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Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome☆

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Aims Obstructive sleep apnoea (OSA) is associated with increased cardiovascular morbidity and mortality. Although it was previously assumed that this was due to its relation with obesity, recent data suggest that OSA is independently associated with the cardiovascular risk factors that comprise metabolic syndrome, including hypertension, insulin resistance, impaired glucose tolerance, and dyslipidaemia. However, as previous studies have only considered these variables individually, it has not been possible to determine the overall association of OSA with this syndrome.
Methods and results We recruited 61 male subjects with OSA and 43 controls. Glucose, insulin, lipids, and blood pressure (BP) were measured following an overnight fast. Insulin resistance was estimated using homeostasis model assessment (HOMA). Metabolic syndrome was diagnosed according to National Cholesterol Education Program (NCEP) criteria. Subjects with OSA were more obese, had higher BP and fasting insulin, were more insulin resistant, had lower HDL cholesterol, and an increased incidence of metabolic syndrome (87% vs. 35%, $p < 0.0001$). In order to determine whether these associations were independent of obesity and other known covariates, a regression analysis adjusted for age, BMI, smoking, and alcohol consumption was performed. This demonstrated that OSA was independently associated with increased systolic and diastolic blood pressure, higher fasting insulin and triglyceride concentrations, decreased HDL cholesterol, increased cholesterol:HDL ratio, and a trend towards higher HOMA values. Metabolic syndrome was 9.1 (95% confidence interval 2.6, 31.2: $p < 0.0001$) times more likely to be present in subjects with OSA.
Conclusions OSA is independently associated with an increase in the cardiovascular risk factors that comprise the metabolic syndrome and its overall prevalence. This may help explain the increased cardiovascular morbidity and mortality associated with this condition.

Introduction

Obstructive sleep apnoea (OSA) is characterised by repeated episodes of apnoea and hypopnoea during sleep.

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Approximately 4% of men and 2% of women from the middle-aged work force have OSA, as defined by an apnoea-hypopnoea index $\geqslant 5$ and daytime hypersomnolence.[1] Although the main symptom of OSA is daytime hypersomnolence, patients with OSA also have a higher incidence of cardiovascular morbidity and mortality.[2] It was previously assumed that this occurred because of the related obesity, however, recent data suggests that OSA may also be associated with a number of cardiovascular risk factors independently of obesity, such as hypertension,[3,4] insulin resistance, impaired glucose tolerance,[5–7] and dyslipidaemia.[8–10]

While many investigators have observed that central obesity, hypertension, insulin resistance and impaired glucose tolerance, and dyslipidaemia frequently coexist in individual patients, it was not until 1988 that Reaven proposed that this did not occur by chance, but rather comprised what has more recently been termed the "metabolic syndrome".[11] Within this syndrome, obesity, a sedentary lifestyle, and genetic propensity cause insulin resistance, impaired glucose tolerance, and hyperinsulinaemia,[12,13] which further lead to higher blood pressure[14] and dyslipidaemia.[15] A number of positive adverse interactions between these risk factors further increase the cardiovascular risk to the individual. However, as previous studies have only considered these variables individually, it has not been possible to determine the overall association of OSA with this syndrome.

We hypothesised that OSA would be associated with an increase in the risk factors that comprise the metabolic syndrome and the overall prevalence of this syndrome, independently of obesity. To test this, we measured blood pressure, fasting glucose, fasting insulin, insulin resistance, fasting lipids, and the prevalence of metabolic syndrome in a case-control study of subjects with OSA and controls recruited from outpatient clinics at the University Hospital Aintree. In order to determine whether these associations were independent of obesity and other known covariates, a regression analysis adjusted for age, BMI, smoking, and alcohol consumption was also performed.

Methods

Subjects

We studied 61 newly diagnosed male OSA patients and 43 male controls. All 61 subjects with OSA and seven of the obese controls were recruited from the Sleep Disordered Breathing and Weight Management Clinics, respectively, at the University Hospital Aintree. These clinics take patients who have been referred from the surrounding region. Referrals are made by general practitioners and other hospital consultants. Eligible subjects were identified prior to their outpatient appointment by inspection of the case notes and were approached by the consulting physician. Two obese control subjects were also recruited using poster advertisements within the hospital, but they were not health professionals. The remaining 34 control subjects were recruited from the general public by poster advertisements in the local press. Subjects were eligible if they were not known to suffer from any other medical conditions, received no medications, and were otherwise healthy. After routine biochemical investigation and baseline ECG, any subject with evidence of diabetes or renal, liver or cardiac disease were excluded and referred back to their general practitioner for further investigation, as were patients with symptoms of peripheral neuropathy or a waking blood pressure $\geqslant 180/110$. OSA was diagnosed by a combination of clinical history and polysomnography, with an apnoea/hypopnoea index greater than 15 h^{-1} defining a positive diagnosis.[16] OSA was excluded in controls using a domiciliary sleep study. Daytime sleepiness was assessed using the Epworth sleepiness score (ESS) with a score of ten or more defining excessive daytime sleepiness.[17] None had commenced nasal continuous positive airway pressure (CPAP) treatment at the time of study. The study complied with the declaration of Helsinki and was approved by the local research ethics committee. All subjects gave written informed consent.

Sleep diagnostic assessments

All subjects with OSA snored and reported excessive daytime sleepiness or two or more other features of the condition from: impaired concentration, unrefreshing sleep, choking episodes during sleep, witnessed apnoeas, restless sleep, irritability/personality change, nocturia, and decreased libido. The diagnosis of OSA was confirmed by polysomnography using the SleepLab 1000p system (Jaeger, Hoechlberg, Germany) with a standard montage of electroencephalogram (EEG), electro-oculogram and electromyogram signals, pulse oximetry, respiratory impedance, and nasal airflow measurements. A limited respiratory sleep study was conducted at home in control subjects (Edentrace® II Plus, Nellcor Puritan Bennett™, Eden Prairie, MN, USA) to exclude sleep-disordered breathing. This technique shows a strong correlation with polysomnography (RDI, $r = 0.96$)[18] and has been previously validated for the home diagnosis of OSA.[19]

Sleep studies were analysed by two technicians using computer software. Apnoea was classified as a cessation of airflow for at least 10 s accompanied by a $\geqslant 4\%$ desaturation in the following 30 s. Hypopnoea was defined as 50% reduction in airflow accompanied by $\geqslant 4\%$ desaturation and a reduction in chest wall movement. Data were expressed as the respiratory disturbance index (RDI) based on the mean number of apnoea and hypopnoea episodes per hour slept (polysomnography) or per hour in bed (home study). Home studies were only considered acceptable if the subject reported a satisfactory night's sleep during the test.

Body composition

Weight and percentage body fat were assessed using Tanita TBF-521 bioimpedance scales (Tanita Corp., Tokyo, Japan), and height was recorded. This method has been validated previously against a four-compartment model and was comparable to other prediction techniques including conventional tetrapolar impedance, skinfold thickness, and BMI-based formulas.[20] BMI was defined as weight (kg)/height^2 (m). Neck circumference was measured at the level of the laryngeal prominence. Waist circumference was measured midway between the lower rib and iliac crest.

Blood pressure

Waking blood pressure was measured between the hours of 8 and 11 a.m. in the supine position after a 5-min rest. It was recorded as the mean of three measurements taken at 1-min intervals,

according to British Hypertension Society guidelines, using an Omron automatic oscillometric digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan).

Fasting glucose

Fasting glucose was measured after an overnight fast in whole blood using a glucose-oxidase-based assay (YSI 2300, Analytical Technologies, Farnborough, UK).

Insulin resistance

Insulin was quantified using the IMMULITE 2000 Insulin assay, a solid-phase, two-site, chemiluminescent enzyme-labelled immunometric assay, and the Immulite 2000 automated analyser (Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin resistance was assessed from fasting glucose and insulin values using homeostasis model assessment (HOMA) calculations, previously validated against the hyperinsulinaemic euglycaemic clamp.[21]

Lipids

Fasting cholesterol, triglyceride (Bayer Corporation, Tarrytown, NY, USA), and HDL cholesterol (Sigma Diagnostics, St. Louis, MO, USA) concentrations were measured after an overnight fast using an immunocolourimetric assay on an ADVIA® 1650 chemistry system (Bayer Corporation, Tarrytown, NY, USA). Low-density-lipoprotein (LDL) cholesterol was derived using the Friedwald equation.

The metabolic syndrome

The metabolic syndrome was diagnosed according to National Cholesterol Education Program (NCEP) guidelines.[22] Patients had a metabolic syndrome if they had three or more of the following risk factors: waist circumference >102 cm, triglycerides $\geqslant 1.7$ mmol/l, HDL cholesterol <1.04 mmol/l, blood pressure $\geqslant 130/\geqslant 85$ mmHg, and fasting glucose $\geqslant 6.1$ mmol/l.

Statistical analysis

Prior to the study, power calculations were made based on systolic and diastolic blood pressure values. This variable was chosen because of its primary importance in the metabolic syndrome and the lack of established criteria for the diagnosis of this syndrome at that time. Published results of blood pressure in subjects with OSA commonly reported a standard deviation of 14 mmHg for systolic and 7 mmHg for diastolic blood pressure. With this information, a power calculation indicated that we would need 32 patients per group to detect a 10-mmHg difference in systolic blood pressure and a 5-mmHg difference in diastolic blood pressure with a power of 80% at a 0.05 significance level.

Normally distributed data were presented as means $\pm$ standard error of the mean, logarithmically transformed data as the geometric mean (95% confidence interval for the mean), skewed data as the median (interquartile range), and categorical data as the number (percentage). Statistical analyses were performed using SPSS version 10 (Chicago, IL, USA). Demographic data were compared using the 95% confidence interval for the difference in the mean, median, and percentage, as appropriate. For the remaining analyses, normal, skewed, and categorical variables were compared using the mean, median, and percentage difference (95% confidence interval for the difference) and by unpaired t tests, Mann–Whitney, and χ^2 tests using the sequential rejective Bonferroni procedure of Holm within each analysis to account for multiple testing.[23] For variables that were logarithmically transformed before analysis, comparisons were made using the anti-logged differences (interpreted as the ratio of the geometric mean and 95% confidence interval for the ratio) and Bonferroni corrected t tests as previously described. In order to determine whether OSA was associated with the outcome variables independent of obesity and other known covariates, a regression analysis adjusted for age, BMI, smoking, and alcohol consumption was also done. Waist circumference, percentage body fat, and fat mass were excluded as covariates because of a high correlation with BMI. Due to the nightly variability of the RDI,[24] OSA was coded as a dummy variable before being entered as a predictor into the regression model. Normally distributed, skewed, and log-transformed outcome data were analysed using multiple linear regression and assumptions were checked by inspection of the residuals. Categorical outcome data were analysed using multiple binary logistic regression and assumptions were checked with the Hosmer–Lemeshow goodness-of-fit test.

Results

Demographics

Subjects with and without OSA did not significantly differ in age. Subjects with OSA had a significantly greater BMI, waist circumference, percentage body fat, and fat mass. By definition, the respiratory disturbance index was greater in subjects with OSA. Subjects with OSA also had a greater neck circumference, higher Epworth sleepiness score, and all snored. Smoking was similar between groups, although there were slightly more smokers in the control group, as well as more alcohol consumption (Table 1).

Components of the metabolic syndrome

Systolic, diastolic, and mean arterial blood pressure were significantly higher in subjects with OSA. Fasting insulin was higher in subjects with OSA whom were also more insulin-resistant, but fasting glucose was similar to controls. HDL cholesterol was lower and the cholesterol:HDL cholesterol ratio was higher in subjects with OSA, but there was no significant difference in total or LDL cholesterol. There was, however, a trend towards a greater triglyceride concentration in subjects with OSA, but this lost significance after adjustment for multiple comparisons. More than twice as many subjects with OSA had the metabolic syndrome according to NCEP criteria (Table 2).

The association of obstructive sleep apnoea with components of the metabolic syndrome

OSA was independently associated with increased systolic, diastolic, and mean arterial blood pressure, fasting insulin, triglyceride concentration, decreased HDL cholesterol and an increased cholesterol:HDL ratio, but not fasting glucose, HOMA, cholesterol, or LDL cholesterol concentrations. There was, however, a trend towards

Table 1 Demographics

	OSA ($N = 61$)	Control ($N = 43$)	Difference (95% CI)
Age (years)[a]	49.6 ± 1.2	47.1 ± 1.4	2.5 (−1.2, 6.1)
BMI (kg/m^2)[a]	35.8 ± 0.9	30.2 ± 1.2	5.6 (2.7, 8.5)
Waist (cm)[a]	116.5 ± 1.9	102.7 ± 2.7	13.8 (7.5, 20.2)
Body fat (%)[a]	38.5 ± 1.1	29.4 ± 1.5	9.1 (5.5, 12.7)
Fat mass (kg)[a]	42.0 ± 1.8	29.3 ± 2.8	12.7 (6.3, 19.1)
Neck (cm)[a]	45.1 ± 0.4	40.9 ± 0.4	4.2 (3.0, 5.5)
RDI (apnoea/h)[b]	42.0 (27.4—56.2)	3.0 (0—7.0)	38.1 (31.0, 44.4)
ESS[b]	14.0 (10.0—17.0)	9.0 (3.0—9.0)	5.0 (2.0, 8.0)
Smoking: *n* (%)[c]	13 (21)	15 (35)	−14 (−31.5, 3.5)
Alcohol (U/week)[c]			
0—4: *n* (%)	26 (43)	10 (23)	20 (2.3, 23.7)
4—12: *n* (%)	22 (36)	14 (33)	3 (−15.2, 21.2)
12—50: *n* (%)	13 (21)	19 (44)	−23 (−41.0, −5.0)

The mean, median and percentage difference (and 95% confidence interval for the difference) were presented for normal, skewed, and categorical data, respectively.
[a] Mean ± SEM.
[b] Median (IQR).
[c] Number (%).

Table 2 Components of the metabolic syndrome

	OSA ($N = 61$)	Control ($N = 43$)	Difference (95% CI)	*p*
Systolic BP (mmHg)[a]	$142.3 \pm 1.9^*$	130.9 ± 2.4	11.4 (5.5, 17.3)	0.0002
Diastolic BP (mmHg)[a]	$90.9 \pm 1.1^*$	85.7 ± 1.4	5.2 (1.8, 8.7)	0.0035
Mean arterial BP (mmHg)[a]	$108.0 \pm 1.1^*$	100.7 ± 1.6	7.3 (3.5, 11.1)	0.0002
Fasting glucose (mmol/l)[b]	4.7 (4.4—5.0)	4.6 (4.4—4.8)	0.1 (−0.1, 0.3)	0.2121
Fasting insulin (pmol/l)[d]	13.7 (11.6, 16.3)*	7.9 (6.5, 9.6)	1.6 (1.2, 2.2)	<0.0001
HOMA IR[b]	3.0 (1.7—4.5)*	1.4 (1.1—2.3)	1.3 (0.6, 2.0)	0.0001
Cholesterol (mmol/l)[a]	5.9 ± 0.1	5.9 ± 0.1	0.0 (−0.4, 0.4)	0.9503
Triglycerides (mmol/l)[d]	2.0 (1.7, 2.2)	1.6 (1.4, 1.8)	1.2 (1.0, 1.5)	0.0219
HDL (mmol/l)[b]	1.1 (0.9—1.3)*	1.3 (1.2—1.5)	−0.2 (−0.3, 0.1)	<0.0001
LDL (mmol/l)[a]	3.8 ± 0.1	3.7 ± 0.2	0.1 (−0.2, 0.5)	0.4578
Cholesterol:HDL[b]	5.0 (4.0—6.0)*	4.0 (4.0—5.0)	1.0 (1.0, 2.0)	0.0001
Metabolic syndrome: *n* (%)[c]	53 (87)*	15 (35)	52 (35.4, 68.6)	<0.0001

The mean, median, and percentage difference (and 95% CI for the difference) were presented for normal, skewed, and categorical data, respectively. For log-transformed data the ratio of geometric means (and 95% confidence interval for the ratio) was presented. Bonferroni-corrected unpaired *t* tests were performed on normally distributed and log-transformed data, Bonferroni-corrected Mann—Whitney on non-normally distributed data and Bonferroni-corrected χ^2 on categorical data. Corrections were performed using a sequential rejective Bonferroni procedure. $^*p < 0.05$ with Bonferroni correction. The metabolic syndrome was diagnosed according to NCEP criteria.
[a] Mean ± SEM.
[b] Median (IQR).
[c] Number (%).
[d] Geometric mean (95% confidence interval).

higher HOMA values in subjects with OSA. The presence of OSA increased the odds of having metabolic syndrome by nine (Table 3).

Discussion

Previous studies have demonstrated that OSA is independently associated with a number of cardiovascular risk factors, such as hypertension,[3,4] insulin resistance, impaired glucose tolerance,[5–7] and dyslipidaemia.[8–10] However, as they only considered these variables individually, it has not been possible to determine the overall association of OSA with metabolic syndrome, a composite of these risk factors that confers additional cardiovascular risk.[11] In this study, we have demonstrated that OSA is associated with significantly higher blood pressures, fasting insulin, greater insulin resistance, reduced HDL cholesterol, and an increased prevalence of the metabolic syndrome. There was also a trend towards higher triglyceride concentrations, but this lost significance after adjustment for multiple comparisons. After adjusting for obesity and other related covariates, OSA was associated with significantly higher blood pressures, fasting insulin, triglyceride concentrations, decreased HDL cholesterol, increased cholesterol:HDL ratio, and a trend towards higher HOMA values. Metabolic syndrome was nine times more likely to be present in subjects with OSA.

The results of this study confirm and extend previous findings. The 24-h ambulatory blood pressure has been shown to be elevated in subjects with OSA compared to

Table 3 The association of obstructive sleep apnoea with components of the metabolic syndrome

Dependent variable	β Coefficient (95% CI)	*p*
Systolic blood pressure (mmHg) $F_{6,97} = 7.00$, $p < 0.0001$. Adj R^2 26%, SE estimate = 13.71	6.8 (0.8, 12.9)	0.0281
Diastolic blood pressure (mmHg) $F_{6,97} = 3.75$, $p = 0.0021$. Adj R^2 14%, SE estimate = 8.42	4.3 (0.5, 8.0)	0.0257
Mean arterial blood pressure (mmHg) $F_{6,97} = 6.22$, $p < 0.0001$. Adj R^2 23%, SE estimate = 8.92	5.1 (1.2, 9.1)	0.0118
Fasting glucose (mmol/l) $F_{6,97} = 1.55$, $p = 0.1691$. Adj R^2 3%, SE estimate = 0.45	0.1 (−0.1, 0.3)	0.5256
Fasting insulin (pmol/l)[a] $F_{6,96} = 6.68$, $p < 0.0001$. Adj R^2 25%, SE estimate = 0.61	1.5 (1.1, 1.9)	0.0137
HOMA IR $F_{6,97} = 5.36$, $p < 0.0001$. Adj R^2 20%, SE estimate = 2.01	0.8 (−0.1, 1.7)	0.0763
Cholesterol (mmol/l) $F_{6,96} = 3.14$, $p = 0.0075$. Adj R^2 12%, SE estimate = 0.96	0.3 (−0.2, 0.7)	0.2018
Triglyceride (mmol/l)[a] $F_{6,96} = 1.88$, $p = 0.0914$. Adj R^2 5%, SE estimate = 0.47	1.3 (1.1, 1.6)	0.0138
HDL (mmol/l) $F_{6,96} = 5.26$, $p < 0.0001$. Adj R^2 20%, SE estimate = 0.27	−0.2 (−0.3, −0.1)	0.0006
LDL (mmol/l) $F_{6,92} = 1.89$, $p = 0.0905$. Adj R^2 5%, SE estimate = 0.89	0.3 (−0.1, 0.7)	0.0951
Cholesterol:HDL $F_{6,93} = 4.65$, $p = 0.0004$. Adj R^2 18%, SE estimate = 1.16	1.1 (0.5, 1.6)	0.0001
Metabolic syndrome (*n*)[b] Hosmer and Lemeshow test, $p = 0.6789$	9.1 (2.6, 31.2)	<0.0001

Due to the nightly variability of the RDI, OSA was coded as a dummy variable before being entered as a predictor into the regression model. Data were analysed using multiple linear regression unless otherwise stated and assumptions were checked by inspection of the residuals. All data were adjusted for age, BMI, smoking, and alcohol consumption. β coefficients were expressed as the β coefficient (95% confidence interval). These represent the average change that OSA causes in each outcome.

[a] Multiple linear regression was performed on log-transformed outcome data. In this instance the β coefficient (95% confidence interval) was antilogged to give the values presented in the table.

[b] Categorical outcome data were analysed using multiple binary logistic regression and assumptions checked using the Hosmer Lemeshow goodness-of-fit test. In this instance the β coefficient refers to the odds ratio (95% confidence interval) of having the outcome in patients with OSA when compared to subjects without.

controls matched for BMI and waist–hip ratio.[25] Likewise, the presence of OSA has been shown to be independently associated with increased fasting insulin concentrations.[6] Triglyceride concentrations have also been shown to be increased in subjects with OSA, but these subjects had significantly more subcutaneous fat than their controls, as reflected by increased skinfold thickness.[10] Investigators studying insulin resistance have identified a significant relationship with OSA even after adjusting for the waist–hip ratio and total adiposity.[6,7] However, because of a high correlation between BMI and waist circumference, percentage body fat, and fat mass, we were not able to adjust our regression analysis for possible differences in fat distribution. Therefore, it is conceivable that these independent relationships may have been confounded by altered fat distribution in the subjects with OSA. A separate regression analysis (data not shown) demonstrated that the addition of waist circumference did not significantly alter the fit or conclusions of the model. This is the first study to show that OSA is independently associated with lower HDL cholesterol concentration and an increased prevalence of metabolic syndrome.

There are a number of possible reasons why OSA may be independently associated with an increase in the risk factors that comprise the metabolic syndrome. It is possible that OSA either directly increases these factors, or that OSA and the metabolic syndrome share a common risk factor other than obesity, such as sedentary lifestyle.[26,27] Intervention studies using CPAP or a structured physical activity program will be needed to clarify this. Furthermore, as higher blood pressures are associated with both metabolic syndrome[11] and OSA,[3,4,25] OSA may only appear to be linked to the metabolic syndrome because of its association with hypertension. However, the independent associations with other components of the metabolic syndrome suggest that this is unlikely.

The independent relationships we have demonstrated may provide a clear rationale for the increased cardiovascular mortality reported in subjects with OSA.

Several epidemiological[28–34] and observational studies[28,35] have demonstrated a strong, independent, etiologically significant continuum of cardiovascular risk across all levels of systolic and diastolic blood pressure. Likewise, several epidemiological studies have identified a low plasma HDL cholesterol concentration as a strong independent predictor of coronary heart disease in the general population.[36–39] In contrast, the trend towards higher triglyceride concentrations in subjects with OSA may not provide any additional information over HDL cholesterol about their long-term cardiovascular risk.[40,41] Furthermore, the metabolic syndrome is associated with a threefold increase in the risk of coronary heart disease and stroke and a significant increase in cardiovascular mortality.[42,43] The trend we demonstrated towards greater insulin resistance in subjects with OSA after adjusting for obesity and other known covariates may also contribute to the increased cardiovascular mortality associated with this group. The San Antonio Heart Study demonstrated a significant trend in increasing risk for cardiovascular events after 7.5 years across all quintiles of HOMA at baseline,[44] even after adjusting results for age, sex, ethnicity, triglycerides, LDL and HDL cholesterol, systolic blood pressure, smoking, alcohol consumption, leisure time exercise, and waist circumference. The magnitude and direction of these associations were also similar when stroke and coronary artery disease were analysed separately.

In order to determine whether OSA was associated with an increase in the risk factors that comprise metabolic syndrome and its overall prevalence independently of obesity, it may have been more appropriate to employ a matched case-control design, with BMI as the matching variable. However, because of our strict exclusion criteria this would have allowed us to recruit only a small number of patients, potentially reducing statistical power. It was particularly important that we avoid this because of the multiple outcomes being investigated. Therefore, we felt it was more appropriate to recruit all eligible subjects and analyse the data using a regression analysis. However a subgroup analysis of 34 subjects with OSA and 29 controls matched for all obesity-related variables (data not shown) demonstrated a 38% absolute increase in the prevalence of metabolic syndrome ($p < .001$), which is consistent with the regression analysis.

This study is likely to minimise the true differences between patients with OSA and BMI-matched controls rather than exaggerate them. We used an RDI of 15 events/h to define OSA. However, the Sleep Heart Health Study found that OSA was associated with hypertension and cardiovascular disease at RDI thresholds as low as 5 events/h.[2] Therefore, it is possible that changes in outcome measures were already present in some individuals in the control group. Nonetheless, clear differences were shown between the groups and an independent relationship between OSA and the outcomes in the regression despite this potential decrease in statistical power. Likewise, a limited respiratory study was used to exclude OSA in the control group, which did not allow us to identify and remove subjects with significant upper airway resistance that may have resulted in sleep fragmentation, a known cause of disturbances in glucose metabolism.[45] Furthermore, the exclusion of subjects with diabetes and severe or treated hypertension, who are known to be over-represented among OSA patients, would strongly mitigate finding a difference. The lack of women in this study means that its conclusions cannot be extrapolated to this group.

In conclusion, OSA is independently associated with an increase in the cardiovascular risk factors that comprise metabolic syndrome and its overall prevalence. This may help explain the increased cardiovascular morbidity and mortality associated with this condition.

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