



Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: the ESADA study

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ABSTRACT Obstructive sleep apnoea (OSA) is associated with increased risk of dysglycaemia but the intimate link of these conditions with obesity makes discerning an independent relationship between them challenging. Glycosylated haemoglobin (HbA1c) levels predict adverse cardiovascular outcomes in nondiabetics but there is a lack of population-level data exploring the relationship of HbA1c with OSA.

A cross-sectional analysis of 5294 participants in the multinational European Sleep Apnoea Cohort (European Sleep Apnoea Database) study was performed, assessing the relationship of OSA severity with HbA1c levels in nondiabetic subjects, with adjustment for confounding factors.

HbA1c levels correlated significantly with OSA severity in univariate analysis. Following adjustment for confounding factors, apnoea-hypopnoea index (AHI) (standardised β 0.158; $p < 0.001$), along with nocturnal hypoxaemia, predicted HbA1c. Adjusted mean HbA1c levels were lower in the lowest AHI quartile (5.24%, 95% CI 5.21–5.27%) than in the second (5.37%, 95% CI 5.34–5.40%), third (5.44%, 95% CI 5.41–5.47%) or highest (5.50%, 95% CI 5.46–5.53%) quartiles. Subjects in the higher quartiles had significantly greater adjusted odds ratios of HbA1c level $\geq 6.0\%$ than those in the first quartile. In stratified analyses, OSA severity predicted glycaemic health irrespective of sleep study modality, sex, obesity or daytime sleepiness.

OSA severity independently predicts glycaemic health in nondiabetic subjects. Further studies should assess the impact of OSA treatment on glycaemic health and elucidate underlying mechanisms.



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Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent disorder affecting at least 4% of men and 2% of women in developed countries [1]. OSA is characterised by sleep disordered breathing, whereby collapse of the upper airway during sleep leads to airflow obstruction, recurrent hypoxaemia and reoxygenation, sympathetic overactivity, and microarousals from sleep. Patients with OSA experience excess daytime sleepiness, impaired cognitive function and reduced quality of life. Of more relevance from a physical health perspective, however, is the relationship between sleep disordered breathing and cardiometabolic comorbidities [2]. There is strong evidence that OSA independently relates to prevalent and incident systemic hypertension [3–5], and growing evidence of an independent association with incident coronary artery disease [6], stroke [7], and overall cardiovascular morbidity and mortality [8]. OSA patients are also at increased risk of metabolic dysfunction [9], but the intimate relationship between OSA and obesity has made the definitive identification of any independent role for OSA here difficult.

Type 2 diabetes mellitus (T2DM) is associated with increased risk of cardiovascular disease and death [10], while glycaemic health, as measured by glycosylated haemoglobin (HbA1c), predicts cardiac mortality in nondiabetic subjects [11]. The relationship between OSA and glycaemic health is a topic of increasing clinical and research interest [12]. Community-based studies have suggested that the presence and severity of OSA are independent predictors of insulin resistance [13] and T2DM prevalence [14]. Furthermore, successful initiation of continuous positive airway pressure (CPAP) therapy may be associated with improved insulin sensitivity [15] and reduced HbA1c levels [16], suggesting a potential contributory role for sleep disordered breathing in dysglycaemia.

However, there is a relative paucity of data examining the relationship of OSA with validated long-term cardiovascular mortality risk markers such as HbA1c in nondiabetic subjects. To address these issues, we examined the relationship between OSA and glycaemic health, as measured by HbA1c levels, in a large patient population without an antecedent diagnosis of diabetes attending sleep clinics across Europe. Some of the results of these studies have been previously reported in the form of an abstract [17].

Methods

The European Sleep Apnoea Cohort (European Sleep Apnoea Database (ESADA)) study is a pan-European, multicentre, prospective study involving 24 sleep clinics across 15 European countries and Israel. The rationale and investigative techniques underlying the establishment of ESADA has been discussed in detail previously [18]. The overall objective of the study is the evaluation of a large cohort of subjects with suspected sleep disordered breathing, in order to identify associations with glycaemic health, metabolic disease, and cardiovascular morbidity and mortality. ESADA employs a web-based collection platform to facilitate transfer of data from individual centres to the central database at the University of Gothenburg (Gothenburg, Sweden) [18].

Subjects

Enrolment for ESADA commenced in March 2007, with subjects recruited up to July 2012 included in the present study. All subjects aged 18–80 years referred for assessment at participating centres were considered eligible for enrolment in ESADA, unless they met one of the three principal exclusion criteria: treatment of pre-diagnosed OSA syndrome (OSAS) with CPAP or a dental device, severe comorbidity conferring limited life expectancy, and alcohol or drug abuse within 1 year of inclusion. A detailed discussion of the data collection protocols is reported elsewhere [18], but key data recorded for each patient included demographic, anthropometric and clinical variables, including body mass index (BMI), waist/hip ratio, smoking history, alcohol intake, and details of comorbidities and medication use. Subjects had blood drawn for measurement of HbA1c levels. Research ethics committee approval for the study was obtained at each of the participating centres.

Sleep data

Either cardiorespiratory polygraphy or full polysomnography were performed according to local practice. Polygraphic recordings included a minimum of four recording channels (level 3 devices according to the American Academy of Sleep Medicine (AASM)) and, as a minimum, the following variables were recorded: analysed time, subjective sleep time, apnoea–hypopnoea index (AHI) and oxyhaemoglobin desaturation index (ODI), and mean oxygen saturation measured by pulse oximetry (SpO_2) and the lowest SpO_2 [19]. PSG

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studies comprised the following variables in addition to those indicated for polygraphic recordings: total sleep time, sleep efficiency, sleep staging and respiratory disturbance index. Scoring rules applied in ESADA were those proposed by the AASM in 2007 [20]. In a polygraphic recording, a hypopnoea event was scored if there was a $\geq 50\%$ decrease in the amplitude of a valid measure of airflow during sleep (with an associated 3% desaturation), or the combination of a $\geq 30\%$ reduction in airflow with $\geq 4\%$ reduction in SpO_2 , with a minimum event duration of 10 s. In a PSG study, in addition to the criteria above, a $\geq 50\%$ decrease in airflow associated with an arousal was also classified as hypopnoea. A detailed discussion of respiratory event scoring is reported elsewhere [18]. The Epworth Sleepiness Scale (ESS) was used to assess subjective daytime sleepiness [21].

Outcome measures and statistical analysis

The principal objective of the present study was to assess the relationship of OSA severity indices with HbA1c levels in nondiabetic subjects enrolled in the ESADA study. Patients were excluded from this analysis if they had an antecedent history of diabetes, were taking diabetic medication and/or had an HbA1c level $\geq 6.5\%$ [22]. Severity of OSA was measured categorically according to AHI and ODI quartiles, with subjects in the first quartile having the lowest AHI or ODI, and serving as a reference category for the estimation of the effect size. Baseline patient characteristics across quartiles were compared using ANOVA with *post hoc* Bonferroni analysis, Kruskal–Wallis and Mann–Whitney U-tests, and Chi-squared tests for parametric, nonparametric, and categorical variables, respectively. To address the relationship of HbA1c levels with OSAS severity, correlations of patient HbA1c levels measured in Diabetes Control and Compliance Trial (DCCT)-accredited laboratories with OSAS severity measures (AHI and ODI), nocturnal oxygenation (mean nocturnal SpO_2), demographic and anthropometric measures, clinical variables and ESS scores were assessed by Pearson's or Spearman's correlation coefficients according to distribution. Variables thus identified as having a statistically significant relationship with HbA1c levels were then incorporated into a multivariate linear regression model, with HbA1c levels as the dependent variable. All statistical models were adjusted for demographic (age, race and sex) and anthropometric (BMI and waist circumference) variables, study site, and relevant clinical factors (smoking history; average sleep duration; statin, oral steroid, diuretic and β -blocker use; and daytime sleepiness).

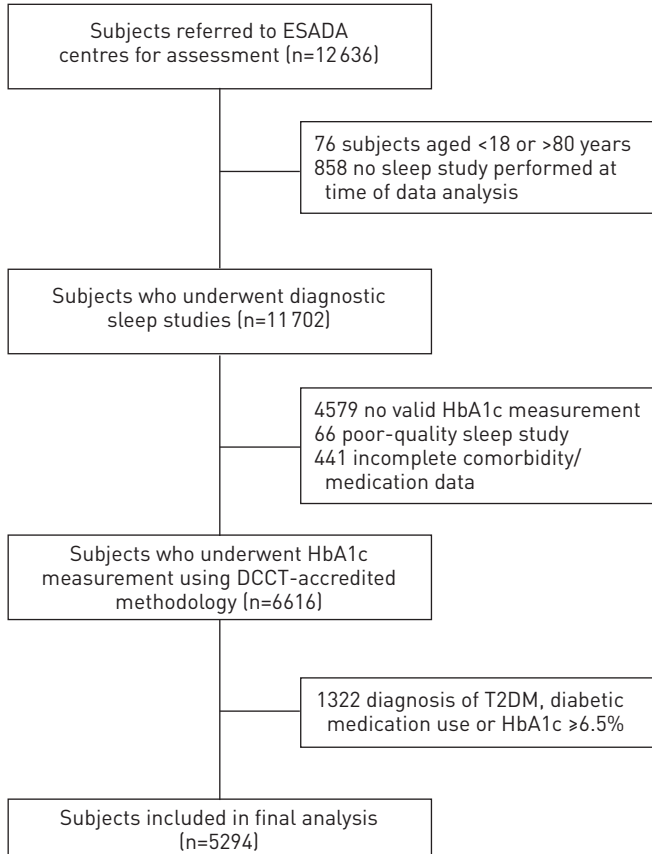


FIGURE 1 European Sleep Apnoea Cohort study patient flow diagram. ESADA: European Sleep Apnoea Database; HbA1c: glycosylated haemoglobin; DCCT: Diabetes Control and Compliance Trial; T2DM: type 2 diabetes mellitus.

TABLE 1 Patient characteristics

	Total population	AHI events per h				p-value
		0.0–6.1	6.2–16.0	16.1–34.6	34.7–147.3	
Subjects n	5294	1329	1329	1314	1322	
Males %	70.3	56.4	66.8	76.0	82.3	<0.001
Age years	50.9 ± 12.4	46.3 ± 12.7	51.6 ± 12.2	52.8 ± 11.8	52.9 ± 11.6	<0.001
Caucasians %	92.5	94.7	92.6	93.5	89.1	0.591
BMI kg·m ⁻²	30.0 ± 6.0	28.0 ± 5.3	29.1 ± 5.4	30.1 ± 5.5	32.9 ± 6.5	<0.001
Waist circumference cm	104.1 ± 14.5	97.8 ± 13.4	101.8 ± 12.3	105.0 ± 13.3	112.3 ± 14.9	<0.001
Neck circumference cm	40.6 ± 4.2	38.8 ± 4.1	39.9 ± 3.7	41.0 ± 3.8	42.9 ± 4.0	<0.001
SBP mmHg	132.1 ± 17.4	128.3 ± 16.9	131.0 ± 17.3	133.0 ± 16.9	136.2 ± 17.4	<0.001
DBP mmHg	82.2 ± 11.4	80.3 ± 11.3	81.4 ± 11.2	82.5 ± 11.2	84.7 ± 11.5	<0.001
ESS score	9.9 ± 5.1	9.5 ± 5.0	9.4 ± 5.0	9.8 ± 4.9	10.7 ± 5.4	<0.001
Alcohol units per week	4.4 ± 7.8	3.4 ± 6.1	3.8 ± 6.6	4.8 ± 8.6	5.7 ± 9.1	<0.001
Smokers %	24.2	25.5	23.3	23.3	25.1	0.226
HTN %	35.0	20.9	32.9	39.1	47.0	<0.001
IHD %	6.1	3.6	7.4	6.6	6.8	<0.001
CHF %	1.7	0.9	1.9	1.6	2.4	0.03
Hyperlipidaemia %	20.1	14.1	19.2	22.8	24.2	<0.001
Gout %	1.8	0.5	1.4	1.4	4.1	<0.001
COPD %	3.9	4.1	3.8	3.9	3.8	0.955
β-blockers %	16.4	9.7	17.5	19.1	19.2	<0.001
RAS drug %	21.3	13.0	22.2	22.4	27.8	<0.001
Statins %	17.2	12.0	18.2	18.9	19.5	<0.001
OCS %	1.2	1.4	0.8	1.2	1.4	0.686
AHI events per h	23.8 ± 23.3	2.7 ± 1.8	10.7 ± 2.8	24.1 ± 5.2	57.7 ± 19.1	<0.001
Mean SpO ₂ %	93.8 ± 3.5	94.9 ± 3.0	94.3 ± 2.6	93.9 ± 3.2	92.0 ± 4.2	<0.001
ODI _{≥4%} events per h	18.4 ± 22.1	3.1 ± 5.0	8.2 ± 7.7	16.7 ± 10.3	46.6 ± 25.1	<0.001
Cholesterol mmol·L ⁻¹	5.26 ± 1.07	5.26 ± 1.02	5.27 ± 1.1	5.28 ± 1.1	5.24 ± 1.07	0.348
Triglycerides mmol·L ⁻¹	1.81 ± 1.11	1.59 ± 0.90	1.77 ± 1.03	1.89 ± 1.20	2.00 ± 1.23	<0.001
Creatinine mmol·L ⁻¹	81.9 ± 31.4	77.8 ± 23.5	80.7 ± 27.3	82.3 ± 16.6	87.0 ± 48.3	<0.001
HbA1c %	5.39 ± 0.56	5.19 ± 0.59	5.37 ± 0.55	5.45 ± 0.52	5.57 ± 0.52	<0.001

Data are presented as mean ± SD unless otherwise stated. AHI: apnoea-hypopnoea index; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ESS: Epworth Sleepiness Scale; HTN: hypertension; IHD: ischaemic heart disease; CHF: congestive heart failure; COPD: chronic obstructive lung disease; RAS: renin-angiotensin system; OCS: oral corticosteroids; SpO₂: arterial oxygen saturation measured by pulse oximetry; ODI: oxyhaemoglobin desaturation index; HbA1c: glycosylated haemoglobin.

To further explore the relationship of HbA1c levels with OSAS severity, factorial ANCOVA was performed to generate adjusted mean HbA1c for each AHI or ODI quartile. This analysis was adjusted for study site, and demographic, anthropometric and clinical variables. Adjusted means were compared following Bonferroni's *post hoc* correction. Finally, in light of recent data demonstrating markedly increased long-term cardiovascular risk among nondiabetic subjects with a baseline HbA1c level ≥ 6% [11], logistic regression analysis was performed to generate adjusted odds ratios for HbA1c ≥ 6% according to OSAS severity quartiles and quartiles of severity for nocturnal hypoxaemia. Analyses stratified by sleep study methodology, obesity, sex and excessive daytime sleepiness (ESS score >10 *versus* ≤ 10) were performed to assess interactions between OSAS severity and glycaemic health in clinically relevant subgroups.

Statistical analyses were performed using SPSS version 18.0 statistical software (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

A total of 6616 subjects enrolled into the ESADA cohort during the study inclusion period had an HbA1c level measured using DCCT-accredited methodology, and 5294 (80.0%) of these had no antecedent diagnosis of T2DM, were not receiving antidiabetic therapy and had an HbA1c level <6.5% (fig. 1). Descriptive characteristics of this study population, stratified by AHI quartiles, and the distribution of covariates are presented in table 1. Subjects with more severe OSAS were more likely to be male, were more obese and had a greater burden of cardiometabolic comorbidities than those with no or mild disease. HbA1c levels correlated significantly in univariate analysis with AHI (Spearman $r=0.259$, $p<0.001$), mean SpO₂ (Spearman $r=-0.271$, $p<0.001$) and ODI (Spearman $r=0.222$, $p<0.001$), along with age, obesity

TABLE 2 Univariate correlations of glycosylated haemoglobin with demographic, clinical and anthropomorphic factors, and indices of obstructive sleep apnoea syndrome severity and nocturnal hypoxaemia

Variable	Correlation coefficient	p-value
Age	0.124	<0.001
SBP	0.096	<0.001
DBP	0.064	<0.001
BMI	0.201	<0.001
Waist circumference	0.192	<0.001
Neck circumference	0.177	<0.001
Waist/hip ratio	0.151	<0.001
ESS score	0.005	0.70
Subjective sleep length	-0.10	<0.001
AHI	0.259	<0.001
Mean SpO₂	-0.271	<0.001
ODI	0.222	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; ESS: Epworth Sleepiness Scale; AHI: apnoea-hypopnoea index; SpO₂: arterial oxygen saturation measured by pulse oximetry; ODI: oxyhaemoglobin desaturation index.

measures, subjective average sleep duration and blood pressure measurements (table 2). No relationship was seen with subjective daytime sleepiness as measured by the ESS.

A linear regression model was built using variables with significant univariate relationships with HbA1c levels. Following adjustment for age, sex, BMI, neck circumference, sleep duration, smoking status, statin use and systolic blood pressure, AHI remained a significant predictor of HbA1c levels (standardised $\beta=0.160$, $p<0.001$) (table 3). Similar relationships were seen between HbA1c levels and ODI and mean SpO₂ (table 3).

Mean HbA1c levels, adjusted for demographic, anthropometric and clinical variables, were significantly higher in more severe AHI quartiles (fig. 2). Adjusted mean HbA1c was 5.24% (95% CI 5.21–5.27%) in the first (lowest) AHI quartile, 5.37% (95% CI 5.34–5.40%) in the second, 5.44% (95% CI 5.41–5.47%) in the third and 5.50% (95% CI 5.46–5.53%) in the fourth (ANCOVA, $p<0.001$; *post hoc* pairwise comparisons with lowest AHI quartile using Bonferroni correction, all $p<0.001$).

Subjects in the higher AHI quartiles had significantly greater odds of having an HbA1c level $\geq 6\%$ (table 4). In comparison with patients in the first AHI quartile, and following adjustment for demographic factors, smoking status, ESS score, BMI and waist circumference, those in the second, third and fourth AHI quartiles had odds ratios of 1.44 (95% CI 1.05–1.97), 1.44 (95% CI 1.04–1.99) and 2.12 (95% CI 1.53–2.94), respectively, of having HbA1c levels $\geq 6\%$. Similarly, increasing severity of nocturnal hypoxaemia conferred markedly increased odds of elevated HbA1c, independently of demographic factors and obesity (table 4).

In analyses stratified by sleep study methodology, sleep apnoea severity predicted elevated HbA1c levels in subjects who underwent either PSG or polygraphy. However, among patients who had undergone PSG ($n=2375$), ODI and mean nocturnal SpO₂ were better predictors of HbA1c levels than AHI. For example, although both AHI and ODI maintained a significant relationship with glycaemic health in multivariate stepwise linear regression analyses (online supplementary table 1), adjusted mean HbA1c levels differed significantly between ODI, but not AHI, quartiles (supplementary fig. 1). Similarly, ODI and mean SpO₂ better predicted the likelihood of subjects undergoing PSG having an HbA1c level $\geq 6\%$ following adjustment for confounding factors (supplementary table 2). Conversely, both AHI and ODI remained significant predictors of HbA1c levels in subjects undergoing polygraphy ($n=2919$) (supplementary fig. 1, and supplementary tables 3 and 4).

Further analyses of subgroups stratified by obesity, sex, and daytime sleepiness (ESS score >10 versus ≤ 10) demonstrated similar findings to the overall cohort (supplementary tables 5–7 and supplementary figs 2–4). Increasing OSA severity was associated with increased HbA1c levels in men and women, and in those with and without subjective daytime sleepiness. A somewhat stronger relationship was seen between OSA severity indices and HbA1c levels in nonobese than those in obese subjects, but a significant relationship was observed in both groups.

TABLE 3 Multivariate stepwise regression analysis of relationship of demographic, clinical and anthropomorphic factors, and indices of obstructive sleep apnoea syndrome severity and nocturnal hypoxaemia with glycosylated haemoglobin (HbA1c) levels

Variable	β (95% CI)	Standard β	p-value
Model 1[#]			
AHI	0.004 (0.003–0.005)	0.160	<0.001
Body mass index	0.012 (0.009–0.015)	0.127	<0.001
Age	0.004 (0.003–0.006)	0.093	<0.001
Smoking status	0.138 (0.102–0.174)	0.106	<0.001
Subjective sleep length	0.04 (0.029–0.051)	0.098	<0.001
Statin therapy	0.099 (0.057–0.141)	0.067	<0.001
Model 2[†]			
ODI	0.003 (0.002–0.004)	0.101	<0.001
Body mass index	0.014 (0.011–0.017)	0.148	<0.001
Age	0.005 (0.004–0.006)	0.108	<0.001
Subjective sleep length	0.039 (0.027–0.05)	0.094	<0.001
Smoking status	0.138 (0.101–0.175)	0.106	<0.001
Sex	0.045 (0.011–0.08)	0.037	0.011
Statin therapy	0.092 (0.05–0.135)	0.062	<0.001
Model 3⁺			
Mean SpO ₂	0.014 (0.009–0.019)	0.08	<0.001
Body mass index	0.016 (0.013–0.019)	0.168	<0.001
Age	0.005 (0.004–0.007)	0.106	<0.001
Subjective sleep length	0.039 (0.028–0.050)	0.096	<0.001
Smoking status	0.127 (0.09–0.163)	0.098	<0.001
Sex	0.054 (0.019–0.088)	0.044	0.002
Statin therapy	0.084 (0.042–0.127)	0.057	<0.001

AHI: apnoea-hypopnoea index; ODI: oxyhaemoglobin desaturation index; SpO₂: arterial oxygen saturation measured by pulse oximetry. [#]: dependent variable, HbA1c; independent variables, AHI, waist circumference, body mass index, age, sex, active smoking, systolic blood pressure, subjective sleep length and statin use; model R²=0.093. [†]: dependent variable, HbA1c; independent variables, ODI, waist circumference, body mass index, age, sex, active smoking, systolic blood pressure, subjective sleep length and statin use; model R²=0.081. ⁺: dependent variable, HbA1c; independent variables, mean SpO₂, waist circumference, body mass index, age, sex, active smoking, systolic blood pressure, subjective sleep length and statin use; model R²=0.081.

Discussion

Sleep disordered breathing and dysglycaemia are intimately linked, but the existence of an independent relationship between them, beyond their shared association with obesity, has been difficult to definitively identify. In the largest reported study on this topic to date, we found OSA severity to be an independent predictor of glycaemic health, adding to a growing body of evidence that OSA has an independent association with insulin resistance and impaired glucose tolerance.

The key finding of the present study is the independent relationship seen between OSA severity indices and HbA1c levels in nondiabetic subjects, which remains significant after adjustment for confounding variables. While prior data from the Sleep Heart Health Study and other reports have demonstrated a detrimental effect of sleep disordered breathing on other measures of insulin resistance [13, 23], we evaluated a marker that is a validated predictor of long-term cardiovascular morbidity and mortality in both diabetic and nondiabetic populations [11, 24]. Therefore, the independent relationship seen between HbA1c levels and sleep disordered breathing severity in this cohort suggests an increased future burden of cardiovascular disease in patients with more severe OSA and more significant nocturnal hypoxaemia.

We observed a significant, if modest, 0.25% difference in adjusted mean HbA1c between subjects in the mildest AHI quartile and those in the most severe quartile. The best data on the relationship of HbA1c levels with long-term outcomes in nondiabetic subjects is probably provided by the Atherosclerosis Risk in the Community (ARIC) study [11]. In that cohort, subjects with an HbA1c at baseline between 5.5% and 6.0% had an 18% increased risk of death, a 23% increased risk of incident coronary artery disease and an 86% increased risk of incident diabetes compared with those with an HbA1c of 5.0–5.5%, over a median follow-up time of 14 years. It is a little difficult to assess the 0.25% difference in adjusted mean HbA1c seen in our cohort in that context, but it is notable that the mildest and most severe AHI quartiles would fall into the two categories mentioned above. We would suggest, however, that the clear increased odds of the more severe OSA severity quartiles having an HbA1c level $\geq 6.0\%$ is the most important finding in this regard, as

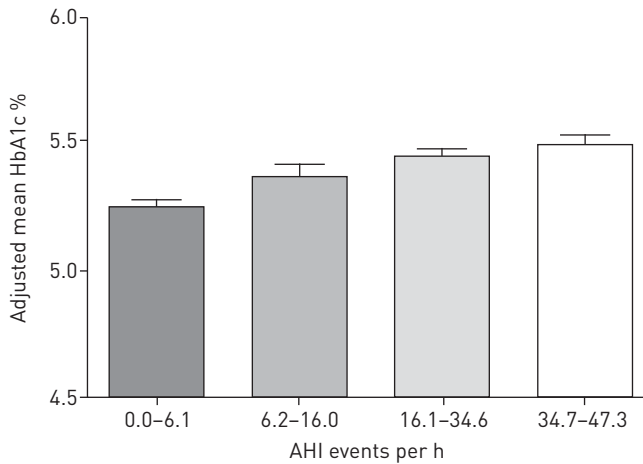


FIGURE 2 Adjusted mean glycosylated haemoglobin (HbA1c) levels by obstructive sleep apnoea syndrome severity quartiles, adjusted for demographic factors (age, race and sex), study site, smoking status, systolic blood pressure, subjective sleep length, statin use, body mass index and waist circumference. Data are presented with 95% confidence intervals. AHI: apnoea-hypopnoea index. ANCOVA: $p < 0.001$.

the data from the ARIC study would indicate that these are the subjects at markedly higher risk of later adverse events [11].

A number of prior reports have suggested that the relationship between OSA and glycaemic health may be particularly strong in sleepy subjects [25]. This has been reported in terms of prevalent T2DM [25] and in terms of insulin resistance in nondiabetic subjects [26]. However, within our population, excessive daytime sleepiness had no significant independent modifying influence on HbA1c levels, which may reflect the clinic-based nature of this cohort or the greater population size studied. In contrast, we observed a particularly marked relationship between HbA1c levels and nocturnal hypoxaemia, as measured by the ODI. We did note a somewhat stronger relationship between OSA severity and HbA1c levels in nonobese patients. While the potential mechanisms underlying this difference remain unclear, one may speculate that increasing concomitant adiposity and adipose tissue dysfunction in obese patients may dilute any detrimental effect of OSA on HbA1c levels.

The present study confirms and extends the findings of the previous report of PRIOU *et al.* [27], which evaluated the relationship between HbA1c levels and OSA severity in French subjects undergoing investigation for suspected OSA. Importantly, our data are derived from a substantially larger, prospectively studied, multinational population. Moreover, the greater proportion of PSG recordings undertaken in ESADA allows for some potentially important insights into the mechanisms underlying the observed

TABLE 4 Crude and adjusted odds ratios of a glycosylated haemoglobin level $\geq 6\%$ across quartiles of obstructive sleep apnoea syndrome severity and oxygenation indices

	AHI events per h				p-value
	0.0-6.1	6.2-16.0	16.1-34.6	34.7-147.3	
AHI					
Model 1 [#]	1	2.02 (1.53-2.62)	2.33 (1.79-3.03)	4.38 (3.41-5.62)	<0.001
Model 2 [†]	1	1.64 (1.20-2.57)	1.88 (1.37-2.57)	3.42 (2.52-4.65)	<0.001
Model 3 [‡]	1	1.44 (1.05-1.97)	1.44 (1.04-1.99)	2.12 (1.53-2.94)	<0.001
ODI					
Model 1 [#]	1	1.68 (1.27-2.22)	2.29 (1.76-2.99)	4.55 (3.54-5.84)	<0.001
Model 2 [†]	1	1.37 (1.00-1.87)	1.83 (1.35-2.45)	3.46 (2.57-4.68)	<0.001
Model 3 [‡]	1	1.12 (0.81-1.54)	1.31 (0.95-1.80)	1.97 (1.42-2.73)	<0.001
Mean SpO₂					
Model 1 [#]	1	1.94 (1.43-2.63)	3.03 (2.25-4.10)	6.27 (4.79-8.21)	<0.001
Model 2 [†]	1	1.78 (1.27-2.51)	2.33 (1.66-3.28)	4.11 (2.98-5.67)	<0.001
Model 3 [‡]	1	1.52 (1.07-2.17)	1.70 (1.18-2.44)	2.36 (1.66-3.35)	<0.001

Data are presented as odds ratio (95% confidence interval). AHI: apnoea-hypopnoea index; ODI: oxyhaemoglobin desaturation index; SpO₂: arterial oxygen saturation measured by pulse oximetry. [#]: unadjusted model; [†]: adjusted for demographic factors (race, age and sex), study centre, sleep length, Epworth Sleepiness Scale score and tobacco use; [‡]: adjusted as model 2, plus statin use, body mass index and waist circumference.

association between OSAS severity and glycaemic health. In particular, that nocturnal hypoxaemia appeared to have a stronger relationship with HbA1c levels than AHI among the subjects undergoing PSG may suggest that tissue hypoxia is an important contributor to impaired glycaemic health in these patients, while other sleep-related events may play a less significant role.

White adipose tissue (WAT) is a key endocrine organ in obese subjects [28] and hypoxia has been demonstrated to lead to WAT inflammation and dysfunction [29]. In particular, WAT hypoxia appears to contribute to insulin resistance *via* a hypoxia-inducible factor-dependent mechanism [30]. Only limited data exist exploring the influence of intermittent hypoxia on WAT function, although intermittent hypoxia does appear to reduce adipocyte secretion of the key antidiabetogenic hormone adiponectin [31]. Other potential drivers of abnormal glucose metabolism in OSA patients include systemic inflammation and oxidative stress [9]. Notably, intermittent hypoxia associated with sleep disordered breathing has been demonstrated in *in vitro* and clinical studies to lead to increased circulating inflammatory cytokines, such as tumour necrosis factor- α [32, 33], which can directly cause WAT to adopt an insulin-resistant, diabetogenic phenotype [34]. Similarly, sympathetic overactivity mediated by OSA may induce lipolysis, with consequent disruption of insulin signalling [35].

There are some important limitations to the present study. First, the reported data are cross-sectional, thereby preventing any robust observations on causality of dysglycaemia in this cohort. A strength of this study is its multinational, multicentre nature. However, this may also be viewed as a limitation in some respects. Sleep diagnostic modalities differed between centres, with approximately half using full PSG and the remainder polygraphy. There was also some variability in the setting of the polygraphy studies, with most performed in the sleep lab, but a number performed on an ambulatory basis. Furthermore, ESADA centres were allowed to use both the “recommended” and “alternative” AASM criteria for respiratory event scoring. Recent data suggest that uniformity of AHI scoring may be significantly reduced by use of the latter [36]. We also cannot exclude the possibility that interlaboratory HbA1c assay variation may have a confounding effect on our results. However, stratification of analyses by sleep testing method continued to show a relationship between OSA severity and nocturnal hypoxaemia, independent of the diagnostic methodology used, and, where feasible, all statistical models were also adjusted to include study site as a covariate.

Not all patients enrolled in the overall ESADA project underwent blood sampling, and a small number of centres utilised International Federation of Clinical Chemistry methods in HbA1c analysis. We cannot exclude the possibility of consequent selection bias contributing to our findings, but it is notable that the demographic, anthropometric and clinical characteristics of the subjects who did not have HbA1c measurement were not significantly different from those who did. Similarly, although we endeavoured to exclude all diabetics from our analysis, there is the possibility that some may not have been successfully identified. Finally, as the cohort studied consisted of subjects attending sleep services, the applicability of our findings to the general population is unproven.

In conclusion, in a large, prospectively recruited, multinational population, we found that OSA severity and nocturnal hypoxaemia independently predict poor glycaemic health in subjects without an antecedent diagnosis of T2DM. Further prospective studies to examine the impact of treatment of sleep disordered breathing on dysglycaemia, as well as mechanistic studies to evaluate the effect of intermittent hypoxia on the adipocyte secretome, are required to tease out the complex interaction between OSA, obesity and metabolic health.

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References

- 1 Young T, Palta M, Dempsey J, *et al*. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230–1235.
- 2 McNicholas WT, Bonsignore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007; 29: 156–178.
- 3 Peppard PE, Young T, Palta M, *et al*. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342: 1378–1384.
- 4 Nieto FJ, Young TB, Lind BK, *et al*. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000; 283: 1829–1836.
- 5 Marin JM, Agusti A, Villar I, *et al*. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* 2012; 307: 2169–2176.
- 6 Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. *Eur Respir J* 2006; 28: 596–602.
- 7 Redline S, Yenokyan G, Gottlieb DJ, *et al*. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *Am J Respir Crit Care Med* 2010; 182: 269–277.
- 8 Punjabi NM, Caffo BS, Goodwin JL, *et al*. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; 6: e1000132.
- 9 Bonsignore MR, McNicholas WT, Montserrat JM, *et al*. Adipose tissue in obesity and obstructive sleep apnoea. *Eur Respir J* 2012; 39: 746–767.
- 10 Haffner SM, Lehto S, Ronnema T, *et al*. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339: 229–234.
- 11 Selvin E, Steffes MW, Zhu H, *et al*. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010; 362: 800–811.
- 12 Shaw JE, Punjabi NM, Wilding JP, *et al*. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008; 81: 2–12.
- 13 Punjabi NM, Shahar E, Redline S, *et al*. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 2004; 160: 521–530.
- 14 Reichmuth KJ, Austin D, Skatrud JB, *et al*. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005; 172: 1590–1595.
- 15 Lam JC, Lam B, Yao TJ, *et al*. A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. *Eur Respir J* 2010; 35: 138–145.
- 16 Sharma SK, Agrawal S, Damodaran D, *et al*. CPAP for the metabolic syndrome in patients with obstructive sleep apnea. *N Engl J Med* 2011; 365: 2277–2286.
- 17 Kent BD, Grote L, Bonsignore MR, *et al*. Severity of sleep disordered breathing is an independent predictor of glycemic health: the European Sleep Cohort (ESADA) study. *Am J Respir Crit Care Med* 2012; 185: A5379.
- 18 Hedner J, Grote L, Bonsignore M, *et al*. The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011; 38: 635–642.
- 19 Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. Standards of Practice Committee of the American Sleep Disorders Association. *Sleep* 1994; 17: 372–377.
- 20 Iber C, Ancoli-Israeli S, Chesson A, *et al*. The AASM Manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st Edn. Westchester, American Academy of Sleep Medicine, 2007.
- 21 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
- 22 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2011; 34: Suppl 1. S62–S69.
- 23 Ip MS, Lam B, Ng MM, *et al*. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002; 165: 670–676.
- 24 Selvin E, Marinopoulos S, Berkenblit G, *et al*. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141: 421–431.
- 25 Ronksley PE, Hemmelgarn BR, Heitman SJ, *et al*. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. *Thorax* 2009; 64: 834–839.
- 26 Barcelo A, Barbe F, de la Pena M, *et al*. Insulin resistance and daytime sleepiness in patients with sleep apnoea. *Thorax* 2008; 63: 946–950.
- 27 Priou P, Le Vaillant M, Meslier N, *et al*. Independent association between obstructive sleep apnea severity and glycated hemoglobin in adults without diabetes. *Diabetes Care* 2012; 35: 1902–1906.
- 28 Trayhurn P, Wang B, Wood IS. Hypoxia and the endocrine and signalling role of white adipose tissue. *Arch Physiol Biochem* 2008; 114: 267–276.
- 29 Wang B, Wood IS, Trayhurn P. Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes. *Pflugers Arch* 2007; 455: 479–492.
- 30 Regazzetti C, Peraldi P, Gremeaux T, *et al*. Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* 2009; 58: 95–103.
- 31 Magalang UJ, Cruff JP, Rajappan R, *et al*. Intermittent hypoxia suppresses adiponectin secretion by adipocytes. *Exp Clin Endocrinol Diabetes* 2009; 117: 129–134.
- 32 Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation* 2005; 112: 2660–2667.

- 33 Ryan S, Taylor CT, McNicholas WT. Predictors of elevated nuclear factor- κ B-dependent genes in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2006; 174: 824–830.
- 34 Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* 1993; 259: 87–91.
- 35 Drager LF, Jun JC, Polotsky VY. Metabolic consequences of intermittent hypoxia: relevance to obstructive sleep apnea. *Best Pract Res Clin Endocrinol Metab* 2010; 24: 843–851.
- 36 Kuna ST, Benca R, Kushida CA, *et al.* Agreement in computer-assisted manual scoring of polysomnograms across sleep centers. *Sleep* 2013; 36: 583–589.