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The association of obstructive sleep apnea (OSA) and nocturnal hypoxemia with the development of abnormal HbA1c in a population cohort of men without diabetes

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ABSTRACT

Aim: To examine the relationship between indices of undiagnosed OSA and the development of abnormal glycaemic control in community-dwelling men free of diabetes.
Methods: The Men, Androgens, Inflammation, Lifestyle, Environment, and Stress (MAILES) Study is a population-based cohort study in Adelaide, South Australia. Clinic visits at baseline (2002–06) and follow-up (2007–10) identified abnormal glycaemic metabolism [HbA1c 6.0 to <6.5% (42 to <48 mmol/mol)] in men without diabetes. At follow-up (2010–11), $n = 837$ underwent assessment of OSA by full in-home unattended polysomnography (Embletta X100).
Results: Development of abnormal glycaemic metabolism over 4–6 years ($n = 103$ "incident" cases, 17.0%) showed adjusted associations [odds ratio (95% CI)] with the 1st [1.7 (0.8–3.8)], 2nd [2.4 (1.1–4.9)], and 3rd [2.3 (1.1–4.8)] quartiles of mean oxygen saturation (SaO_2) compared to the highest quartile. Prevalent abnormal glycaemic metabolism ($n = 140$, 20.8%) was independently associated with the third and fourth quartiles of percentage of sleep time with oxygen saturation <90% and lowest quartile of mean SaO_2. Linear regression analysis showed a significant reduction in HbA1c [unstandardized B, 95% CI: −0.02 (−0.04, −0.002), $p = 0.034$] per percentage point increase in mean SaO_2. OSA as measured by the apnea-hypopnea index showed no adjusted relationship with abnormal glycaemic metabolism.

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Conclusions: Development of abnormal glycaemic metabolism was associated with nocturnal hypoxemia. Improved management of OSA and glycaemic control may occur if patients presenting with one abnormality are assessed for the other.

1. Introduction

Obstructive sleep apnea (OSA) is a condition characterized by repeated total or partial closure of the upper airway during sleep, leading to recurrent falls in arterial oxygen saturation (SaO_2), arousals and sleep fragmentation. The prevalence of OSA is increasing in line with that of obesity and has been reported to be present in up to 50% of men aged over 40 years [1,2]. OSA has been associated with glucose intolerance and insulin resistance in cross-sectional studies from clinic [3] and population-based samples [4–7]. A measure of glycaemic control, glycated hemoglobin (HbA1c) is an independent predictor of future cardiovascular morbidity and mortality [8,9] and has been associated with subclinical atherosclerosis [10] in people without diabetes.

A significant, independent cross-sectional association has been reported between OSA and HbA1c levels in people *without diabetes* referred to sleep clinics [11,12]. However, with clinic-based samples there is the possibility that referral bias related to the severity of both OSA and co-morbidities may influence the association of OSA with HbA1c. Thus, the applicability of these findings to the general population is unproven, and the paucity of data evaluating the association between OSA severity and HbA1c in populations without diabetes [12] or in the context of a population sample or within a ''healthy'' check-up in a primary care population has been identified as a limitation of the evidence to date [11].

It is also unclear if polysomnographic (PSG) indices, such as hypoxia, are better associated with glycaemic control than the apnea-hypopnea index (AHI) [13]. Sleep oxygen desaturation has been associated with fasting hyperglycaemia (at levels of desaturation as low as 2%) [14] and impaired glucose tolerance [4,7] and in samples without diabetes, with elevated HbA1c [11,12] and decreased insulin sensitivity [5]. There is also conflict in relation to the role of sleepiness in the association of OSA and glucose metabolism. Studies have reported an independent association of severe OSA (but not hypoxemia) and insulin resistance without diabetes only in patients who report excessive sleepiness [15]. However, others have found no metabolic differences among sleepy and non-sleepy OSA patients [12,16–20].

Our aim, using data from a population-based cohort of men aged 40 years and over without a prior diagnosis of OSA, was to examine the cross-sectional relationship between undiagnosed OSA and abnormal glycaemic control [HbA1c 6.0 to <6.5% (42 to<48 mmol/mol)] in men without diabetes mellitus. We also determined the relationship of other PSG characteristics (oxygen saturation/desaturation and arousals) with HbA1c levels and the association between undiagnosed OSA with the development of abnormal glycaemic control over the previous 4–6 years.

2. Subjects, materials and methods

2.1. Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study is comprised of randomly selected community dwelling men aged at least 40 years and has been described previously [21]. Initial random recruitment by electronic white pages and computer assisted telephone interviews (CATI) occurred in 2000–02. Biomedical assessment was conducted in two hospital-based clinics, using standardized and reproducible study protocols. Detailed demographic, biographical, self-reported co-morbidities, and risk factor information was collected via a self-completed questionnaire. Data for the current analyses were derived from assessments in 2002–06 (MAILES 1), 2007–10 (MAILES 2) and in 2010–11 (MAILES CATI and PSG studies). The study was approved by the North West Adelaide Health Service and the Royal Adelaide Hospital institutional ethics committees, and all subjects gave written informed consent.

2.2. Sleep data

At follow-up, MAILES study participants completed a CATI survey in August 2010 (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. Of these, a random sample of 1000 men were chosen for inclusion, and in 2010–11, subjects underwent 8-channel in-home unattended polysomnography (Embletta X100, Embla Systems, Colorado) to measure EEG, EOG, EMG, nasal pressure, thoracic and abdominal effort, oximetry, body position, and limb movements. By the conclusion of the study period 857 had undergone PSG testing. Trained staff visited study participants in their homes to set-up and attach the sleep study equipment. Failed studies were repeated if possible. The Epworth Sleepiness Scale (ESS) [22] was administered and measurements of height, weight, neck, waist circumference (WC) and a record of current medications were also taken. A physician investigator coordinated any necessary clinical follow-up.

A single experienced sleep technician, who was blinded to all other survey or biomedical data, performed manual scoring of all home PSGs according to 2007 AASM (alternate) criteria [23]. Fortnightly meetings were held with three other sleep technicians to discuss and review difficult studies. Concordance testing of four technicians scoring on random samples of PSGs throughout the study period showed good agreement within statistical control limits on Bland–Altman plots for the apnea hypopnea index, sleep onset, sleep efficiency and total sleep time. The study sleep technician also participated in

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quarterly external QSleep scoring concordance assessments, a national external proficiency testing program (www.qsleep.com.au), where performance was consistently within the middle two quartiles of national assessments. Studies were considered acceptable with 3.5 h of sleep and 5.5 h of total recorded study time. Apneas were defined as cessations of nasal flow lasting ≥10 s and hypopneas 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 apnea hypopnea index (AHI) ≥10/h of sleep, with further categorisation; mild: AHI of 10–19/h, moderate: 20–29/h, and severe: ≥30/h. These cut points were also used to identify OSA in rapid eye movement (REM) sleep. The 2007 AASM alternate criteria were used as these were recommended for use in prospective epidemiological studies by the AASM [24] and by an expert panel of the Australasian Sleep Association [25]. The cut-offs for classification were chosen because Ruehland et al. have shown that an AHI of 5/h of sleep used to define sleep disordered breathing scored by the ''recommended'' AASM criteria is equivalent to an AHI of 10/h of sleep using the alternate AASM definition, and 15/h using the older 1999 criteria [26]. In order to maintain comparability with previous work a cut-off of 10/h was chosen. We used the number of oxygen desaturation measurements of 3% or more per h (3% oxygen desaturation index [ODI 3%]) as the indicator of nocturnal intermittent hypoxia, with ODI 3% ≥16 events per h, corresponding to moderate-to-severe nocturnal intermittent hypoxia. Similarly, we used percentage of sleep time with oxygen saturation <90% (TST90) as the indicator for nocturnal hypoxia.

2.3. Sample profile

The obesity prevalence in the MAILES sleep study sample was identical to national data [27]. Self-selection bias was examined by comparing those who underwent a sleep study with those men in the MAILES cohort who did not. Sleep study participants (n = 857, included 20 unsuccessful studies) did not differ from non-participants in frequency of sleep symptoms (sleepiness, snoring, waking frequently) or socio-economic status (data not shown) but were on average younger (mean age 59.7y vs 61.6y), and less likely to have a low income (<$AUD 40,000) compared with non-participants. They were on average less obese (BMI 28.4 kg/m^2 [SD 4.2] vs 29.3 kg/m^2 [5.0]) and were less likely to report poor-to-fair general health (13.1% vs 21.7%).

2.4. Clinic assessment

Clinic assessment at baseline and follow-up included measurement of blood pressure, height, weight, and waist circumference and a fasting blood sample was drawn for glucose, glycated hemoglobin (HbA1c) and lipid measurement. Participants with diabetes mellitus were excluded from the present analyses based upon having at least one of the following criteria: fasting plasma glucose (FPG) ≥7.0 mmol/L; HbA1c of ≥6.5% (≥48 mmol/mol); self-reported physician diagnosis of diabetes; treatment for diabetes using linkage to Pharmaceutical Benefits Scheme data recorded in the six months prior to MAILES participant study clinic visits using Anatomical Therapeutic Chemical code A10. Abnormal glycaemic metabolism was defined as an HbA1c of 6.0 to <6.5% (42 to <48 mmol/mol), given data demonstrating markedly increased long-term cardiovascular risk among people without diabetes and with a baseline HbA1c level of >6.0% [8,9].

2.5. Risk factors

Self-completed questionnaires determined smoking status and recreational physical activity levels [21]. Body mass index (kg/m^2, weight/height squared) and waist circumference (WC, cm) were categorized according to international criteria: BMI- underweight/normal ≤24.9, overweight 25.0–29.9, and obesity: ≥30.0; WC- normal <95 cm, overweight 95–101 cm, obese ≥102 cm [28]. Questionnaires assessed sleep-related issues including usual sleep hours and engagement in shift work.

2.6. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS Inc, Chicago, IL, USA). Abnormal glycaemic metabolism (HbA1c 6.0 to <6.5; 42 to <48 mmol/mol) was identified at baseline and follow-up and the univariate associations of prevalent and incident HbA1c 6.0 to <6.5 with different follow-up PSG indices of OSA including clinical categories of AHI, oxygen desaturation index 3% (ODI 3% ≥16/h [29]), and quartiles of ODI 3%, percentage of total sleep time with oxygen desaturation <90% (TST90), total arousal index (ArI), and mean oxygen saturation (SaO_2) were determined with Chi^2 tests. Logistic regression analyses identified associations of prevalent and recently developed HbA1c 6.0 to <6.5 with these categorical PSG variables adjusted for variables including age, waist circumference and medication use, income, marital status and physical inactivity (if $p < 0.25$ at the univariate level). Linear regression analysis determined relationships between PSG variables (mean oxygen saturation, ArI and log transformed AHI, and ODI) adjusted for age, waist circumference and other confounders including excessive daytime sleepiness (ESS scores) smoking, shift work for at least 3 months, physical inactivity, sleep hours, and use of one or more of antidepressant, statin, beta-blocker, or oral steroid therapies. Analysis of covariance computed mean HbA1c levels in relation to PSG variable categories adjusted for confounders as above.

3. Results

3.1. Cross-sectional analysis of factors associated with abnormal glycaemic control

Of the 837 men who completed a sleep study, diabetes status was known in 824, and 673 (81.7%) of these men had no antecedent physician diagnosis of diabetes, were not receiving treatment for diabetes and did not have either a fasting plasma glucose (FPG) ≥7.0 mmol/L or an HbA1c of ≥6.5%. Abnormal glycaemic metabolism (HbA1c 6.0 to <6.5%) was found in n = 140 (20.8%) of these men without diabetes (''prevalent'' cases). Compared to men with HbA1c <6.0%,

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Table 1 – Characteristics [% (n)] of sleep study participants without diabetes identified with prevalent and incident abnormal glycaemic metabolism (HbA1c 6.0 to <6.5).

	Prevalent			Incident		
	No glycaemic control problem (n = 533)	HbA1c 6.0 to <6.5 (n = 140)	p	Never glycaemic control problem (n = 503)	HbA1c 6.0 to <6.5 (n = 103)	
Age, years			0.001			0.003
≤50	29.5 (157)	20.0 (28)		48.1 (242)	36.9 (38)	
51–64	44.1 (235)	37.1 (52)		39.4 (198)	37.9 (39)	
≥65	26.5 (141)	42.9 (60)		12.5 (63)	25.2 (26)	
Annual household income			0.04			0.12
Not stated	3.8 (20)	5.8 (8)		1.0 (5)	1.9 (2)	
<$40,000	24.5 (129)	35.0 (48)		32.4 (163)	42.7 (44)	
$40,000 to $79,000	36.6 (193)	32.1 (44)		45.1 (227)	34.0 (35)	
≥$80,000	35.1 (185)	27.0 (37)		21.5 (108)	21.4 (22)	
Highest education			0.27			0.40
High school or less	26.8 (143)	30.0 (42)		26.8 (135)	28.2 (29)	
Diploma/Trade certificate	58.0 (309)	60.0 (84)		57.3 (288)	61.2 (63)	
University	15.2 (81)	10.0 (14)		15.9 (80)	10.7 (11)	
Not Married/no partner	19.7 (105)	17.1 (24)		19.5 (98)	13.7 (14)	0.17
Waist circumference, cm			0.001			0.026
≤94	44.7 (238)	30.7 (43)		39.4 (198)	32.4 (33)	
95–101	23.3 (124)	20.0 (28)		27.5 (138)	20.6 (21)	
≥102	32.1 (171)	49.3 (69)		33.1 (166)	47.1 (48)	
Body mass index (kg/m^2)			0.048			0.30
≤24.9	25.3 (135)	19.3 (27)		26.5 (133)	19.4 (20)	
25.0–29.9	47.1 (251)	42.9 (60)		49.4 (248)	52.4 (54)	
≥30.0	27.6 (147)	37.9 (53)		24.1 (121)	28.2 (29)	
Waist circumference change ≥5.0 cm	16.2 (86)	16.5 (23)	0.91	16.1 (81)	16.7 (17)	0.89
Family history of diabetes	28.9 (154)	26.4 (37)	0.56	27.4 (138)	24.3 (25)	0.51
Physically Inactive	22.9 (119)	21.0 (29)	0.64	24.9 (119)	32.7 (32)	0.11
Smoking status			0.69			0.60
Never	37.3 (197)	33.8 (47)		39.2 (197)	34.0 (35)	
Current	45.1 (238)	48.9 (68)		20.5 (103)	21.4 (22)	
Former	17.6(93)	17.3 (24)		40.4 (203)	44.7 (46)	
Medication use[a] ≥1	18.8 (64)	34.3 (37)	0.001	18.4 (58)	35.5 (27)	0.001
Epworth Sleepiness Scale ≥11	12.3 (65)	9.4 (13)	0.33	12.1 (60)	9.7 (10)	0.50
Hours of sleep			0.11			0.57
≤5	15.2 (81)	14.3 (20)		14.7 (74)	17.5 (18)	
6–8	82.9 (441)	80.7 (113)		83.5 (419)	79.6 (82)	
≥9	1.9 (10)	5.0 (7)		1.8 (9)	2.9 (3)	
Shift worker ≥3 months	31.9 (170)	35.7 (50)	0.39	32.2 (162)	34.0 (35)	0.73

Epworth sleepiness, usual sleep hours and shift work were obtained at follow-up only.
[a] Medications including beta-blockers, anti-depressants, statins and oral steroids.

those with HbA1c 6.0 to <6.5% were significantly more likely to be older, have lower levels of household income, have central obesity, and be using medications associated with weight gain (Table 1). No relationship was seen with excessive daytime sleepiness, sleep hours or shift work.

Prevalent abnormal glycaemic metabolism (HbA1c 6.0 to <6.5%) showed significant univariate associations with OSA severity (but not REM OSA severity), increasing quartiles of ODI 3% and TST90, and the lowest quartiles of mean SaO_2 (Table 2). In multiple logistic regression models, only the relationships with TST90 quartiles of 0.7% to 3.7% and ≥3.8% (compared to 0 to <0.05%), and mean SaO_2 quartiles of 93.9% to 92.9% and ≤92.8% (compared with ≥95.0%) persisted after adjustment for important confounders including age, central obesity, medication use and income. The relationship with severe OSA approached statistical significance (p = 0.076).

Linear regression of HbA1c against PSG indices in men without diabetes (Table 3) showed a significant decrease in HbA1c per percentage point increase in SaO_2 after adjustment for confounding variables. The significant correlations of HbA1c with $\log_{10}$ transformed AHI and ODI 3% were confounded by age, and central obesity. Consistent with findings when ArI was categorized, no significant correlation of HbA1c with ArI as a continuous variable was observed (r = 0.06, p = 0.15).

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Table 2 – Prevalent HbA1c 6.0- < 6.5% in relation to apnea-hypopnea index (AHI) during all sleep and rapid eye movement (REM) sleep, oxygen desaturation (≥3%) index (ODI), and quartiles of arousal index (ArI), ODI 3%, percentage time with oxygen saturation <90% (TST90) and mean oxygen saturation (SaO_2) and odds ratios [OR, 95% confidence interval (CI)] for HbA1c 6.0- < 6.5%.

Prevalent HbA1c 6.0 to <6.5% (*n* = 140)			
	% (*n*)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
OSA severity (AHI)	*p* = 0.03		
No OSA (<10)	18.7 (64)	1.0	1.0
Mild (10–19)	22.0 (37)	1.2 (0.7–1.9)	1.1 (0.7–1.8)
Moderate (20–29)	16.8 (16)	0.6 (0.3–1.2)	0.6 (0.3–1.2)
Severe (≥30)	33.8 (23)	1.7 (0.94–3.1)	1.7 (0.9–2.9)
REM OSA severity (AHI_{REM})	*p* = 0.62		
No OSA (<10)	19.9 (52)	1.0	
Mild (10–19)	22.9 (33)	1.1 (0.7–1.9)	
Moderate (20–29)	17.8 (16)	0.8 (0.4–1.6)	
Severe (≥30)	24.3 (27)	1.0 (0.6–1.8)	
ODI (3%)	*p* = 0.10		
<16	19.3 (99)	1.0	
≥16	25.3 (40)	1.2 (0.7–1.8)	
Quartiles ArI	*p* = 0.63		
Lowest	17.9 (30)	1.0	
2nd	19.8 (33)	1.3 (0.7–2.3)	
3rd	21.8 (38)	1.4 (0.8–2.4)	
Highest	23.3 (38)	1.3 (0.7–2.2)	
ODI (3%)	*p* = 0.042		
Lowest	14.3 (27)	1.0	1.0
2nd	25.1 (44)	1.7 (1.0–3.0)	1.7 (1.0–3.0)
3rd	19.9 (32)	1.3 (0.7–2.3)	1.3 (0.7–2.3)
Highest	24.5 (36)	1.5 (0.8–2.6)	1.5 (0.8–2.6)
TST90 Quartiles	*p* = 0.005		
Lowest	13.4 (24)	1.0	1.0
2nd	18.3 (32)	1.3 (0.7–2.3)	1.6 (0.8–2.9)
3rd	23.9 (39)	1.7 (0.93–3.0)	1.8 (1.0–3.3)
Highest	28.4 (44)	1.7 (0.95–3.1)	1.8 (1.0–3.4)
Mean O_2 saturation	*p* = 0.003		
Lowest	29.0 (45)	1.9 (1.0–3.4)	1.9 (1.0–3.5)
2nd	22.9 (38)	1.6 (0.9–3.0)	1.7 (0.9–3.1)
3rd	19.2 (33)	1.5 (0.8–2.7)	1.5 (0.8–2.7)
Highest	12.8 (23)	1.0	1.0

Model 1 adjusted for age and waist circumference.
Model 2 adjusted for age and waist circumference, medication use, and income.
ODI percentiles 25th: 3.7665, 50th: 8.2894, 75th: 16.3339.
TST 90 percentiles 25th: 0.0563, 50th: 0.6917, 75th: 3.8747.
Mean O_2 saturation percentiles 25th: 92.8137, 50th: 93.8665, 75th: 95.0307.

Table 3 – Linear regression analysis of PSG variables associated with HbA1c in participants without diabetes.

	R	*p*	Model 1[a]			Model 2[b]			Model 3[c]		
			B (95% CI)]	Beta	*p*	B (95% CI)]	Beta	*p*	B (95% CI)]	Beta	*p*
Log AHI	0.117	<0.01	0.08 (0.01, 0.16)	0.09	0.03	0.05 (−0.03, 0.12)	0.059	0.22			
Mean O_2 saturation	−0.196	<0.01	−0.04 (−0.05, −0.02)	−0.16	<0.01	−0.03 (−0.04, −0.01)	−0.11	<0.01	−0.02 (−0.04, −0.002)	−0.09	0.034
Log ODI	0.091	0.02	0.14 (−0.01, 0. 29)	0.16	0.07	0.05 (−0.10, 0.21)	0.03	0.51			
Total arousal index	0.057	0.15	0.002 (−0.002, 0.005)	0.03	0.38	0.001 (−0.002, 0.005)	0.03	0.49			

[a] Model 1: Adjusted for age.
[b] Model 2: Model 1 plus waist circumference.
[c] Model 3: Model 2 plus Epworth Sleepiness Scale score, shift work, smoking, recreational physical activity, sleep hours, medication use.

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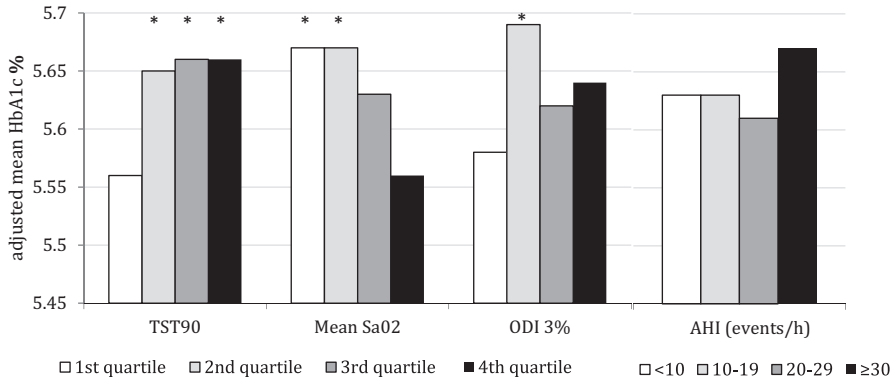

Fig. 1 – Mean HbA1c % in relation to percentage of total sleep time with oxygen saturation (SaO_2) <90% (TST90), mean SaO_2 and oxygen desaturation index (ODI 3%) and apnea hypopnea index (AHI) in men without diabetes adjusted for age, waist circumference, smoking, epworth sleepiness scale scores, medications associated with weight gain, shift work and income. Asterix indicates significant differences compared to 1st quartiles of TST90 and ODI 3% and 4th quartile of mean SaO_2. ANCOVA TST90: F (3, 616) = 2.72, p = 0.04; Mean SaO_2: F (3, 615) = 2.87, p = 0.04; ODI 3%: F (3, 615) = 2.98, p = 0.03, AHI severity categories: F (3, 616) = 0.33, p = 0.81

Consistent with these findings, Fig. 1 shows that the adjusted mean follow-up HbA1c levels were (1) significantly higher in the second to fourth quartiles of TST90, and the second quartile of ODI 3% compared to the 1st quartiles for these parameters and (2) significantly lower for the bottom two quartiles of mean SaO_2 compared to the highest quartile. Mean adjusted HbA1c levels were not significantly different by clinical categories of OSA although HbA1c was elevated in severe OSA.

3.2. *Longitudinal analysis of factors associated with the development of abnormal glycaemic control*

In the 824 men with sleep studies, $n = 606$ were without diabetes and had HbA1c levels <6.0% at baseline (4–6 years earlier). Of these, 103 men (17.0%) had developed abnormal glycaemic metabolism (HbA1c 6.0 to <6.5%) without diabetes at follow-up (''incident'' cases). Compared to men with HbA1c levels consistently <6.0%, incident cases were similar to prevalent cases and were significantly more likely to be older and have central obesity, and be using medications associated with weight gain (Table 1). Incident abnormal glycaemic metabolism showed significant univariate associations with PSG measures of severe OSA and low mean SaO_2 only (Table 4). In logistic regression models, only the relationship with lower quartiles of SaO_2 persisted after adjustment for confounding factors. No association with ArI was observed.

4. Discussion

In an unselected cohort sample of community-dwelling men aged at least 40 years and free of diabetes mellitus, current mean nocturnal oxygen saturation, was significantly associated with current HbA1c levels as well as the development of abnormal glycaemic metabolism over a 4–6 year follow-up period after adjustment for age, waist circumference, smoking, physical inactivity, daytime sleepiness, shift work and hours of sleep. Abnormal HbA1c (prevalent and incident) was more likely in those in the severe category of the standard OSA metric, the apnea-hypopnea index, but these associations did not reach statistical significance after adjustment for confounders. Given the evidence that HbA1c at values above 6.0% (42 mmol/mol) accurately predicts long-term risk of subsequent cardiovascular disease and future diabetes in middle-aged adults without diabetes [8,9], and the high prevalence of OSA in our population, the present findings suggest a substantial future burden of cardiovascular disease in men related to nocturnal hypoxemia (and possibly severe OSA).

Our results are consistent with putative pathophysiological mechanisms linking OSA to diabetes mellitus. Animal and laboratory studies have shown untreated OSA may contribute to the development of disturbed glucose metabolism via oxidative stress caused by chronic intermittent hypoxemia [30,31], sleep deprivation [32], hemodynamic disturbances and alterations in sympathetic activity [33]. Our finding that nocturnal oxygen level has a linear relationship with HbA1c is a good indicator that hypoxia from sleep-disordered breathing plays a predominant role in disturbed glucose metabolism and consequent associated cardiovascular risk without diabetes.

Our finding that mean nocturnal oxygen saturation is associated with HbA1c in men without diabetes is consistent with those of Priou et al., who found AHI and nocturnal hypoxia (TST90, ODI 3% and mean SaO_2) were associated with a HbA1c between 6.0% and less than 6.5% [11]. Kent et al. also found both ODI and severe OSA were independently associated with a HbA1c ≥6.0%, where the relationship was stronger for nocturnal hypoxemia than sleep related events, among a large study of sleep clinic patients without diabetes [12]. However, these studies were performed in clinic-based samples, with the possibility that the severity of OSA and referral bias with the severity of co-morbidities may influence the association of OSA with HbA1c. We were unable to find previously published studies showing a cross-sectional or longitudinal association of sleep-disordered breathing and

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Table 4 – Incident HbA1c 6.0 to <6.5% in relation to apnea-hypopnea index (AHI) during all sleep and rapid eye movement (REM) sleep, oxygen desaturation (≥3%) index (ODI), and quartiles of arousal index (ArI), ODI 3%, percentage time with oxygen saturation <90% (TST90) and mean oxygen saturation (SaO_2) and odds ratios [OR, 95% confidence interval (CI)] for HbA1c 6.0 to <6.5%.

Incident HbA1c 6.0 to <6.5% (n = 103)			
	% (n)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
OSA severity (AHI)	p = 0.03		
No OSA (<10)	15.5 (48)	1.0	1.0
Mild (10–19)	17.1 (26)	1.1 (0.6–1.8)	1.3 (0.7–2.1)
Moderate (20–29)	12.3 (10)	0.6 (0.3–1.2)	0.6 (0.3–1.3)
Severe (≥30)	29.7 (19)	1.8 (0.93–3.3)	1.6 (0.8–3.3)
REM OSA severity (AHI)	p = 0.68		
No OSA (<10)	17.2 (41)	1.0	
Mild (10–19)	16.3 (20)	0.9 (0.5–1.6)	
Moderate (20–29)	12.7 (10)	0.6 (0.3–1.3)	
Severe (≥30)	19.4 (20)	1.0 (0.5–1.8)	
ODI (3%)	p = 0.15		
<16	15.7 (73)	1.0	
≥16	20.9 (29)	1.2 (0.7–1.9)	
ArI Quartiles	p = 0.65		
Lowest	15.0 (23)	1.0	
2nd	15.4 (24)	1.2 (0.6–2.2)	
3rd	17.2 (26)	1.3 (0.7–2.4)	
Highest	20.0 (29)	1.3 (0.7–2.4)	
ODI (3%) Quartiles	p = 0.184		
Lowest	12.3 (21)	1.0	
2nd	19.6 (31)	1.5 (0.8–2.8)	
3rd	15.9 (23)	1.2 (0.6–2.2)	
Highest	20.6 (27)	1.4 (0.7–2.8)	
TST90 Quartiles	p = 0.137		
Lowest	11.9 (20)	1.0	
2nd	16.9 (27)	1.4 (0.7–2.6)	
3rd	17.9 (26)	1.3 (0.7–2.6)	
Highest	22.0 (29)	1.5 (0.7–2.9)	
Mean O_2 saturation Quartiles	p = 0.010		
Lowest	20.5 (27)	1.9 (0.9–4.0)	1.7 (0.8–3.8)
2nd	20.9 (31)	2.4 (1.2–4.8)	2.4 (1.1–4.9)
3rd	18.5 (30)	2.3 (1.2–4.6)	2.3 (1.1–4.8)
Highest	8.6 (14)	1.0	1.0

Model 1 adjusted for baseline age and waist circumference.
Model 2 adjusted for baseline age and waist circumference, medication use, income, marital status and physical activity.
ODI percentiles 25th: 3.7665, 50th: 8.2894, 75th: 16.3339.
TST 90 percentiles 25th: 0.0563, 50th: 0.6917, 75th: 3.8747.
Mean O_2 saturation percentiles 25th: 92.8137, 50th: 93.8665, 75th: 95.0307.

HbA1c in unselected population-based adult samples. Our findings show the potential scope of the problem of future cardio-metabolic risk in the community associated with unrecognized OSA and highlight the importance of clinicians in primary care being aware of the potential of the metabolic risks associated with undiagnosed sleep apnea in men, irrespective of the presence of daytime sleepiness.

We found no relationship with sleep fragmentation as assessed by the arousal index. This is consistent with previous work showing the severity of intermittent hypoxia, but not arousal frequency, is associated with glucose intolerance and insulin resistance [4]. Older studies in sleep clinic populations have suggested that impaired glucose metabolism was more prominent in OSA patients with excessive daytime sleepiness [15,34]. Our data is consistent with recent work showing no relationship between subjective daytime sleepiness as measured by the ESS and HbA1c [12] however, ESS sleepiness was uncommon in our cohort preventing stratified analyses by sleepiness. In addition, REM OSA has recently been associated with (1) increasing levels of HbA1c in people with diabetes [35] and (2) the development of hypertension in a population-based study [36]. However, we found no relationship between REM OSA and elevated HbA1c levels, suggesting different features of OSA present different cardio-metabolic risks.

Study limitations include the conduct of sleep studies only at follow-up of the cohort which limited us to cross-sectional analyses and examining retrospective associations of the development of glycaemic control problems. Given that this is

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a study of men only, the generalisability of these findings to women is uncertain. Strengths of our study include our population-based sample of randomly recruited, community dwelling men, and the use of current AASM criteria to categorize hypopneas (3% desaturations) for all participants.

In conclusion, we have found in a community sample of middle-aged and older men without diabetes, that nocturnal hypoxemia was independently associated with the recent development impaired glycaemic metabolism. In addition, severe OSA showed a borderline relationship with levels of HbA1c that may place men at risk of developing diabetes and cardiovascular disease in the future. Further work is needed to determine if treating OSA in these men, irrespective of the presence of daytime sleepiness, will reduce risk of developing diabetes or mitigate cardiovascular risks associated with HbA1c $\geq$6.0% (42 mmol/mol) in those without diabetes. Regardless of that however, given the high prevalence of both conditions together, consideration should be given to expanding the 2008 International Diabetes Federation Task-force recommendation so that clinicians managing OSA or men ''at risk'' for metabolic abnormalities should incorporate screening methods to ensure that a patient presenting with one abnormality/disorder is assessed for the other [37].

Conflict of interest

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Author contributions

Study concept and design: G.W., R.A., A.T.; Acquisition of funding: G.W., R.A., A.T., D.M.; Acquisition of data: A.V., P.C., R.A., S.M., J.G.; Statistical analysis: S.A., P.C.; Interpretation of data: All authors. Drafting of the manuscript: R.A., S.A.

Critical revision of the manuscript for important intellectual content: All authors. All authors have approved the final article.

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