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METHODS • ORIGINAL ARTICLE

The association between obstructive sleep apnea syndrome and metabolic syndrome: a confirmatory factor analysis

Fan Wang[1,2,3] · Xiaolu Xiong[4] · Huajun Xu[1,2,3] · Hengye Huang[5] · Yue Shi[5] · Xinyi Li[1,2,3] · Yingjun Qian[1,2,3] · Jianyin Zou[1,2,3] · Hongliang Yi[1,2,3] · Jian Guan[1,2,3] · Shankai Yin[1,2,3]

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Abstract

Background Growing evidence suggests an independent relationship between obstructive sleep apnea syndrome (OSAS) and metabolic syndrome (MS). Patients with OSAS always show clustering of metabolic components. However, the understanding of interplay between OSAS and metabolic components is still lacking.

Methods Participants were consecutively enrolled from our sleep center during the period 2009–2013. Anthropometric variables, metabolic indicators, and sleep parameters were collected from all participants. The factor structure for MS in OSAS and non-OSAS was examined by confirmatory factor analysis.

Results The OSAS and non-OSAS demonstrated clustering of metabolic components. MS in patients with OSAS was strongly associated with insulin resistance (standardized factor loading = 0.93, $p < 0.001$), obesity (loading = 0.92, $p < 0.001$), and the lipid profile (loading = 0.72, $p < 0.001$). Furthermore, insulin resistance was correlated with obesity and lipid profile ($r = 0.86$, $p < 0.001$; $r = 0.68$, $p < 0.001$, respectively). Obesity and lipid profile were also highly correlated in OSAS ($r = 0.66$, $p < 0.001$). In non-OSAS, MS was strongly associated with insulin resistance, obesity, and lipid profile (loading = 0.95, $p < 0.001$; loading = 0.74, $p < 0.001$; loading = 0.68, $p < 0.001$, respectively). Insulin resistance was most strongly associated with fasting insulin (loading = 0.65, $p < 0.001$). Lipid profile was most strongly associated with TG (loading = 0.88, $p < 0.001$). Obesity was most strongly associated with BMI (loading = 0.80, $p < 0.001$).

Conclusions OSAS is more prone to show clustering of metabolic components compared with non-OSAS. In particular, insulin resistance, obesity, and the lipid profile were independently and strongly correlated with MS in OSAS.

Keywords Confirmatory factor analysis · Insulin resistance · Obesity · Obstructive sleep apnea syndrome · Metabolic syndrome

Introduction

According to the guidelines of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), metabolic syndrome (MS) is characterized by a constellation of metabolic abnormalities, including dyslipidemia, visceral obesity, hyperglycemia, and hypertension [1]. The prevalence of MS varies from 20 to 40% worldwide and has increased commensurate with the

Fan Wang and Xiaolu Xiong contributed equally to this work.

✉ Huajun Xu
sunnydayxu2010@163.com

✉ Hengye Huang
huanghy1107@qq.com

✉ Jian Guan
guanjian0606@sina.com

[1] Department of Otolaryngology Head and Neck Surgery & Center of Sleep Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Yishan Road 600, Shanghai 200233, China

[2] Shanghai Key Laboratory of Sleep Disordered Breathing, Yishan Road 600, Shanghai 200233, China

[3] Otolaryngological Institute, Shanghai Jiao Tong University, Yishan Road 600, Shanghai 200233, China

[4] Department of Endocrinology, Drum Tower Hospital, Affiliated to Nanjing University Medical School, Nanjing 210008, China

[5] Department of Epidemiology, School of Public Health, Shanghai Jiao Tong University, 225 South Chongqing Road, Shanghai 200020, China

obesity epidemic [2–4]. MS is commonly recognized as an important risk factor for cardiovascular disease (CVD) and even all-cause mortality [5, 6].

Obstructive sleep apnea syndrome (OSAS) is considered to be one of the important sleep disorders, affecting 2–4% of the general population and increased with obesity, with a prevalence of 9~17% recently [7, 8]. OSAS is a chronic respiratory condition, characterized by repeated/partial upper airway obstruction, evidenced by repetitive hypopnea/apnea events during sleep [9]. It is widely recognized that OSAS is not only a sleep disorder per se but also a heterogeneous metabolic disorder [10, 11]. Given that OSAS is highly prevalent, it has become a major public healthcare concern.

According to our previous meta-analysis addressing the relationship between OSAS and MS, we demonstrated that OSAS is significantly associated with increased MS risk [12]. However, small sample sizes (range 79–546), standard polysomnography (PSG) monitoring, and inadequate adjustment for confounding factors, such as obesity, are common problems leading to inconsistent results among previous studies (seven papers reported positive associations and six non-significant associations). More importantly, MS does not represent a single entity and has several underlying pathways. Considering that none of the aforementioned studies explored the relationship between distinct metabolic components and the risk of OSAS, in-depth understanding of the relationship between OSAS and these components will help establishing screening and preventive interventions for OSAS with high metabolic risk.

We applied a more sophisticated and rigorous statistical method, called confirmatory factor analysis (CFA) to OSAS and non-OSAS groups to understand the complex relationship better. This statistical approach has rarely been used in the context of OSAS. CFA is more capable of modeling the associations among various metabolic factors compared with traditional multivariate models. In addition, CFA allows for a deeper understanding of the magnitude of the effect of each MS component and subcomponent.

Materials and methods

Study participants

Our study was approved by the ethics committee at our clinical institution and conducted in accordance with the Declaration of Helsinki. A consecutive sample of all adult participants referred for suspected OSAS, and who presented with snoring and/or daytime sleepiness, was recruited from our Sleep Center between January 2007 and November 2013. A questionnaire capturing basic information, such as health status and personal medical history, was completed by all participants. Participants who accepted a previous OSAS treatment, such as continuous positive airway pressure (CPAP) therapy, upper airway surgery, or application of oral appliances, prior to our study were excluded. Other exclusion criteria for selecting subjects included a clinical history of diabetes mellitus, hypertension, or hyperlipidemia; acute or chronic cardiorespiratory, hepatic, or nephric diseases; other sleep disorder (e.g., central sleep apnea (CSA), insomnia, restless leg syndrome (RLS), upper airway resistance syndrome (UARS), or narcolepsy); alcoholism, and drug addiction. All eligible participants signed an informed consent form.

Clinical and biochemical measurements

Five anthropometric indices (i.e., height, weight, waist circumference (WC), neck circumference (NC), and hip circumference (HC)) were measured at baseline by trained physicians when wearing only undergarments and standing upright. A horizontal position was assumed for measurement of the cricothyroid membrane, the midpoint between lowest rib and iliac crest, and the widest girth at greater trochanters, corresponding to the NC, WC, and HC, respectively. After a 15-min rest, blood pressure, such as systolic blood pressure (SBP) and diastolic blood pressure (DBP), was measured by a mercury sphygmomanometer, with the participant in a seated position. All of the basic parameters mentioned above were measured twice and mean values were calculated.

After fasting venous blood of each subject was collected at 7 a.m., the serum lipid profile (i.e., triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)) was examined by the clinical laboratory of the hospital. Fasting serum glucose was determined with an H-7600 autoanalyzer (Hitachi, Tokyo, Japan), and serum insulin levels were determined by an immunoradiological method.

Sleep evaluation

The Chinese version of the self-administered Epworth Sleepiness Scale (ESS) with a total score of 0–24 was applied to evaluate the daytime sleepiness of each participant [13]. Sleepiness was considered clinically significant if the total ESS score was > 10. To objectively evaluate sleep status, participants underwent hospital-based standardized PSG monitoring for 1 night (Alice 4 or 5; Respironics, Pittsburgh, PA, USA), which comprised electroencephalography (EEG) (including the C3-M2 and C4-M1 channels), electrooculography (EOG), chin/leg electromyography, airflow measurements, thoracoabdominal movement measurements (using piezo bands), use of a snoring sensor, electrocardiography, and body position and oxygen saturation measurements. The raw PSG data were transferred automatically for scoring. The complete set of PSG data were manually reviewed by experienced sleep technicians using the internationally recognized 2007 criteria of the American Academic Sleep Medicine (AASM) [14].

Calculation and definitions

As a general measure of obesity, body mass index (BMI) was defined as weight divided by height squared (kg/m^2). The waist/hip ratio was defined as WC/HC. The homeostatic model of insulin resistance (HOMA-IR) was defined as glucose (mmol/L) × insulin (μU/mL)/22.5. MS was defined as the presence of three or more of the following clinical factors: WC ≥ 85 cm (in males) and ≥ 80 cm (in females); serum TG ≥ 1.70 mmol/L; HDL-C < 1.03 mmol/L in males and < 1.30 mmol/L in females; high blood pressure (SBP more than 130 mmHg or DBP more than 85 mmHg); and fasting blood glucose more than 5.6 mmol/L, according to the NCEP ATP III criteria for Asians [15].

Apnea was defined as an absence of oronasal airflow lasting at least 10 s or an at least 90% decrease more than 10 s. Hypopnea was defined as any upper airflow reduction lasting at least 10 s, with either a decrease in oxyhemoglobin saturation at least 3% or oxyhemoglobin saturation terminated by awakening. The apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and arousal were given by the number of apnea and hypopnea, desaturation events ≥ 3%, and shifts in EEG more than 3 s per hour of sleep, respectively. Following the AASM 2007 criteria [14], the micro-arousal index (MAI) was defined as average events of arousals per hour. OSAS was defined if AHI was more than five times per hour.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the distribution of raw data. If data are normally distributed, it provided as means and standard deviation. If data are skewed, it provided as medians (interquartile range). If data are categorical, it provided as percentages. Comparisons between groups were

Table 1 Demographic characteristics of the subjects

Variables	Total sample ($N = 794$)	Non-OSAS ($n = 397$)	OSAS ($n = 397$)	p value
Age	38 (31–47)	39 (31–47)	38 (32–47)	0.989
BMI (kg/m^2)	24 (22.20–25.95)	23.88 (22.15–25.65)	24.16 (22.25–26.30)	0.067
Male (%)	567 (71.4)	231 (58.2)	336 (84.6)	< 0.001**
NC (cm)	37 (35–39)	36 (33.75–38)	38 (36–40)	< 0.001**
WC (cm)	88 (83–94)	86 (80–91)	91 (85–96)	< 0.001**
HC (cm)	97 (93–100)	96 (92–100)	98 (93–101)	< 0.001**
Waist/hip ratio	0.92 (0.87–0.95)	0.90 (0.85–0.94)	0.93 (0.90–0.97)	< 0.001**
Fasting glucose (mmol/l)	5.06 (4.73–5.42)	4.93 (4.58–5.29)	5.19 (4.84–5.54)	< 0.001**
Fasting insulin (mmol/l)	7.88 (5.45–11.68)	7.33 (5.01–10.31)	8.71 (5.98–13.42)	< 0.001**
HOMA-IR	0.57 (0.65)	0.41 (0.60)	0.73 (0.66)	< 0.001**
TC (mmol/l)	4.56 (3.99–5.27)	4.38 (3.85–5.07)	4.74 (4.17–5.42)	< 0.001**
TG (mmol/l)	1.28 (0.87–1.90)	1.14 (0.75–1.64)	1.46 (1.02–2.13)	< 0.001**
HDL (mmol/l)	1.09 (0.95–1.27)	1.10 (0.96–1.33)	1.07 (0.94–1.25)	0.039*
LDL (mmol/l)	2.88 (2.39–3.44)	2.70 (2.24–3.23)	3.07 (2.59–3.65)	< 0.001**
SBP (mm/Hg)	120 (110–127)	118 (108–125)	120 (112–129)	< 0.001**
DBP (mm/Hg)	77 (70–82)	76 (69–81)	79 (70–83)	0.020*
Mean $Sa0_2$ (%)	96 (94–97)	97 (96–98)	94.9 (93–96)	< 0.001**
$LSpO_2$ (%)	89 (80–93)	93 (90–96)	81 (72–87)	< 0.001**
ODI	5.8 (1.3–29.3)	1.4 (0.5–3.4)	29.1 (12–52.7)	< 0.001**
MAI	16.85 (7.10–30.10)	11.6 (6.3–20.3)	23.9 (10.2–39.45)	< 0.001**
AHI	5 (1.30–29.20)	1.3 (0.4–2.77)	29.2 (12.7–50.9)	< 0.001**
ESS	6 (2–11)	4 (0–9)	8 (4–12)	< 0.001**

OSAS obstructive sleep apnea syndrome, *BMI* body mass index, *NC* neck circumference, *WC* waist circumference, *HC* hip circumference, *HOMA-IR* homeostasis model of assessment for insulin resistance index, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, SaO_2 oxygen saturation, $LSpO_2$ lowest pulse oxygen saturation, *ODI* oxygen desaturation index, *MAI* micro-arousal index, *AHI* apnea-hypopnea index, *ESS* Epworth Sleepiness Scale

*$p < 0.05$; **$p < 0.001$

performed with the *t* test for normally distributed or the Mann–Whitney *U* test for skewed variables. Either the chi-square or Fisher's exact test was applied for categorical data. SPSS software (ver. 22.0, SPSS Inc., Chicago, IL, USA) was used to address most of the statistical analyses. Propensity score matching was used to account for baseline differences in age and BMI using the caliper method. We conducted the CFA using AMOS software (ver. 21.0, IBM Corp., Armonk, NY, USA). Maximum likelihood estimation was used for robust assessment of non-normally distributed variables. We used the chi-square test to evaluate the fit of the models. These fit indices included chi-square value (CMIN), degree of freedom (df), and chi-square value/degree of freedom (NC). Two further indices of model congruence were then applied, i.e., root mean square error of approximation (RMSEA) (threshold, < 0.08) and the comparative fit index (CFI) (threshold, > 0.90). Two-sided p values < 0.05 were considered to be significant.

Results

Subjects

A total of 2046 participants were finally included, of whom, 397 were without OSAS and 1649 were with OSAS. The overall propensity score was 0.78 ± 0.18. We chose a caliper value of 0.045 according to the principle that the caliper value should be less than one-quarter of the standard deviation of the propensity score. Thus, 397 non-OSAS and 397 age and BMI-matched OSAS subjects were chosen for additional analyses. The basic characteristics, biochemical variables, and sleep parameters are presented in Table 1. Age and BMI were similar between OSAS and non-OSAS groups. All metabolic variables and sleep parameters were worse in patients with OSAS than in those without (Table 1).

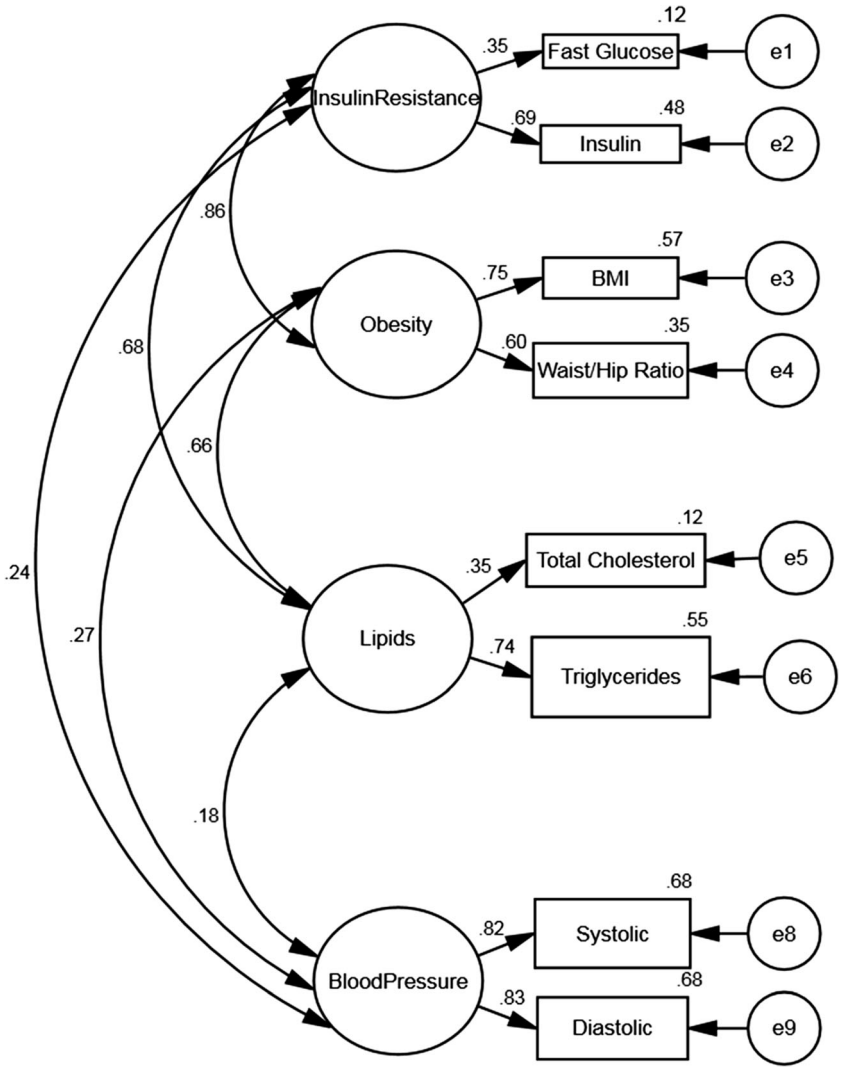

Fig. 1 Model estimation of metabolic risk factors associated with OSAS (model 1). Hierarchical 4-factor model of MS for OSAS. CMIN = 18.655, df = 16, $n = 397$, $p = 0.287$, NC = 1.166, CFI = 0.996, RMSEA = 0.020. "e" represents residual covariance

OSAS model (model 1)

MS in the OSAS group was indexed by four components (i.e., HOMA-IR, lipids, obesity, and blood pressure). A hierarchical four-factor model of MS was devised and showed a very high goodness-of-fit value (CMIN = 18.655, df = 16, $n = 397$, $p = 0.287$, NC = 1.166, CFI = 0.996, RMSEA = 0.020) (Fig. 1). As shown in Fig. 1, HOMA-IR, lipid profile, and obesity had associations with MS of varying strength. MS was most strongly associated with insulin resistance, obesity, and lipid profile (standardized factor loading = 0.93, $p < 0.001$ (86%), loading = 0.92, $p < 0.001$ (85%), loading = 0.72, $p < 0.001$ (52%), respectively). Insulin resistance was most strongly associated with fasting insulin and fasting glucose (loading = 0.70, $p < 0.001$ (48%), loading = 0.35, $p < 0.001$ (12%), respectively). Obesity was most strongly associated with BMI and waist/hip ratio (loading = 0.75, $p < 0.001$ (57%), loading = 0.59, $p < 0.001$ (35%), respectively). The lipid profile was most strongly associated with TG and TC (loading = 0.74, $p < 0.001$ (55%), loading = 0.35, $p < 0.001$ (13%), respectively). Finally, blood pressure factor was strongly associated with both SBP and DBP (loading = 0.80, $p < 0.001$ (64%), loading = 0.72, $p < 0.001$ (55%)).

Non-OSAS model (model 2)

The model for the non-OSAS group showed a poor fit (CMIN = 43.065, df = 16, $n = 397$, $p < 0.001$, NC = 2.692, CFI = 0.958, RMSEA = 0.065; Fig. 2). Here, MS was strongly associated with insulin resistance, obesity, and lipid profile (loading = 0.95, $p < 0.001$ (89%), loading = 0.74, $p < 0.001$ (55%), loading = 0.68, $p < 0.001$ (46%), respectively), but not blood pressure ((loading = 0.17, $p = 0.09$) (3%)). Insulin resistance was most strongly associated with fasting insulin and fasting glucose (loading = 0.65, $p < 0.001$ (42%), loading = 0.34, $p < 0.001$ (11%), respectively). Obesity was most strongly associated with BMI and the waist/hip ratio (loading = 0.80, $p < 0.001$ (64%), loading = 0.68, $p < 0.001$ (46%), respectively). Lipid profile was most strongly associated with TG (loading = 0.88, $p < 0.001$) (77%).

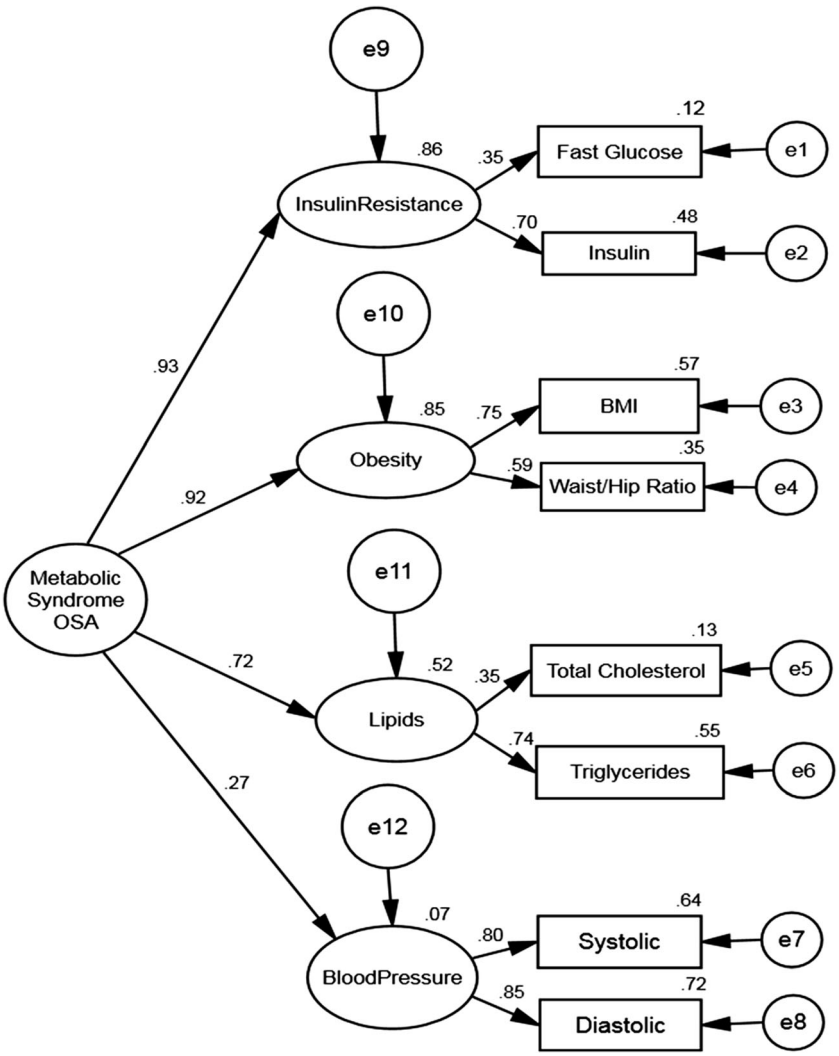

Fig. 2 Model estimation of metabolic risk factors associated with non-OSAS (model 2). Hierarchical 4-factor model of MS for non-OSAS. CMIN = 43.065, df = 16, $n = 397$, $p < 0.001$, NC = 2.692, CFI = 0.958, RMSEA = 0.065. "e" represents residual covariance

Relationship among metabolic variables in the OSAS (model 3) and the non-OSAS groups (model 4)

To further understand the relationship among the four metabolic variables (i.e., obesity, lipid profile, insulin resistance, and blood pressure), we also performed a four-factor correlation analysis in the OSAS group (Fig. 3). This model showed a goodness of fit (CMIN = 18.478, df = 14, $n = 397$, $p = 0.186$, NC = 1.320, CFI = 0.993, RMSEA = 0.028). Insulin resistance was correlated with obesity and lipid profile ($r = 0.86$, $r = 0.68$ respectively) (Fig. 3). The lipid profile and obesity were also highly correlated ($r = 0.66$). However, blood pressure was poorly correlated with obesity ($r = 0.27$), insulin resistance ($r = 0.24$), and the lipid profile ($r = 0.18$). Model 4 also showed a relatively good fit (CMIN = 36.524, df = 14, $n = 397$, $p = 0.001$, NC =2.609, CFI = 0.965, RMSEA = 0.064), where insulin resistance showed a similarly strong correlation with obesity and the lipid profile ($r = 0.71$ and $r = 0.68$, respectively) (Fig. 4). Obesity and lipid profile were also highly correlated ($r = 0.50$).

Discussion

Our study is the first to compare factor structure of MS between patients with and without OSAS. We found that metabolic factors were highly clustered in OSAS, but less so in those without OSAS. Furthermore, insulin resistance was the factor most strongly associated with metabolic status.

CFA is a data reduction technique specifically designed for validating amalgamated data [16]. CFA allows for construction of latent variables which cannot be directly measured [17]. When applied to clinical/epidemiological data, this method can be effective for testing specific hypotheses regarding the nature of underlying mechanisms [17]. Previous studies using CFA demonstrated that four core components

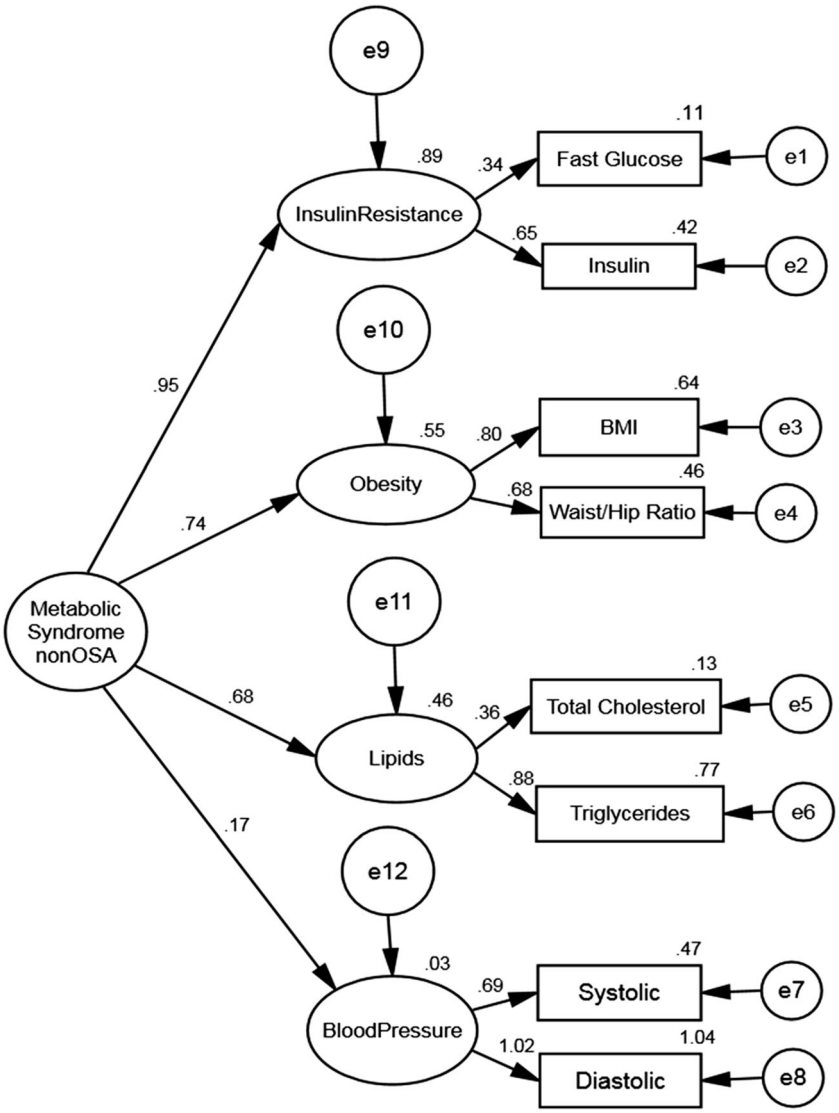

Fig. 3 Alternative model for the OSAS (model 3). Correlated 4-factor model for the OSAS. CMIN = 18.478, df = 14, $n = 397$, $p = 0.186$, NC = 1.320, CFI = 0.993, RMSEA = 0.028. "e" represents residual covariance

(obesity, insulin resistance, hypertension, and dyslipidemia) underlie MS [18, 19]. A deeper understanding of the pathophysiological process of OSAS could ultimately lead to the development of treatment strategies targeting the mechanism underlying the co-occurrence of MS components.

The independent contributions of single MS components in OSAS remain unclear. Some clinical studies have posited that obesity is the main metabolic component of OSAS [20], while others indicated that insulin resistance and the lipid profile are also important contributors [21–23]. In our study, MS was independently associated with obesity, insulin resistance, and lipid profile, explaining 85%, 86%, and 52% of the variance therein, respectively. Our study supports the notion that obesity, insulin resistance, and lipid profile are equally important in MS. The relationship between OSAS and these metabolic components can be explained as follows: (1) the majority of OSAS exhibit obesity and central adiposity, but not all patients [24]. Obesity can directly or indirectly contribute to upper airway narrowing during sleep, and OSAS can worsen obesity due to insulin resistance. Thus, a vicious circle is established. (2) Atherogenic lipoprotein abnormalities are also well documented in patients with OSAS, and they are closely related to insulin resistance [25]. (3) Reactive oxygen species, generated after intermittent hypoxia, combined with catecholamines impair pancreatic islet beta cell function and decrease insulin secretion, resulting in insulin resistance [26]. In patients with non-OSAS, MS was also independently associated with obesity, insulin resistance, and lipid profile. Snoring was as an important risk factor of dyslipidemia and MS, but not hypertension [27]. Daytime sleepiness and MS appear to be driven by adiposity measures in women and older age for men [28].

Our study is the first to examine the characteristics of MS patients with and without OSAS using a rigorous and innovative method. We also matched the OSAS and non-OSAS groups for age and BMI and included a relatively large sample. Furthermore, standard PSG ensured accurate diagnosis of OSAS. However, along with these strengths, there were some limitations that should be addressed. First, most of the subjects were enrolled from our sleep center, so the sample may not be representative of the whole population. Second, we used glucose and insulin levels to calculate insulin resistance, and not

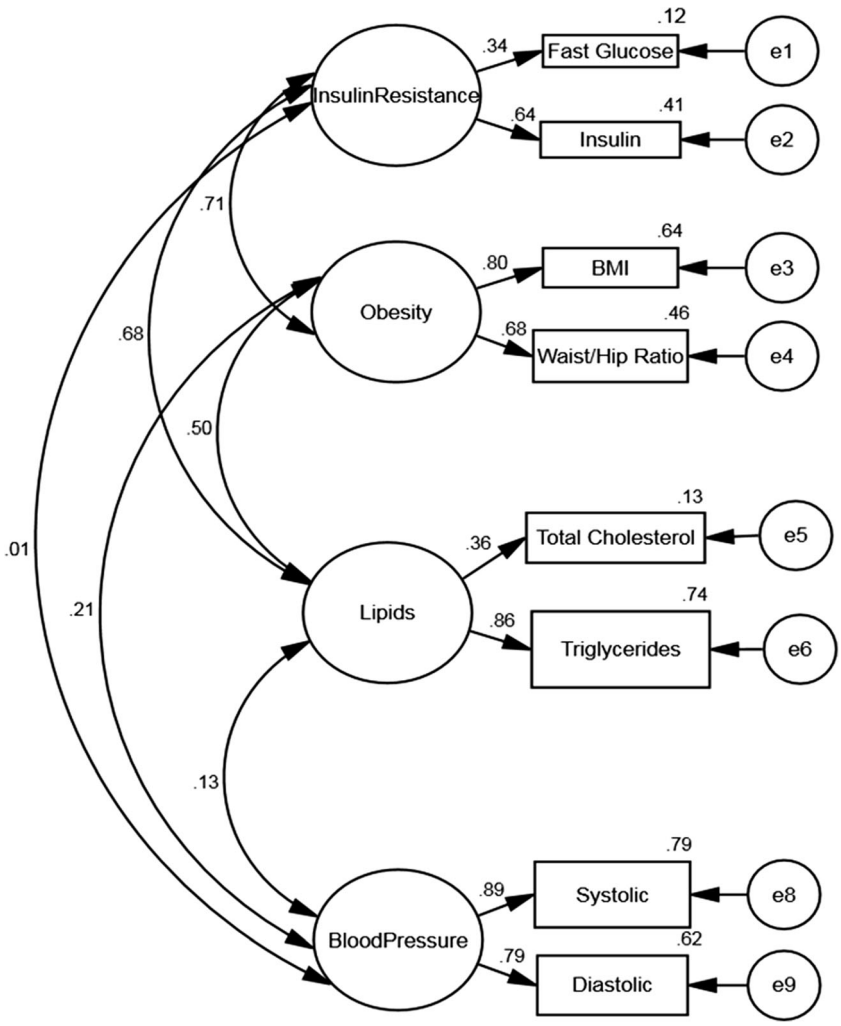

Fig. 4 Alternative model for the non-OSAS (model 4). Correlated 4-factor model for the non-OSAS. CMIN = 36.524, df = 14, $n = 397$, $p = 0.001$, NC = 2.609, CFI = 0.965, RMSEA = 0.064. "e" represents residual covariance

the glucose clamp technique. Third, MS was defined according to the NCEP ATP III criteria; however, definition of MS varies (c.f. International Diabetes Federation guidelines and Japanese criteria), and our findings may not be applicable to studies using other definitions of MS. Finally, the inherent limitations of a cross-sectional design prevent determination of direct causal relationships.

Overall, our study is the first specifically designed to explore the characteristics of MS patients with and without OSAS. In patients with OSAS, MS components were more highly clustered than in those without OSAS. In particular, obesity and insulin resistance were positively and independently correlated with MS in patients with OSAS. Our findings highlight the fundamental role of obesity and insulin resistance in OSAS and suggest that screening and management of metabolic risk factors in patients with OSAS are needed to reduce OSAS-related cardiometabolic complications.

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Author contribution statement Prof. HX, HY, and JG had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Study design: HX and SY; data collection: FW, HX, XX, XL, JZ, YQ, and HY; statistical analysis: HX, HH, and YS; manuscript draft: HX, FW, HY, and JG.

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Data availability The corresponding authors will provide the accessibility of clinical data applied to support conclusions after receiving request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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