Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong

Jamie C.M. Lam, Bing Lam, Chi-leung Lam, Daniel Fong, Julie K.L. Wang, Hung-fat Tse, Karen S.L. Lam, Mary S.M. Ip

Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, SAR, China
Department of Nursing Studies, The University of Hong Kong, Hong Kong, SAR, China

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Summary
Objective: To investigate the relationship between obstructive sleep apnea (OSA) and the metabolic syndrome, an established cardiovascular risk factor, in middle-aged Chinese subjects.
Design: A prospective cross-sectional study from community-dwelling volunteers.
Subjects: Subjects of either sex between 30 and 60 years old were recruited from the staff in public institutions or visitors to community centers in Hong Kong.
Methods: Demographic and anthropometric indices, blood pressure and metabolic profile (fasting blood glucose, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol and triglycerides) were measured. Overnight polysomnographic studies were conducted. Presence of obstructive sleep apnea (OSA) was defined as apnea–hypopnea index (AHI) ≥ 5. Metabolic syndrome was defined by the criteria of the National Cholesterol Education Panel, but using Asian cut-off values for abdominal obesity.
Results: A total of 255 subjects (150 men, 105 women) were studied. Subjects with OSA had five-fold risk of having metabolic syndrome. OSA was associated with the metabolic syndrome or its components, including waist circumference, diastolic blood pressure and fasting glucose, after adjusting for confounding variables. The independent determinants of OSA were age, gender, body mass index (BMI) and the metabolic syndrome.
Conclusion: Among community-based middle-aged Chinese subjects, the metabolic syndrome was independent predictor of OSA.

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Introduction

Obstructive sleep apnea (OSA) has been associated with increased cardiovascular and cerebrovascular morbidity and mortality, and there is growing evidence of an independent contribution of OSA towards this, although much of the causal role and mechanisms are still being unraveled. The hypothesized link between OSA and cardiovascular disease (CVD) is complex and likely involves interactions of pathophysiologic mechanisms in sleep-disordered breathing with various metabolic risk factors for CVD.

The clustering of several metabolic and morphologic features in the metabolic syndrome including insulin resistance or glucose intolerance, dyslipidemia, hypertension and abdominal obesity is well recognized as a risk factor for CVD. It has long been observed in clinical practice that OSA is highly associated with various features of the metabolic syndrome, in particular, obesity. Research has focused on the association between OSA and individual components of the metabolic syndrome independent of obesity, and there is now good evidence to support an independent adverse effect of OSA on hypertension, while evidence on other factors is also increasing. The Sleep Heart Health Study, a cross-sectional epidemiologic study of over 6000 middle-aged subjects in the USA, reported on the association of sleep-disordered breathing and a number of cardiovascular risk factors, including parameters in the metabolic syndrome. Recently, a European study comparing male OSA subjects from a sleep clinic with controls without OSA showed independent associations between OSA and the metabolic syndrome as well as its components.

In Chinese subjects, despite the lesser severity of obesity compared with non-Asian populations, obesity has also been demonstrated to be a major risk factor for OSA. Recently, the World Health Organization (WHO) has recommended lower threshold values for definitions of obesity and abdominal obesity and for intervention of obesity-related diseases in the Asian population. We have also observed in clinic populations that OSA is highly associated with the features seen in the metabolic syndrome. The aim of this prospective study was to investigate the relationship between OSA and the metabolic syndrome or its components in a cohort of middle-aged community-based Chinese adults in Hong Kong.

Methods

Subjects and protocol

This study was part of a territory-wide community-based project investigating the epidemiology of sleep-disordered breathing in middle-aged (30–60 years) Chinese adults in Hong Kong. Subjects were recruited from staff in public institutions and visitors to community centers, and those who had participated in a study on the prevalence of sleep-disordered breathing in Chinese in Hong Kong, the methodology and results of which have been reported previously. The public institutions were government departments for non-health-related functions, while the community centers were operated by non-government organizations that provided a variety of welfare activities. A questionnaire on demographics, sleep symptoms and medical history was completed. Subjects who agreed to undergo in-laboratory polysomnograms (PSG) comprised the cohort investigated in this study. Anthropometric indices were taken, and fasting blood samples for metabolic parameters were collected in the morning after the sleep study. The study was approved by the Ethics Committee of The University of Hong Kong and all subjects gave their written informed consent.

Polysomnography

Subjects underwent an overnight 16-channel PSG (Alice 3 system; Respironics, Pittsburgh, PA) at the Sleep Laboratory, Queen Mary Hospital, as described previously. PSG recordings were manually scored according to standard criteria. OSA was defined by an apnea–hypopnea index (AHI) $\geq 5$.

Anthropometric and biochemical measurements

Body weight and height were measured (Detecto scale, MO, USA) in bare feet and light clothing in the morning. Body mass index (BMI) was defined as weight (kg)/height$^2$ (m). Waist circumference was
measured at a level midway between the lower costal margin and the iliac crest. Blood pressure was measured with Dinamap (Critikon Inc., Florida) and the average of three readings taken at a 1-min interval was documented. Fasting blood was taken in the morning for estimation of serum glucose and lipid profile comprising total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides. Fasting blood glucose was measured by the glucose oxidase method on a Beckman autoanalyzer (Beckman Instruments, Bream, CA). Total cholesterol, triglycerides and HDL-cholesterol concentrations were measured using an immunocolorimetric assay on an ADVIA 1650 chemistry system (Bayer Corporation, Tarrytown, NY, USA). LDL-cholesterol was derived using the Friedwald equation.

**Definition of the metabolic syndrome**

The definition of the metabolic syndrome was based on the clinical diagnostic criteria of the Third Report of the National Cholesterol Education Program (NCEP), as the presence of three or more of the following five risk factors: hypertension as defined by a history of hypertension and taking anti-hypertensive drugs, or a recorded systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg; insulin resistance or glucose intolerance as defined by a history of diabetes mellitus and receiving drug treatment, or a fasting blood glucose concentration ≥ 6.1 mmol/L; HDL-cholesterol in men < 1.03 mmol/L or in women < 1.29 mmol/L; a serum total triglyceride concentration ≥ 1.69 mmol/L; and abdominal obesity as defined by waist circumference according to the recommended criteria for Asians, at ≥ 90 cm in men and ≥ 80 cm in women. These threshold criteria for abdominal obesity were recommended by WHO and have been subsequently validated in Asians or southern Chinese populations in Singapore and Hong Kong, respectively. Obesity was defined at BMI ≥ 25, as recommended for Asians. We also accepted two subjects on lipid-lowering drugs as fulfilling the criteria for hyperlipidemic parameters.

**Data analysis**

Descriptive statistics were used to summarize subject characteristics and questionnaire data. Continuous variables were expressed as mean values ± SD. The primary study parameter, OSA, was used as the dependent categorical variable in all analyses. Those data that were not normally distributed were log-transformed before analysis. Comparisons between OSA and non-OSA groups of baseline characteristics were made with the Student’s t-test for continuous variables, while categorical variables were assessed by the Chi-square test and analysis of variance. Correlations between OSA and metabolic variates were evaluated with the Pearson’s correlation test, after excluding those on drug treatment, for the relevant metabolic condition.

In order to determine whether the associations between OSA and the individual metabolic parameters were independent of obesity and other known covariates, logistic regression analysis was performed, adjusted for age, gender, BMI, smoking and alcohol consumption. The independent variables were: age, gender, BMI, smoking, alcohol consumption, and the metabolic syndrome entity. The interactions between the metabolic syndrome and age, BMI, and gender, respectively, were considered in the regression analysis to assess the strength of the associations. A P-value of < 0.05 was considered to indicate statistical significance. Statistical analyses were performed with SPSS for Windows software (version 12.0).

**Results**

Of 1612 questionnaire respondents 259 (16%) subjects came for PSG. Four were rejected due to insufficient sleep time (< 4 h sleep time) in 3, and a technical fault in 1, recordings. Thus, 255 subjects (150 men, 105 women) had data for both sleep parameters and metabolic profile. Compared to BMI data obtained in a community study of over 7000 subjects in Hong Kong (22), the men in our study had a slightly higher BMI (mean age 41.8 years with a mean BMI of 25.9 vs. 40–44 years old with a mean BMI 24.4), while women had comparable BMI (mean age 44.3 years with a mean BMI 24.3 vs. 40–49 years old with a mean BMI of 24.3). Self-reported history of relevant medical diseases on treatment was: hypertension: 33; diabetes mellitus: 18; and hyperlipidemia: 2. There were 17 (6.7%) current smokers, 11 (4.3%) current alcoholic drinkers (defined as regularly drinking more than 3 days a week).

Of 255 participants, 95 (37%) were found to have an AHI ≥ 5 and 160 (63%) had an AHI < 5. Table 1 shows that subjects with OSA had a significantly worse metabolic profile compared to those without OSA.
Of 255 subjects, 88 (34.5%) fulfilled the criteria of metabolic syndrome. Fifty-five of these 88 subjects (62.5%) with the metabolic syndrome had OSA, while only 40 of 167 (24%) subjects without the metabolic syndrome had OSA (62.5% vs. 24%, \( P < 0.001 \)). Subjects with OSA had a 5-fold risk of...
having the metabolic syndrome (OR 5.3, CI 3.03–9.26, \(P<0.001\)) compared to subjects without OSA (Table 2).

A linear trend effect of increasing association with the metabolic syndrome as the severity of OSA increased in terms of AHI was demonstrated (Table 3).

On univariate analysis, OSA was significantly correlated with age (\(r = 0.259, P<0.001\)), BMI (\(r = 0.449, P<0.001\)), waist circumference (\(r = 0.448, P<0.001\)), systolic blood pressure (\(r = 0.289, P<0.001\)), diastolic blood pressure (\(r = 0.289, P<0.001\)), triglycerides (\(r = 0.377, P<0.001\)) and HDL-cholesterol (\(r = -0.237, P<0.001\)). After adjusting for age, gender, BMI (except for analysis of waist circumference) and history of smoking and alcohol consumption, independent associations were observed between OSA and the following variables: waist circumference, diastolic blood pressure, fasting glucose concentration and the metabolic syndrome. Analysis of the influence of age, BMI or gender on the associations between OSA and the metabolic syndrome or its components did not reveal any substantial effect (Table 4).

In the stepwise logistic regression models, the independent determinants of OSA were age, gender, BMI, and the metabolic syndrome in our study population (Table 5).

### Discussion

This study is the first to address the relationship between the metabolic syndrome and sleep-disordered breathing in a group of community-based Asian subjects, using overnight polysomnography objectively and measured metabolic parameters. Those with OSA had 5-times more likelihood of suffering from the metabolic syndrome and vice versa. The metabolic syndrome and several of its components were independently associated with OSA.

Obesity and abdominal obesity are established risk factors for OSA\(^3\),\(^4\) while abdominal obesity is known to play an important role in the development of insulin resistance and the metabolic syndrome.\(^3\),\(^25\),\(^26\) Thus, abdominal obesity plays a pivotal role in the link between OSA and the metabolic syndrome.

### Table 4

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Obstructive sleep apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Waist circumference(a)</td>
<td>3.56</td>
</tr>
<tr>
<td>Systolic blood pressure(a)</td>
<td>1.47</td>
</tr>
<tr>
<td>Diastolic blood pressure(a)</td>
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</tr>
<tr>
<td>HDL-cholesterol(a)</td>
<td>1.29</td>
</tr>
<tr>
<td>Triglycerides(a)</td>
<td>1.42</td>
</tr>
<tr>
<td>Fasting glucose(a)</td>
<td>2.74</td>
</tr>
<tr>
<td>Metabolic syndrome(\geq 3) risk factors</td>
<td>2.65</td>
</tr>
</tbody>
</table>

Metabolic variables were defined according to NCEP cut-off values (except waist circumference as recommended for Asians by WHO).

Interactions between the metabolic syndrome and gender, age, and BMI were considered.

\(a\)Adjusted for age, gender, history of smoking and alcohol consumption.

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### Table 5

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Obstructive sleep apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Gender(a)</td>
<td>0.51</td>
</tr>
<tr>
<td>Age (year)(a)</td>
<td>1.10</td>
</tr>
<tr>
<td>BMI (kg/m(^2))(a)</td>
<td>1.30</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>2.62</td>
</tr>
</tbody>
</table>

Independent variables: age, gender, body mass index, history of smoking and alcohol consumption and the metabolic syndrome were considered.

By stepwise logistic regression analysis.

\(a\)Female gender was an independent factor for a lower risk of obstructive sleep apnea.

\(a\)Age and BMI were analyzed as continuous variables and the odds ratios reflected the risk associated with each incremental year of age and unit of BMI, respectively.
metabolic syndrome.\textsuperscript{27} Despite the confounding effect of obesity, previous studies have shown that there is an independent association between OSA and other parameters of the metabolic syndrome such as hypertension\textsuperscript{28–30} and insulin resistance.\textsuperscript{27,31–34}

There is a consensus of evidence to support that OSA has an adverse effect on elevation of blood pressure and OSA patients have an increased risk of hypertension, independent of obesity and age.\textsuperscript{28–30} This was again illustrated in the independent association of OSA and elevated diastolic blood pressure in this cohort study. It has been well demonstrated in previous studies that the diastolic blood pressure was more strongly associated with OSA\textsuperscript{14,28,32} and the observed decrease in 24-h diastolic blood pressure was greater after continuous positive airway pressure (CPAP) treatment, as compared to systolic blood pressure.\textsuperscript{35}

Subjects with diabetes mellitus are often obese and they have been shown to have a high prevalence of OSA.\textsuperscript{31} Although the relationship between insulin resistance and OSA has not been fully delineated yet, there is accumulating evidence to support the fact that OSA is associated with insulin resistance, independent of obesity,\textsuperscript{27,12,33} and treatment of OSA has been reported to improve insulin sensitivity.\textsuperscript{34} Consistent with these previous findings, we demonstrated a significant association between fasting blood glucose and OSA, independent of confounding variables.

The relationships between OSA and various lipid parameters have not been as extensively investigated as that of other components in the metabolic syndrome and the results have been more diverse. The American Heart Health Sleep Study reported that AHI was inversely related to HDL-cholesterol levels in younger men and women, but not in older men, and triglyceride levels in younger men and women only.\textsuperscript{8} Studies of sleep clinic cohorts have consistently reported a higher prevalence of dyslipidemia in OSA subjects compared to those without OSA,\textsuperscript{14,36,37} including a recent study of Caucasian men, which reported an independent association between increased triglyceride concentrations, decreased HDL-cholesterol levels, and increased total cholesterol:HDLC-cholesterol ratio.\textsuperscript{9} An association between the number of apolipoprotein E4 alleles, a gene leading to higher LDL-cholesterol levels has also been reported, while the severity of OSA was associated with higher levels of LDL-cholesterol.\textsuperscript{38} The treatment of OSA was reported to result in a decrease of total cholesterol levels.\textsuperscript{37} In this study, although there were correlations between OSA and the lipid levels, the associations did not manifest when controlled for confounding variables, and we did not identify an association between OSA and the lipid syndrome-defining parameters. Compared to the relationships between OSA and various individual metabolic variates, there are much less data in the literature regarding the relationship between OSA and the metabolic syndrome entity. The European study of Caucasian men with OSA reported a nine-fold risk for the metabolic syndrome,\textsuperscript{9} while Chinese men in this study demonstrated a lower association at a five-fold risk. Similar to their findings, an independent association between the metabolic syndrome and sleep-disordered breathing was seen. The Caucasian study comprised OSA subjects who were recruited from sleep clinics while our recruitment was targeted at community-based subjects. Sleep clinic subjects have inherent referral bias for those with features of both sleep apnea and obesity with or without an obesity-related metabolic profile, thus predisposing towards a higher association,\textsuperscript{39} while this tendency would be less in community-based recruitment, although self-selection bias for study participation could not be eliminated. Our subjects came for sleep study on a voluntary basis, and those who believed they were more likely to have sleep apnea (usually those who were more obese) tended to come. On comparing the BMI of age-matched subjects from a previous large-scale study in the local community,\textsuperscript{22} the men in our study were only slightly more obese while women had similar BMIs. Thus, the effect of self-selection bias was probably not significant. The discrepancy in the degree of association between OSA and the metabolic syndrome reported in the two studies may also be due to variations in genetic or environmental predisposition to either condition in these two cohorts of different ethnicity and locality.

There is ongoing research to understand the genetics of OSA, and initial work has focused on the search for genetic loci contributing to OSA and its associated phenotypes such as obesity. In a genomewide scan for OSA genes, there was some evidence of a linkage to AHI and BMI on chromosome 2p in white American subjects. This region coincides with the loci for propiomelanocortin (POMC), a hormone which is known to be closely connected to obesity and related phenotypes.\textsuperscript{40} It is plausible, although highly postulative at this point of our knowledge, that the genetic determinants of OSA and the metabolic syndrome may be closely linked to each other. On the other hand, OSA is characterized by increased sympathetic output and other pathophysiological mechanisms that may provide an independent predisposition to
the generation of atherosclerosis, either directly or through aggravation of some of these metabolic risk factors, resulting in an independent association. Our findings highlight the importance of a high index of suspicion for OSA in Chinese subjects with the metabolic syndrome and vice versa. Prompt recognition and effective treatment of co-existent risk factors may reduce cardiovascular morbidity and mortality, and concerted community and professional efforts on appropriate lifestyle behavioral modifications should be propagated.

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