | Statistical analyses

Data were analysed using IBM the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Univariate differences in the distribution (%, *n*) of health and sleep factors according to T2DM status or OSA severity categories were determined using Pearson chi-square (Andayeshgar et al., 2022) tests for categorical variables. Continuous variables were described using means and SDs or median and interquartile ranges according to their distribution, and significant differences by T2DM status were determined by the Student's *t*-test or Mann–Whitney *U*-test, respectively. The Kruskal–Wallis test determined differences in median values of PSG variables across OSA severity categories. Cohen's d values for normally distributed covariate/predictor variables are reported as a measure of effect size in relation to the presence or absence of or incident T2DM. Poisson regressions were used to assess adjusted associations of PSG metrics as continuous and categorical variables (e.g. 25th versus 75th percentile), including clinical categories of AHI and ODI 3% with the onset of T2DM identified at three follow-up assessments as described above. Incidence rate ratios (IRRs) and 95% CIs are reported. Hierarchical models were conducted as follows: adjustment for age in Model 1; with additional adjustment for waist circumference (Janiszewski et al., 2007) in Model 2; and baseline

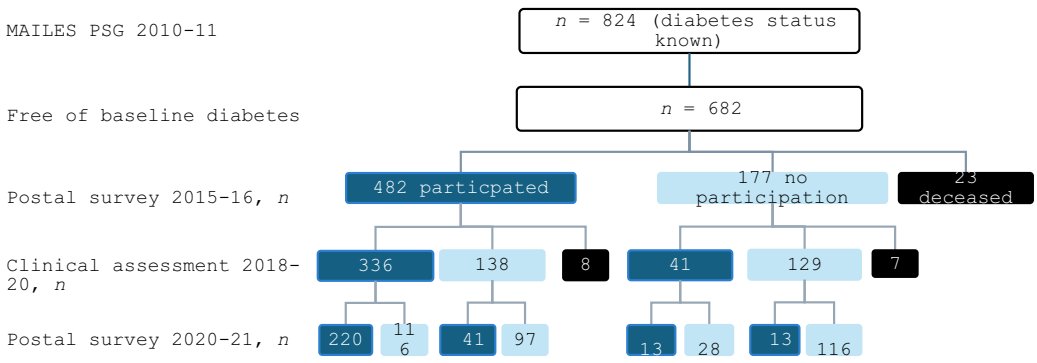

FIGURE 1 Flow diagram of the study and follow-up assessments in 837 participants who underwent a home-based eight-channel sleep study in 2010–2011 of whom 824 participants had information on diabetes status. Dark blue boxes indicate participation in follow-up data collection stage, light blue indicates non-participation, and black boxes indicate numbers of deceased participants. MAILES, Men Androgens Inflammation Lifestyle Environment and Stress study; PSG, polysomnography.

fasting plasma glucose, and total testosterone were added in Model 3. Multivariable Poisson regression assumptions were tested, including multicollinearity. All variance inflation factors values were acceptable (maximum observed was <1.3) indicating minimal multicollinearity.

Given the small number of incident T2DM cases, we could not perform moderation analyses for OSA treatment status. As an alternative, sensitivity analyses were undertaken excluding participants with adequate OSA treatment.

Missing data on covariates of interest were waist circumference (n = six, replaced with temporally closest measure [which was the PSG night measure in three cases]), glucose (n = six, imputed based on the mean of available values in the PSG sub-study sample, i.e., n = 812), and total testosterone (n = 37). Given the relationship of sex hormones with adiposity, missing cases were replaced with the waist circumference category-specific mean testosterone values available on the PSG sub-study sample (n = 767).

4 | RESULTS

Of the 837 men at baseline with a valid PSG study, data on baseline diabetes status was available in 824 men of whom 142 had pre-existing diabetes. Of the remaining 682 men, 23 were determined to be deceased prior to the first follow-up in 2015/2016 leaving 659 for inclusion in the analysis. As shown in the study flow diagram (Figure 1), of these 659 men, 81.3% (n = 536) participated in at least one of three follow-up assessments, while 123 men completed none (including 15 identified as deceased after the 2015–2016 assessment and prior to the commencement of the 2018–2020 clinical assessment based upon data linkage until December 2018). Of these 536 participants, incident T2DM (n = 52, 9.7%) was identified based upon participation in at least one of three follow-up assessments, and 484 were free of T2DM, based upon a mean (SD, range) follow-up period of 8.3 (1.8, 3.5–10.5) years.

Analysis of responder bias (Table S1) showed that of men free of diabetes at baseline, those participating in at least one follow-up assessment had better self-rated health, were more likely to be in the 55–64-year age group, and report better socioeconomic position at baseline than non-participants. No significant differences were observed in relation to PSG metrics.

Table 1 shows the characteristics of the participants who were free of baseline diabetes overall and in relation to OSA severity (AHI) categories. The mean (range) age of participants was 60.1 (41.6–87.2) years. High rates of overweight or obesity were observed (79.2% with BMI ≥25.0 kg/m^2, and 58.5% with waist circumference ≥95 cm) and hypertension (49.4%) was common. However, behavioural risk factors (current smoking, high-risk alcohol use and lack of physical activity) were infrequently reported. At least mild OSA (AHI ≥10 events/h) was present in 49.8%, while moderate-to-severe (AHI ≥20 events/h) occurred in 22.8%, with severe OSA, AHI ≥30 events/h present in 9.6%. Excessive daytime sleepiness was uncommon (11.7%), but 45.7% of the sample reported poor subjective sleep quality (PSQI scores >5). The mean (SD) PSG recorded sleep time was 376 (58) min and 57.2% reported at least 7 h of sleep in the past month (PSQI assessed), while short sleep (<6 h) was infrequently reported (14.6%). Both overall OSA severity, as measured by AHI, and REM-specific OSA severity (Table S2) were positively associated with age, adiposity, and hypertension, but not fasting glucose concentration.

4.1 | Demographic and health characteristics associated with incident T2DM

Individuals who were found to have incident T2DM were more likely to be in the 60–69 years age range, experiencing household financial stress, and with higher adiposity, higher concentration of plasma glucose and HbA1c, and lower concentration of total testosterone at baseline (Table 2). Based on crude mean values of covariates for those with and without incident T2DM (shown in Table 2), the Cohen's d estimates suggest at least medium effects for testosterone 0.48 (95% CI 0.19, 0.77), large effects for waist circumference −0.74 (95% CI −1.03, −0.45) and very large effects for glucose −1.16 (95% CI −1.46, −0.869).

4.2 | Sleep and PSG characteristics associated with incident T2DM

As shown in Table 3, significantly higher median values of AHI_{REM}, TST90, HBI, delta index and lower levels of oxygen saturation metrics were observed in those with incident T2DM compared to participants who remained free of T2DM. The Cohen's d estimate for the normally distributed mean oxygen saturation was 0.46 (95% CI 0.17, 0.75) (based on a 0.74 percentage point difference in mean [SD] oxygen saturation for no T2DM 94.06 [1.63] versus incident T2DM 93.32 [1.57]). There were no significant differences in relation to total AHI, $AHI_{non\text{-}REM}$, ODI (3% or 4% desaturations), or total arousal index. Similarly, there were no differences in measures of sleep architecture, insomnia symptoms, sleep quality, or excessive daytime sleepiness between those with and without the subsequent onset of T2DM.

4.3 | Adjusted associations of PSG measures with incident T2DM

In Poisson regression analyses (Table 4), age-adjusted associations of incident T2DM with AHI_{REM} ≥20 events/h, and highest quartile values of TST90, HBI and delta index, and lower quartile groups of mean oxygen saturation were observed. After additional adjustment for waist circumference, the associations with AHI_{REM} ≥20 events/h, mean oxygen saturation and the delta index persisted. With further adjustment for baseline glucose and total testosterone, the association with AHI_{REM} was attenuated; however, the IRRs for incident T2DM associated with mean oxygen saturation and delta index remained elevated. When PSG variables were entered as continuous

TABLE 1 Demographic, health, and polysomnographic characteristics of the sample overall and in relation to obstructive sleep apnea severity.

	AHI <10 events/h $n = 271$	AHI 10–19 events/h $n = 141$	AHI 20–29 events/h $n = 73$	AHI ≥30 events/h $n = 49$	p	Total, $N = 536$
Demographic factors						
Age, years, mean (SD)	58.8 (9.7)	60.0 (10.5)	63.4 (9.9)	63.1 (11.0)	0.001	60.1 (10.2)
% (*n*)						
Highest education – high school	18.5 (50)	19.1 (27)	17.8 (13)	15.7 (8)	0.96	18.3 (98)
Financial stress (spend ≥ earn)	12.5 (34)	19.1 (27)	17.8 (13)	17.6 (9)	0.29	15.5 (83)
Chronic disease risk factors						
Adiposity, mean (SD)						
Waist circumference, cm	97 (11)	97 (11)	102 (11)	104 (10)	0.002	98 (11)
Body mass index, kg/m^2	27.7 (3.7)	28.2 (4.2)	29.8 (4.1)	30.7 (4.4)	<0.001	28.4 (4.1)
Fasting glucose, mmol/L, mean (SD)	5.08 (0.52)	5.04 (0.53)	5.17 (0.68)	5.24 (0.65)	0.11	5.10 (0.56)
% (*n*)						
Smoking status					0.77	
Ex-smoker	45.0 (122)	46.1 (65)	43.8 (32)	56.9 (29)		46.3 (248)
Current smoker	18.1 (49)	14.9 (21)	17.8 (13)	13.7 (7)		16.8 (90)
Alcohol: moderate–very high risk	5.9 (16)	12.8 (18)	6.9 (5)	3.9 (2)	0.059	7.7 (41)
Physical activity–sedentary	22.6 (60)	20.0 (28)	20.8 (1)5	26.0 (13)	0.83	22.0 (116)
Triglyceride ≥1.7 mmol/L	35.4 (96)	29.9 (41)	34.2 (25)	36.7 (18)	0.70	34.0 (180)
Comorbidities						
Hypertension	40.9 (110)	54.0 (74)	64.4 (47)	61.2 (30)	<0.001	49.4 (261)
Cardiovascular disease	11.1 (30)	9.9 (14)	19.2 (14)	15.7 (8)	0.18	12.3 (66)
Depressive symptoms	12.2 (32)	16.2 (22)	5.7 (4)	16.0 (8)	0.16	12.3 (66)
Sleep and polysomnographic factors						
PSQI score >5, % (*n*)	50.4 (131)	39.0 (53)	40.3 (29)	47.9 (23)	0.13	45.7 (236)
ESS score >10, % (*n*)	11.1 (30)	12.9 (18)	9.7 (7)	14.0 (7)	0.84	11.7 (62)
Total sleep time[a], min, mean (SD)	375 (61)	371 (53)	382 (55)	383 (57)	0.45	376 (58)
Median (IQR)						
AHI, events/h	5.7 (3.39, 8.1)	14.3 (11.9, 16.9)	24.4 (22.3, 26.8)	44.1 (36.7, 50.7)	<0.001	9.9 (5.6, 19.0)
AHI_{REM}[b], events/h	8.2 (4.7, 16.1)	16.5 (9.2, 27.5)	22.8 (11.5, 35.8)	41.1 (25.8,62.0)	<0.001	13.5 (6.3, 25.6)
AHI_{NREM}, events/h	4.71 (2.3, 7.1)	13.5 (10.5, 16.6)	24.29 (21.2, 28.0)	45.9 (37.1, 52.9)	<0.001	9.3 (4.6,18.4)
TST90, %	0.17 (0.00, 1.08)	0.68 (0.14, 2.32)	2.20 (0.39, 5.7)	7.5 (1.66, 15.42)	<0.001	0.56 (0.04, 3.38)
Mean SaO_2, %	93.79 (92.65, 95.13)	93.61 (92.15, 94.90)	93.08 (92.11, 94.42)	92.86 (91.47, 93.76)	<0.001	93.55 (92.26, 94.82)
Lowest SaO_2, %	88 (85, 90)	86 (83, 88)	82 (78, 86)	78 (72, 84)	<0.001	86 (82, 89)
Hypoxic burden index, %	0.62 (0.0, 3.61)	1.86 (0.29, 5.57)	5.30 (0.87, 12.90)	14.71 (4.59, 25.01)	<0.001	1.64 (0.13, 9.03)

TABLE 1 (Continued)

	AHI <10 events/h $n = 271$	AHI 10–19 events/h $n = 141$	AHI 20–29 events/h $n = 73$	AHI ≥30 events/h $n = 49$	*p*	Total, $N = 536$
Delta index, %	0.85 (0.74, 0.98)	1.08 (0.90, 1.21)	1.29 (1.12, 1.49)	1.78 (1.45, 2.25)	<0.001	0.99 (0.82, 1.26)
ODI 3%/h	3.6 (2.1, 6.2)	11.2 (8.0, 14.2)	19.1 (15.3, 22.5)	40.0 (30.6, 45.3)	<0.001	7.4 (3.4, 14.8)
ODI4 %/h	1.6 (0.7, 3.4)	6.2 (3.9, 8.8)	11.7 (7.4, 14.7)	29.0 (20.7, 37.4)	<0.001	3.9 (1.4, 8.9)

Abbreviations: AHI, apnea–hypopnea index; ESS, Epworth Sleepiness Scale; IQR, interquartile range; ODI, oxygen desaturation index; PSQI, Pittsburgh Sleep Quality Index; (N)REM, (non-) rapid eye movement; SaO_2, oxygen saturation; SD, standard deviation; TST90, total sleep time with oxygen saturation <90%.

Note: Hypertension: systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg or medication; Depressive symptoms score of >12 on the Beck Depression Inventory or ≥21 on the Center for Epidemiological Studies Depression Scale or treatment. Cardiovascular disease: self-reported records of myocardial infarction, angina, stroke, and transient ischaemic attack or identified from public hospital administrative data using International Classification of Diseases-10 codes I21, I25, I40, I46, I47, I48 and I49, I50, I51, and I52.

[a]From polysomnography.

[b]≥20 min REM sleep, $n = 516$.

variables, similar findings were observed; however, the HBI showed significant independent associations with incident T2DM (Table 5).

4.4 | Sensitivity analyses

When participants self-reporting CPAP use of ≥4 h/night, MAS use, or surgery for OSA ($n = 32$) were excluded from the analysis (leaving 446 men including 44 incident T2DM cases), we observed significant associations of incident T2DM with lower quartiles of oxygen saturation, the highest quartile of delta index and TST90 (Table 4) after adjustment for age, waist circumference, and baseline fasting glucose and total testosterone concentrations. Similar findings were observed when PSG variables were entered as continuous variables, with an additional association seen with the HBI; however, TST90 was no longer significant (Table 5).

5 | DISCUSSION

In this study of middle-aged and older community dwelling men free of T2DM at baseline, nocturnal oxygen saturation metrics (mean and variability) were associated with incident T2DM over a mean (range) follow-up of 8.3 (3.5–10.5) years. The association of moderate-to-severe REM OSA with incident T2DM was attenuated after adjustment for fasting glucose and testosterone concentrations at baseline. No crude association was seen with OSA severity as measured by the AHI, or ODI (3% or 4%). An independent association of the HBI (Chen et al., 2018) with T2DM incidence was inconsistent and evident only when considered as a continuous variable. When we excluded men with OSA considered adequately treated, these findings generally persisted. As expected, baseline glucose, testosterone, and central adiposity were also significant predictors of incident T2DM, emphasising the importance of adjusting for these potential confounders in analyses examining OSA–diabetes associations.

The potential importance of REM sleep- predominant OSA for endocrine function is supported by cross-sectional human and animal model studies (Varga & Mokhlesi, 2019). Our findings with AHI_{REM} in models prior to adjustment for baseline glucose and testosterone are consistent with the association reported by Kendzerska et al. (2014) in a large clinical cohort. Ding et al. (2021) reported an association of incident T2DM with a PSG phenotype characterised by frequent events in REM sleep with hypoxia, which was attenuated after adjusting for adiposity. Although the evidence is limited, longitudinal data suggest that REM OSA is not a strong independent predictor of incident T2DM.

Consistent with recent findings by Wojeck et al. (2023) in the DREAM Study of United States Veterans, we have shown that hypoxaemia/nocturnal oxygen saturation and not frequency of respiratory event-related metrics of OSA (i.e., AHI) were predictors of incident T2DM. In earlier cluster analyses in the DREAM Study, the association of incident T2DM was seen in a group with a PSG-derived OSA

TABLE 2 Sociodemographic and biomedical correlates of incident type 2 diabetes mellitus (T2DM).

Variable	No T2DM ($n = 484$)	Incident T2DM ($n = 52$)	p
Sociodemographic factors			
% (n)			
Age, years			0.014
≤59	54.3 (263)	42.3 (22)	
60–69	27.1 (131)	46.2 (24)	
≥70	18.6 (90)	11.5 (6)	
Highest education – high school or less	17.6 (85)	25.0 (13)	0.19
Family financial status			0.005
Financial stress (spending ≥ earnings)	13.8 (67)	30.8 (16)	
Some surplus, saved or spent	60.1 (291)	46.2 (24)	
Saves a lot	26.0 (126)	23.1 (12)	
Marital status-married/partner	83.7 (405)	78.8 (41)	0.38
Biomedical factors			
% (n)			
Smoking status			0.26
Non-smoker	38.0 (184)	26.9 (14)	
Ex-smoker	45.2 (219)	55.8 (29)	
Current smoker	16.7 (81)	17.3 (9)	
Alcohol use – intermediate–very high risk	7.2 (35)	11.8 (6)	0.25
Physical activity level – Sedentary	21.8 (104)	23.1 (12)	0.84
Waist circumference, cm			<0.001
<95	44.1 (211)	11.5 (6)	
95–101	22.2 (106)	32.7 (17)	
≥102	33.7 (161)	55.8 (29)	
Body mass index, kg/m^2			0.004
<25	21.1 (102)	7.7 (4)	
25–29	49.4 (239)	42.3 (22)	
≥30	29.5 (143)	50.0 (26)	
Triglyceride ≥1.7 mmol/L	26.4 (125)	37.3 (19)	0.098
Depression/treatment	12.6 (59)	14.3 (7)	0.73
Hypertension[a]	48.7 (232)	55.8 (29)	0.34
Cardiovascular disease[b]	12.2 (59)	13.5 (7)	0.79
Mean (standard deviation)			
Waist circumference, cm	97.6 (11)	105.8 (11.3)	<0.001
Body mass index, kg/m^2	28.1 (4.0)	30.7 (4.2)	<0.001
Glucose, mmol/L	5.0 (0.5)	5.7 (0.6)	<0.001
Glycated haemoglobin, %	5.6 (0.4)	5.8 (0.3)	<0.001
Total testosterone, nmol/L	17.2 (5.8)	14.5 (4.9)	0.002

[a]Hypertension –systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg or medication use;
[b]Cardiovascular disease: self-reported records of myocardial infarction, angina, stroke, and transient ischaemic attack or identified from public hospital administrative data using International Classification of Diseases-10 codes I21, I25, I40, I46, I47, I48 and I49, I50, I51, and I52.

phenotype characterised by frequent hypopneic events and hypoxia, a high BMI and high baseline glucose levels (Ding et al., 2021). In a community-based study in Japan (Muraki et al., 2010), an ODI 3% ≥15 and nadir oxygen saturation were associated with incident T2DM, adjusted for pre-diabetes status but TST90 was not; however, the highest category of TST90 was relatively low at ≥0.8% (66th percentile for participants with >0% duration of oxygen saturation <90%).

TABLE 3 Sleep characteristics in relation to incident type 2 diabetes mellitus (T2DM) status.

	No T2DM ($n = 483$)	Incident T2DM ($n = 52$)	p
Median (IQR)			
AHI, events/h	9.87 (5.45, 18.9)	11.3 (6.9, 20.9)	0.20
AHI_{REM}[a], events/h	13.0 (6.2, 24.5)	20.2 (8.0, 37.1)	0.012
AHI_{NREM}, events/h	9.24 (4.41, 18.1)	10.5 (5.9, 20.3)	0.32
ODI 3%/h	7.2 (3.4, 14.7)	10.0 (3.6, 16.4)	0.157
ODI 4%/h	3.8 (1.3, 8.4)	5.6 (1.7, 10.4)	0.110
TST90, %	0.54 (0.03, 2.92)	1.97 (0.18, 7.93)	0.004
Mean SaO_2, %	94.09 (93.15, 95.27)	93.63 (92.25, 94.49)	0.001
Mean SaO_2 REM[a], %	94.09 (92.80, 95.28)	93.55 (92.05, 94.41)	0.007
Mean SaO_2 NREM, %	93.98 (93.00, 95.17)	93.50 (91.95, 94.44)	0.003
Lowest SaO_2, %	87.0 (82.0, 89.0)	84 (79.5, 88.0)	0.012
Hypoxia burden index, %	1.56 (0.12, 7.30)	4.96 (0.47, 21.02)	0.005
Delta Index, %	0.97 (0.81, 1.23)	1.13 (0.93, 1.52)	0.001
Arousal Index	16.8 (12.8, 21.9)	16.7 (14.0, 21.9)	0.70
Mean (SD)			
TST, min	375 (58)	384 (57)	0.30
N1, %	14.6 (6.2)	15.2 (6.0)	0.52
N2, %	54.6 (9.4)	54.7 (8.5)	0.97
N3, %	15.7 (8.8)	15.7 (9.6)	0.97
REM, %	14.8 (4.9)	14.3 (5.9)	0.50
%, (*n*)			
Insomnia symptoms[b] ≥3 times/week			
Sleep initiation difficulty	10.8 (52)	17.3 (9)	0.16
Sleep maintenance difficulty	52.6 (252)	57.7 (30)	0.48
≥1 difficulty	54.2 (262)	59.6 (31)	0.46
≥1 difficulty + fatigue	12.8 (62)	7.7 (4)	0.28
PSQI score >5	45.7 (214)	45.8 (22)	0.99
ESS score >10	12.3 (59)	5.9 (3)	0.18
OSA treatment			0.18
No OSA diagnosis	70.6 (305)	57.4 (27)	
CPAP ≥4 h, MAS, surgery	6.7 (29)	6.4 (3)	
Untreated or CPAP <4 h	22.7 (98)	36.2 (17)	

Abbreviations: AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; MAS, mandibular advancement splint; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index; (N)REM, (non-)rapid eye movement sleep; SaO_2, oxygen saturation; T2DM, type 2 diabetes mellitus; TST90, percentage total sleep time with oxygen saturation <90%.

[a]≥20 min REM sleep, $n = 516$.

[b]Insomnia symptoms – PSQI questions 5a/5b: during the past month have you had trouble sleeping because you …(a) 'cannot get to sleep within 30 min?', (b) 'wake up in the middle of the night or early morning?' Fatigue – SF-36 Vitality score at least one SD below the mean.

Bold values statistically significant at $p < 0.05$.

The definitions and methods of calculating parameters provide different information about sleep-related hypoxaemia (He et al., 2023). Sample participant characteristics, such as clinical or community-based samples, baseline co-morbidities, diabetes definitions, survivor effects, as well as sample variable distributions, may also influence published findings. Assuming a linear relationship between PSG metrics and diabetes may not be valid for all metrics and applying arbitrary cut-offs for metrics to address non-linearity may not fully resolve this issue. These factors may be particularly contributing to the inconsistency in the reported associations of different parameters of oximetry with T2DM across different studies in various populations. Adjusted associations of T2DM incidence with a HBI (Chen et al., 2018) in our study were present when used as a continuous variable but not when the variable was quartiled. Respiratory

TABLE 4 Type 2 diabetes mellitus (T2DM) incidence in relation to polysomnography (PSG) metrics over a mean follow-up period of 8.3 years and Poisson regression analysis of PSG variables associated with incident T2DM.

	All participants ($n = 536$)								Participants with OSA treatment[b] excluded ($n = 447$)	
			Model 1		*Model 2*		*Model 3*			
Variable	Incident T2DM ($n = 52$), % (n)	p	IRR (95% CI)	p	IRR (95% CI)	p	IRR (95% CI)		IRR (95% CI)	p
AHI, events/h		0.79								
<10	9.2 (25)		1.0		1.0		1.0		1.0	
10–19	9.2 (13)		1.0 (0.5–1.9)	0.96	1.1 (0.6–2.1)	0.78	1.2 (0.7–2.2)	0.52	1.1 (0.6–2.0)	0.42
≥20	11.3 (14)		1.2 (0.7–2.3)	0.54	1.0 (0.5–1.8)	0.94	0.8 (0.4–1.4)	0.36	0.9 (0.5–1.8)	0.79
AHI_{REM}, events/h[a]		0.004								
<20	6.6 (22)		1.0		1.0		1.0		1.0	
≥20	14.2 (26)	1	2.1 (1.2–3.6)	0.006	1.8 (1.05–3.1)	0.031	1.4 (0.8–2.5)	0.19	1.5 (0.8–2.7)	0.18
TST90 ≥75th percentile		0.002								
<3.9%	7.5 (31)		1.0		1.0		1.0		1.0	
≥3.9%	16.9 (21)		2.1 (1.3–3.6)	0.004	1.6 (0.9–2.7)	0.086	1.6 (0.9–2.6)	0.091	1.9 (1.1–3.4)	0.029
ODI 3%/h		0.45								
<5	7.7 (14)		1.0		1.0		1.0		1.0	
5–15.9	10.0 (23)		1.3 (0.7–2.4)	0.42	1.1 (0.6–2.1)	0.74	1.1 (0.6–1.8)	0.86	1.0 (0.6–1.7)	0.95
≥16.0	12.0 (15)		1.5 (0.8–3.1)	0.22	1.1 (0.6–2.3)	0.70	1.0 (0.5–2.1)	0.94	1.2 (0.5–2.8)	0.60
ODI (4%) >75th percentile[e]		0.20								
≤1.5 (<25th)	7.9 (11)		1.0		1.0		1.0		1.0	
1.5–9.9 (25th–74th)	9.6 (27)		1.2 (0.6–2.4)	0.25	1.0 (0.5–2.0)	0.93	1.0 (0.6–1.8)	0.96	1.0 (0.5–1.8)	0.95
≥10.0 (≥75th)	12.3 (14)		1.6 (0.7–3.3)	0.56	1.2 (0.5–2.5)	0.70	1.0 (0.5–2.2)	0.94	1.3 (0.5–3.1)	0.59
Mean oxygen saturation percentage, <25th percentile[f]		0.001								
≤92.99 (<25th)	15.9 (20)		5.4 (1.9–15.6)	0.002	3.3 (1.1–9.8)	0.029	4.2 (1.7–10.3)	0.029	4.0 (1.7–9.4)	0.001
93.00–95.08 (25th–74th)	10.5 (28)		3.6 (1.3–10.1)	0.015	2.5 (0.9–7.0)	0.089	2.7 (1.1–6.6)	0.026	2.4 (1.1–5.5)	0.033
≥95.09 (≥75th)	2.8 (4)		1.0		1.0		1.0		1.0	
Delta Index ≥75th percentile[d]		0.004								
≤0.83 (<25th)	4.8 (7)		1.0		1.0		1.0		1.0	
0.84–1.29 (25th–74th)	9.2 (25)		1.9 (0.9–4.3)	0.11	1.6 (0.7–3.5)	0.29	1.5 (0.8–3.0)	0.25	1.6 (0.8–3.3)	0.22
≥1.30 (≥75th)	17.1 (20)		3.4 (1.5–7.8)	0.003	2.4 (1.02–5.7)	0.045	2.1 (0.95–4.6)	0.066	2.6 (1.1–6.2)	0.028
Hypoxia burden index ≥75th percentile[c]										
≤0.16 (<25th)	6.3 (9)	0.007	1.0		1.0		1.0		1.0	

TABLE 4 (Continued)

Variable	All participants ($n = 536$)						Participants with OSA treatment[b] excluded ($n = 447$)	
	Incident T2DM ($n = 52$), % (n)	*p*	*Model 1* IRR (95% CI)	*p*	*Model 2* IRR (95% CI)	*p*	*Model 3* IRR (95% CI)	IRR (95% CI)	*p*
0.17–10.13 (25th–74th)	8.2 (22)		1.2 (0.6–2.6)	0.56	1.0 (0.5–2.1)	0.98	1.1 (0.6–2.0)	0.87	0.9 (0.5–1.8)	0.85
≥10.14 (≥75th)	16.9 (21)		2.5 (1.2–5.2)	0.017	1.6 (0.7–3.4)	0.25	1.5 (0.8–3.0)	0.22	1.7 (0.8–3.4)	0.16

Abbreviations: AHI, apnea–hypopnea index; CI, confidence interval; IRR, incidence rate ratio; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; REM, rapid eye movement sleep; SaO_2, oxygen saturation; T2DM, type 2 diabetes mellitus; TST90, percentage total sleep time with oxygen saturation <90%.

[a]Restricted to participants with ≥20 min of REM sleep (incident T2DM $n = 48$, $N = 516$ in model). NB incident T2DM % REM AHI <10, 10–19 and ≥20 events/h = 6.3%, 7.2% and 14.2%, respectively. *Model 1* adjusted for age. *Model 2* adjusted for age, waist circumference, baseline glucose and testosterone. *Model 3* adjusted for age, waist circumference, baseline glucose and testosterone.

[b]Participants reporting continuous positive airway pressure use >4 h/night, mandibular advancement splint use, or surgery for OSA. REM AHI model restricted to participants with ≥20 min of REM sleep (incident T2DM $n = 41$, $N = 430$).

[c]Total sample incident T2DM prevalence according to the second, and third quartile of the hypoxia burden index = 8.1% and 8.4%, respectively.

[d]Total sample incident T2DM prevalence according to the second, and third quartile of the delta index = 8.6% and 9.9%, respectively.

[e]Total sample incident T2DM prevalence according to the second, and third quartile of the ODI (4%) = 6.6% and 13.0%, respectively.

[f]Total sample incident T2DM prevalence according to the second, and third quartile of the mean oxygen saturation = 10.2% and 10.9%, respectively.

event-related hypoxic burden has been reported as having better performance than the AHI in predicting cardiovascular outcomes and mortality (Martinez-Garcia et al., 2023). However, the term 'hypoxic burden' has been used to refer to several different metrics calculated based upon varying criteria and it is unclear how important these are for risk stratification. It has been noted that there is 'some confusion in the reproducibility of the hypoxic burden calculation' (He et al., 2023). Azarbarzin et al. (2019) calculated the area under the desaturation curve from pre-event baseline saturation over the TST, and have reported hypoxic burden outperformed T90 in predicting CVD mortality in patients from the Sleep Heart Health Study. In contrast, Trzepizur et al. (2022) compared the performance of the ODI, T90, and hypoxic burden in predicting major adverse cardiovascular events, and concluded that T90 performed better, and Linz et al. (2020) found that both traditional and novel nocturnal oxygen saturation metrics had limited predictive utility for identifying cardiovascular outcomes in the SAVE study. Our method for determining hypoxic burden calculated the total desaturation area of oxygen saturation <90% for the TST and is not respiratory event specific (Chen et al., 2018) but it is uncertain how important this in relation to diabetes. T90 has also been strongly associated with the development of T2DM in patients with moderate–severe OSA (Labarca et al., 2019) and a clinical cohort referred for sleep studies (Kendzerska et al., 2014). In a recent small study in a sleep laboratory sample (Thanaviratananich et al., 2022), another measure of hypoxaemia independent of respiratory events or a threshold level, the hypoxic load (HL 100), was cross-sectionally associated with fasting plasma glucose. We also found an association between incident T2DM and lower levels of mean oxygen used either as a continuous variable or based on a population distribution rather than a threshold. Of note, the cut-off for the lower quartile of mean oxygen saturation was 93%, which is the threshold previously reported as a predictor of mortality in women (Terrill et al., 2018).

A metric of oxygen saturation variability that is not specifically event related, the delta index, has received little attention since it was first described (Levy et al., 1996; Olson et al., 1999). We found a strongly elevated risk of T2DM associated with a delta index >75th percentile, which was modestly attenuated when adjusted for glucose and testosterone. Given the small incident T2DM sample size of 52, and that statistical significance persisted after we excluded participants whose OSA was considered adequately treated from the analysis, we suggest that this finding is still important. In our sample the AHI and delta index were highly correlated (Spearman's rho 0.675), yet we observed no association of the AHI with incident T2DM, again suggesting a more prominent role of nocturnal hypoxaemia in T2DM onset. The evidence suggests that nocturnal hypoxaemia is important, but given the several 100 metrics generated by PSG (that are highly skewed in non-clinical populations), and the low incidence of diabetes in community-based samples, future work could benefit from the advantages of using machine learning techniques (Rajula et al., 2020). Compared to traditional statistical methods, machine learning techniques are not limited by traditional statistical model assumptions, they are suitable when there are few observations and many possible predictors, and importantly, do not rely on a priori selection of predictor variables and can therefore utilise the large number of PSG metrics that may provide additional insight into diabetes risk.

TABLE 5 Poisson regression analysis of polysomnographic variables (continuous) associated with incident type 2 diabetes mellitus ($n = 52$) after mean follow-up of 8.3 years.

	All participants ($N = 536$)						Participants with OSA treatment[b] excluded ($n = 447$)	
	Model 1		*Model 2*		*Model 3*			
Polysomnography metric	**IRR (95% CI)**	***p***	**IRR (95% CI)**	***p***	**IRR (95% CI)**	***p***	**IRR[a] (95% CI)**	***p***
AHI, events/h	1.010 (0.994–1.025)	0.213	1.003 (0.988–1.019)	0.676	0.994 (0.976–1.013)	0.553	1.004 (0.980–1.030)	0.728
AHI_{REM}, events/h*	1.016 (1.004–1.028)	0.007	1.010 (0.997–1.022)	0.121	1.002 (0.987–1.017)	0.787	1.007 (0.988–1.026)	0.461
TST90	1.021 (1.006–1.036)	0.005	1.013 (0.998–1.029)	0.096	1.009 (0.990–1.028)	0.351	1.014 (0.992–1.036)	0.210
ODI 3%/h	1.013 (0.997–1.029)	0.123	1.005 (0.988–1.022)	0.581	0.998 (0.979–1.018)	0.854	1.009 (0.983–1.035)	0.524
ODI 4%/h	1.016 (0.998–1.033)	0.076	1.007 (0.989–1.026)	0.466	1.000 (0.997–1.023)	0.998	1.015 (0.985–1.046)	0.338
Mean oxygen saturation	0.788 (0.694–0.895)	<0.001	0.865 (0.749–1.00)	0.049	0.860 (0.751–0.984)	0.028	0.827 (0.719–0.951)	0.008
Delta Index, %	1.382 (1.091–1.752)	0.007	1.213 (0.938–1.569)	0.141	1.181 (0.873–1.597)	0.280	1.691 (1.034–2.765)	0.036
Hypoxia burden index, %	1.024 (1.014–1.034)	<0.001	1.018 (1.007–1.028)	<0.001	1.015 (1.006–1.024)	0.007	1.015 (1.006–1.024)	<0.001

Abbreviations: AHI, apnea–hypopnea index; CI, confidence interval; IRR, incidence rate ratio; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; REM, rapid eye movement sleep; TST90, percentage total sleep time with oxygen saturation <90%.

Note: *Model 1* adjusted for age. *Model 2* adjusted for age and waist circumference. *Model 3* adjusted for age, waist circumference, glucose, and total testosterone.

[a]Adjusted for age, waist circumference, glucose, and total testosterone. Model for AHI_{REM} restricted to participants with ≥20 min of REM sleep* (incident T2DM $n = 48$, $N = 516$ in model; in model with OSA treatment excluded incident T2DM $n = 41$, $N = 430$ in model).

[b]479 participants responding to questions about OSA treatment at follow-up assessments, $n = 32$ participants reported continuous positive airway pressure average use of ≥4 h/night, mandibular advancement splint use or surgery for OSA.

Outcomes of incident analyses may be time dependent and influenced by responder bias and survivor effects. In the present analyses, cohort participants undertaking follow-up assessments reported marginally better self-rated health than non-participants, and men aged ≥70 years (7.7%) had similar rates of T2DM onset as those aged <60 years (6.3%) and the at-risk group were those aged 60–69 years (15.5%). The recent study by Siddiquee et al. (2023) demonstrated associations of at least moderate–severe OSA with incident T2DM after 8 years of follow-up, which were not present in the analysis of the 4-year follow-up data.

The strengths of our study include baseline diabetes assessment based on an objective assessment of fasting glucose and HbA1c, doctor diagnosis or anti-diabetic medication. We also used a conservative modelling approach for small incident case numbers. Our study has limitations, and our results should be interpreted with caution. At the time of the first follow-up assessment after the PSG study, participants had been involved in the study cohorts for 10–15 years. Follow-up data were completely missing on 146 men (including 23 who were already deceased at the first follow-up) and this is a limitation of the study. However, where it is possible to identify response rates, ours (any participation by ~80%) is not dissimilar to studies we have cited including 92% obtained in annual CVD surveys as part of a prospective Japanese stroke prevention study (Muraki et al., 2010), 91% in a study using administrative clinical data (Xu et al., 2019), 82.5% in a Swedish population study (Lindberg et al., 2012), and 58% for participation in both the 4- and 8-year follow-up of the Korean Genome and Epidemiology Study (Siddiquee et al., 2023). A blood measure of diabetes was not obtained on all participants in the 2018–2020 follow-up; however, we triangulated incident T2DM at the three follow-ups based on glucose, HbA1c, anti-diabetic medication use, and self-report of doctor-diagnosed diabetes given that blood measures may misclassify participants whose diabetes is controlled by medication or diet alone. The validity of self-report of diabetes has been demonstrated in a number of studies (Comino et al., 2013). We were unable to exclude from the analyses diabetes cases that developed after the clinical testing in 2007–2010 and before the sleep study, that may have been misclassified as incident cases. Furthermore, subjective reports of OSA treatment in our study may not reflect objectively determined use. We categorised participants self-reporting the use of CPAP <4 h/night as being untreated and although it unlikely this level of use influenced glycaemic control, their retention in the sensitivity analysis may have underestimated the strength of the associations observed. Exclusion of men considered adequately treated further reduced the analytical sample (446 including, 44 incident cases). Chronic obstructive pulmonary disease is a risk factor for diabetes onset via factors including smoking, inflammation, hypoxaemia, physical activity impairment, and corticosteroid use (Rogliani et al., 2015). We were unable to control for respiratory disease. However, incident T2DM was independent of smoking history and smoking-related lung disease was uncommon in this sample (data not shown). The findings in our study of men may not be generalisable to women, as worse beta-cell function has been demonstrated in men with OSA compared to women, which may impart a greater risk of T2DM in men (Temple et al., 2018). There is some evidence of a bi-directional relationship between diabetes and OSA; however, we were not able to examine the possibility of diabetes conferring an increased risk of OSA (Ceron et al., 2015; Subramanian et al., 2019),.

In conclusion, our findings suggest that nocturnal oxygen saturation metrics, but not event-related metrics (AHI, ODI) are important in the development of T2DM. We have accounted for baseline glucose status, the best biological predictor of diabetes, and testosterone, and not doing so is a limitation of previous studies. There is a need for individual participant level analysis of diabetes incidence in merged study cohorts that provides adequate female representation while increasing statistical power when limited incident cases are available in individual cohorts. Future work should utilise machine learning approaches to more systematically identify PSG predictors of diabetes, and also assess the contribution of the derived respiratory event-related hypoxic burden to diabetes development; however, understanding the underlying OSA pathophysiology (endotypes) that generates the hypoxaemia may provide important opportunities for diabetes prevention and improved glycaemic control.

PARTICIPANT CONSENT STATEMENT

All participants provided written informed consent for the conduct of biomedical measures, and self-completed surveys including postal and on-line surveys.

AUTHOR CONTRIBUTIONS

Sarah L. Appleton: Conceptualization; funding acquisition; data curation; writing – original draft; writing – review and editing; formal analysis. **Ganesh Naik:** Writing – review and editing; software; resources. **Duc Phuc Nguyen:** Software; resources; writing – review and editing. **Barbara Toson:** Formal analysis; writing – review and editing. **Bastien Lechat:** Conceptualization; writing – review and editing. **Kelly Loffler:** Conceptualization; writing – review and editing. **Peter G. Catcheside:** Data curation; writing – review and editing. **Andrew Vakulin:** Data curation; writing – review and editing. **Sean A. Martin:** Data curation; writing – review and editing. **Gary A. Wittert:** Funding acquisition; writing – review and editing; conceptualization. **Robert J. Adams:** Funding acquisition; writing – review and editing; writing – original draft; conceptualization.

ACKNOWLEDGEMENT

Open access publishing facilitated by Flinders University, as part of the Wiley - Flinders University agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

The Men, Androgens, Inflammation, Lifestyle, Environment and Stress (MAILES) Study was supported by the National Health and Medical Research Council (NHMRC) of Australia (grant numbers NHMRC 627227 and 1122342), the Hospital Research Foundation Group, and Freemasons Centre for Male Health and Wellbeing.

CONFLICT OF INTEREST STATEMENT

Barbara Toson reports an Early Career Fellowship from the National Health and Medical Research Council of Australia and research grants and equipment support from Withings outside of the submitted work. Duc Phuc Nguyen reports grant support unrelated to this work from the National Health and Medical Research Council of Australia. Robert J. Adams reports grant support from the National Health and Medical Research Council of Australia, the Flinders Foundation and Hospital Research Foundation and equipment support from Philips RS North America outside of the submitted work. Andrew Vakulin receives grant support from the National Health and Medical Research Council of Australia, the Flinders Foundation and Hospital Research Foundation, and equipment support from Philips RS North America outside of the submitted work. Gary A. Wittert has received research funding (Lawley, Bayer, Lilly) and speaker (Besins, Bayer) and consultancy (Elsevier) fees outside of the submitted work. Peter G. Catcheside reports grant support unrelated to this work from the National Health and Medical Research Council of Australia, Australian Government Defence of Defence, Flinders University, REDARC, Flinders Foundation and a Flinders University collaboration grant with Compumedics Ltd. and equipment support unrelated to the submitted work from Withings, CREMedical and Philips. Sarah L. Appleton reports grant support from the Flinders Foundation and Hospital Research Foundation outside of the submitted work. Bastien Lechat, Ganesh Naik, Kelly Loffler, Sean A. Martin have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Appleton, S. L., Naik, G., Nguyen, D. P., Toson, B., Lechat, B., Loffler, K., Catcheside, P. G., Vakulin, A., Martin, S. A., Wittert, G. A., & Adams, R. J. (2025). Associations of polysomnographic measures of obstructive sleep apnea, and nocturnal oxygen saturation with incident type 2 diabetes mellitus in middle-aged and older men. *Journal of Sleep Research*, *34*(3), e14357. https://doi.org/10.1111/jsr.14357