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Metabolic syndrome is a risk factor for nonalcoholic fatty liver disease: evidence from a confirmatory factor analysis and structural equation modeling

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Abstract. – OBJECTIVE: It has been demonstrated that nonalcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome (MS). This study used confirmatory factor analysis (CFA) and structural equation modeling (SEM) to characterize the relationship between MS and NAFLD.

PATIENTS AND METHODS: A cross-sectional study was performed on 3440 NAFLD patients. Of the 3440 subjects, 1160 were diagnosed with MS. BMI, SBP, DBP, UN, Scr, UA, FPG, Fructosamine, TC, TG, lipoprotein alpha, HDL-C, LDL-C, ALT, AST, TP, albumin, globulins, TB, DB, ALP and GGT were measured. CFA was used to identify a latent structure of NAFLD and MS, respectively. SEM approach was used to analyze the latent relationship between MS and NAFLD.

RESULTS: Second-order CFA revealed that the observed variables for NAFLD could be loaded onto seven latent factors, which were further loaded together onto an unobserved NAFLD factor. CFA of MS showed that overweight, hyperglycemia, dyslipidemia, and hypertension clustered together under a single latent factor of MS. In both MS and NAFLD models, hypertension showed higher factor loading than other factors. Factor models of MS and NAFLD showed a good fit to the data. As a latent factor, MS was significantly associated with increased risk of NAFLD.

CONCLUSIONS: MS may be a risk factor of NAFLD. MS and its components may play important roles in the development of NAFLD.

Key Words:
Metabolic syndrome, Nonalcoholic fatty liver disease, Risk factor, Steatosis.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease characterized by fat deposit in liver and is not attributed to excessive alcohol consumption[1,2]. There is evidence that increased visceral adiposity, insulin resistance and free fatty acid release play key roles in the onset and perpetuation of liver steatosis[3,4]. Obesity, diabetes, dyslipidemia, and insulin resistance have been identified as risk factors for NAFLD in adult subjects, which are also the primary components of metabolic syndrome (MS)[5,6]. Increasing studies have demonstrated that NAFLD is strongly associated with MS[7-9]. Furthermore, patients with NAFLD have increased risk of MS, and NAFLD is a hepatic manifestation of MS[10-12]. Despite these significant findings, the relationship between NAFLD and MS has not been fully elucidated.

Factor analysis including exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) is a statistical technique that could be applied to identify a small number of latent variables, which are responsible for the variations among a large number of observed variables[13]. EFA has been used to evaluate the correlations between the components of MS in terms of a few latent variables and results in establishment of several factor models. These models have been compared for validity by using CFA[12,14]. Previous CFA studies have demonstrated 4 core components underlying MS: obesity, insulin resistance, hypertension and dyslipidemia[15,16]. A recent EFA in a US population has found that although NAFLD is closely associated with MS, NAFLD is not an independent component of MS[8]. The ethnic age and gender has been suggested to be factor for MS definition[17]. It has been reported that biochemical blood tests such as glucose, renal function and albumin provide useful information for

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diagnosis of NAFLD, and abnormal levels of relevant biochemical variables are important manifestations of NAFLD[18]. However, the question why these manifestations cluster in patients with NAFLD remains unanswered.

Structural equation modeling (SEM) is a useful method which enables evaluating simultaneous causal relationships among variables. It integrates CFA with path analysis[19]. The study employed factor analysis and SEM approaches to further unravel the association between NAFLD and MS. In order to explore whether there was a factor structure underlying these biochemical variables in patients with NAFLD, we performed a EFA analysis of these biochemical variables. Latent factors were then extracted, and a second-order CFA model was constructed to evaluate whether the extracted latent factors indicated NAFLD. CFA model of MS was also constructed to confirm the latent structure of MS. The study also utilized the SEM approach to characterize the causal relationship between MS and NAFLD.

Patients and Methods

Patients

After approval by the Ethics Committee of Weifang Medical College, we performed a cross-sectional analysis on data from 3440 subjects (male, 84.9%) diagnosed with NAFLD in the Medical Centre of Affiliated Hospital of Weifang Medical College between 1 January and 31 December 2013. Informed consent was obtained from all participants before the survey. NAFLD was defined as presence of primary hepatic steatosis without excessive alcohol consumption or positive hepatitis C virus (HCV) antibody, and is diagnosed by live biopsy. The 3440 Subjects diagnosed with NAFLD based on the result of liver biopsy, were included in the present study. Exclusion criteria were listed as follow: (1) excessive alcohol consumption (> 20 g/day); (2) treatment with medications known to precipitate fatty liver during the 6 months prior to the study; (3) seropositivity for hepatitis B virus surface antigen (HBsAg) or anti-hepatitis C virus antibody (anti-HCV); (4) other defined liver disorders

MS was operationally defined using a slightly modified version of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) guidelines[12,20]. Hyperglycemia: fasting plasma glucose (FPG) ≥ 5.6 mmol/L or application of glucose lowering medication; Overweight: body mass index (BM) ≥ 23 for males and females[11]; Hypertension: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressures ≥ 85 mmHg and/or application of antihypertensive medication; Hypertriglyceridemia: triglyceride > 1.7 mmol/L, HDL < 1.03 mmol/L for males, < 1.29 mmol/L for females. It should be mentioned that BMI was a surrogate marker for central adiposity[21] because our data did not include measurement of waist circumference. BMI = weight (kg)/height (m^2). According to the criteria, 1160 of the 3440 subjects with NAFLD, were also diagnosed with MS.

Data Collection

Each subject was asked to fill out a standardized questionnaire and to undergo anthropometric assessments and laboratory tests. The self-administered questionnaire included questions about sex, age and medical history (clinical diagnosis and/or the use of medication) of diabetes mellitus, dyslipidemia, and hypertension. Liver biopsy was performed by experienced surgeons unaware of the results of laboratory examinations and other clinical tests. Height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DSP) were measured in a standardized way as previously described[21]. Systolic blood pressure and diastolic blood pressure were averaged by the second and third measurements.

Laboratory Examinations

Venous blood samples were drawn from all subjects before 11:00 AM after a 12-h overnight fast. Laboratory tests for serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), urea nitrogen (UN), serum creatinine (Scr), serum uric acid (UA), serum FPG, total cholesterol (TC), triglycerides (TG), total protein (TP), albumin, globulins, total bilirubin (TB), direct bilirubin(DB), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HBsAg and anti-HCV were carried out as previously reported[22,23]. All biochemical determinations were performed in the same laboratory room using standard laboratory methods. All participants had complete data for primary variables of interest.

Factor Analysis and Statistical Analysis

In order to identify the latent variables underlying the indicator variables (biochemical vari-

ables) of NAFLD, EFA analysis was performed on the matrix of all data of the biochemical variables: including SBP, DBP, UN, Scr, UA, FPG, Fructosamine, TC, TG, lipoprotein alpha, HDL-C, LDL-C, ALT, AST, TP, albumin, globulins, TB, DB, ALP and GGT. Latent factors were extracted by principal component analysis and orthogonally underwent varimax rotation[24]. The number of the extracted factors was chosen based on the factor eigenvalue (> 1) and scree plot[25]. Then, a second-order CFA[26] was performed to evaluate whether the extracted latent factors indicated NAFLD.

Additionally, CFA with categorical data was carried out to examine the underlying 4 components of MS. Using the robust weighted least squares estimation method available in Mplus® Version 5[27], CFA with categorical data was conducted with four indicator variables (overweight, hyperglycemia, dyslipidemia and hypertension) of MS, which were derived from the guidelines for establishing a working definition of MS suggested by the NCEP ATP III expert panel. BMI was measured for the definition of overweight; SBP and DBP were measured for the definition of hypertension; TG and HDL were measured for the definition of dyslipidemia; FPG was measured for the definition of hyperglycemia.

SEM could be applied to both non-normally distributed and normally distributed variables and capable of decomposing multidirectional effects and potential causal pathways in diseases with complex origins such as NAFLD[28,29]. In the present study, SEM with continuous factor indicators was utilized to construct our CFA model for estimating and evaluating simultaneous causal relationships among variables and to test the theoretical model against the observed dataset. In the model, all observable variables were linked to the extracted latent factors. Path coefficient was used to describe the impact of an independent variable on a dependent variable in the model.

Statistical Analysis

EFA, CFA and SEM were implemented by using the Statistical Package for the Social Sciences Version 13.0 (SPSS Inc., Chicago, IL, USA) and Mplus® Version 5. Factor loading of different variables (both latent and observed variables) were calculated.

Since some of the data was not normally distributed, the robust maximum likelihood estimation procedure was used to estimate the model fit and parameters[30,31]. Several model fit indices were utilized to assess the goodness of fit of all models. These fit indices included chi-square (χ^2) statistic, root mean squared error of approximation (RMSEA), standardized root mean square residual (SRMR), weighted root mean square residual (WRMR), and comparative fit index (CFI)[32]. A lower indicates a good fit of a model to data. Because of the large sample size, statistic was not the primary mean for assessing the global fit. CFI ≥ 0.90, RMSEA ≤ 0.08, SRMR ≤ 0.06 and WRMR ≤ 0.09 suggested a good fit of a model[33]. All tests were two-tailed. Additionally, p-value < 0.05 was defined as statistically significant.

Results

Characteristics of the Included Subjects

Demographic and clinical characteristics of the included subjects were summarized in Table I. The 3440 participants with NAFLD included 2973 (84.9%) males and 520 (15.1%) females, with mean age 44.0 years (range: 24-86 years). The subjects were randomly divided into the training cohort (n = 1720) and the validation cohort (n = 1720). There was no significant differences between the two cohorts in gender, age, height, weight, BMI, SBP, DBP, UN, Scr, UA, FPG, Fructosamine, TC, TG, lipoprotein alpha, HDL-C, LDL-C, ALT, AST, TP, albumin, globulins, TB, DB, ALP and GGT (p-value > 0.05, Table I).

EFA for NAFLD

EFA with varimax rotation was performed on the training cohort (n = 1720) to examine the factor structure underlying these biochemical determinants (SBP, DBP, UN, Scr, UA, FPG, Fructosamine, TC, TG, lipoprotein alpha, HDL-C, LDL-C, ALT, AST, TP, albumin, globulins, TB, DB, ALP and GGT) in patients with NAFLD. The scree plot test was used to determine the most appropriate number of retained factors by selecting those factors with EIGENVALUES > 1. As shown in Table II, the EFA revealed 7 latent factors. Factor 1 (lipid factor) possessed the highest loadings for LDL-C (0.957), HDL-C (0.943), and TC (0.933). Factor 2 (enzymology factor) shown highest loadings for AST (0.922), ALT (0.903), and GGT (0.673). Factor 3 (blood pressure factor) was loaded on SBP and DBP; factor 4 (bilirubin factor) was loaded on TB and DB; factor 5 (protein factor) was loaded on globulins and TP; factor 6 (renal function) was

Table I. Demographic and clinical characteristics of the subjects (mean ± SD, N = 3440).

Variables	Training cohort (n = 1720)	Validation cohort (n = 1720)	*p*-value
Gender (male, %)	1451 (84.4)	1469 (85.5)	0.392
Age (year)	44.08 ± 11.73	43.87 ± 11.67	0.589
Height (cm)	170.89 ± 6.80	171.14 ± 6.40	0.274
Weight (kg)	80.02 ± 9.85	79.95 ± 9.56	0.827
BMI (kg/m^2)	27.02 ± 2.63	26.95 ± 2.64	0.429
SBP (mm Hg)	126.17 ± 15.15	126.06 ± 15.29	0.827
DBP (mm Hg)	85.64 ± 9.75	85.26 ± 10.08	0.257
UN (mmol/L)	5.27 ± 1.27	5.31 ± 1.24	0.326
Scr (μmol/L)	73.37 ± 13.89	73.53 ± 13.39	0.727
UA (μmol/L)	363.01 ± 80.60	363.08 ± 78.63	0.978
FPG (mmol/L)	5.90 ± 1.50	5.92 ± 1.45	0.700
Fructosamine (mmol/L)	2.09 ± 0.52	2.09 ± 0.54	0.993
TC (mmol/L)	5.19 ± 1.05	5.17 ± 1.04	0.658
TG (mmol/l)	2.32 ± 1.75	2.32 ± 1.74	0.991
Lipoprotein alpha (mg/L)	145.47 ± 78.09	145.97 ± 75.91	0.849
HDL-C (mmol/l)	1.42 ± 0.29	1.42 ± 0.28	0.921
LDL-C (mmol/l)	3.15 ± 0.63	3.15 ± 0.60	0.931
ALT (U/L)	33.26 ± 22.51	32.55 ± 19.96	0.332
AST (U/L)	26.56 ± 12.97	26.10 ± 11.42	0.271
TP (g/L)	76.33 ± 3.96	76.27 ± 4.63	0.689
Albumin (g/L)	48.36 ± 2.67	48.38 ± 2.65	0.839
Globulins (g/L)	27.93 ± 3.47	27.87 ± 4.18	0.645
TB (μmol/L)	16.78 ± 5.72	16.80 ± 5.76	0.945
DB (μmol/L)	3.84 ± 1.44	3.84 ± 1.39	0.962
ALP (U/L)	77.65 ± 22.17	77.07 ± 21.22	0.434
GGT (U/L)	47.04 ± 57.07	44.20 ± 43.38	0.100
GGT (median/interquartile)	31 (20-56)	31 (21-55)	0.856

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UN, urea nitrogen; Scr, serum creatinine; UA, uric acid; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; TB, total bilirubin; DB, direct bilirubin; ALP, alkaline phosphatase; GGT, gamma glutamyltransferase.

loaded on Scr, UN and UA; factor 7 (glucose factor) was loaded on Fructosamine and FPG. To test the reliability of the factor structure for NAFLD, an EFA was also performed on the validation cohort (n = 1720), revealing similar results of factor loadings (Table II).

CFA of NAFLD

The second-order CFA model of NAFLD was constructed including the 7 indicator variables derived from the result of EFA on the training cohort. CFA revealed that the observed variables (biochemical variables) of NAFLD could be loaded onto the 7 latent factors which were then loaded together on an unobserved NAFLD factor (Figure 1, right half). Of the 7 latent factors, the factor loadings of latent factor 2 (enzymology factor) and factor 6 (blood pressure) were 11.97 and 69.66, respectively for the unobserved NAFLD factor, which were higher than the other 5 factors. The fit of the model was examined with CFI, RMSEA, SRMR and χ^2 statistic. The factor model showed a good fit (CFI = 0.93, RMSEA = 0.06, SRMR = 0.04). The χ^2 test of model fit was insignificant, indicating that the model fitted the data well.

CFA of MS

As shown in Table III, there was no significant differences in the four features (Overweight, Hyperglycemia, Hypertension and Dyslipidemia) of the MS between the training cohort and the validation cohort (p-value > 0.05). A CFA model was constructed including overweight, hyperglycemia, hypertension and dyslipidemia. The 4 components were clustered together under a latent factor (MS) (Figure 1, left half). The hypertension component displayed the highest loading (11.56). Indices such as CFI, RMSEA, and WRMR were used to assess the validity of the one-factor model derived from CFA on the validation cohort. Our analysis showed that CFI,

Table II. Factor loadings of exploratory factor analysis with varimax rotation using the training cohort (factor loadings using the validation cohort).

Variables	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
LDL-C	0.957 (0.958)						
HDL-C	0.943 (0.948)						
TC	0.933 (0.926)						
AST		0.922 (0.930)					
ALT		0.903 (0.907)					
GGT		0.673 (0.638)					
SBP			0.939 (0.930)				
DBP			0.938 (0.932)				
TB				0.942 (0.919)			
DB				0.933 (0.915)			
Globulin					0.946 (0.938)		
TP					0.934 (0.926)		
Scr						0.757 (0.683)	
UN						0.705 (0.712)	
UA						0.685 (0.689)	
Fructosamine							0.800 (0.800)
FPG							0.776 (0.757)

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase; FPG, fasting plasma glucose; TP, total protein; TB, total bilirubin; DB, direct bilirubin; SBP, systolic blood pressure; DBP, diastolic blood pressure; UN, urea nitrogen; Scr, serum creatinine; UA, uric acid.

RMSEA, and WRMR were 0.94, 0.06, and 0.67, respectively, indicating that the model had a desirable fit.

SEM Procedures

SEM procedures were used to model the causal relationship between MS latent construct and NAFLD latent factor indicator. The graphic representation of this model and its path coefficient were shown in Figure 1. The goodness of fit indices for the model were CFI = 0.91, RMSEA = 0.07, and SRMR = 0.05, suggesting overall excellence of fit. The relationship between MS and NAFLD, was statistically significant (path coefficient = 0.130, $p < 0.05$), indicating that MS was significantly associated with increased risk of NAFLD.

Discussion

By using EFA, CFA and SEM procedures, this study provided useful information regarding the pathophysiological mechanism that underlay the clustering of factors in NAFLD, and the relationship between MS and NAFLD. To our knowledge, this was the first attempt to utilize both measurement models (second-order CFA) and structural path components (SEM) for a better understanding of the relationship in a Chinese population. The study determined a single latent factor as the underlying link among the variables of the NAFLD, and confirmed a latent factor underlying the 4 components of MS. Besides, the study suggested that MS might be an important

Table III. Features of the metabolic syndrome (MS) in the training and validation cohorts (n/%).

Features	Training cohort (n = 1720)	Validation cohort (n = 1720)	*p*-value
Overweight	1624 (94.4)	1629 (94.7)	0.707
Hyperglycemia	423 (24.6)	444 (25.8)	0.410
Hypertension	804 (46.7)	810 (47.1)	0.838
Dyslipidemia	1020 (59.3)	1023 (59.5)	0.917

The following cut-points are used: overweight (BMI ≥ 23 kg/m^2 in both sexes); hyperglycemia (fasting plasma glucose [FPG] ≥ 5.6 mmol/l), hypertension (systolic blood pressure [SBP] ≥ 130 mm Hg or diastolic blood pressure [DBP] ≥ 85 mm Hg), dyslipidemia (triglycerides ≥ 1.7 mmol/l or HDL < 1.03 mmol/l in men, < 1.29 mmol/l in women, or treatment with a lipid-lowering medication).

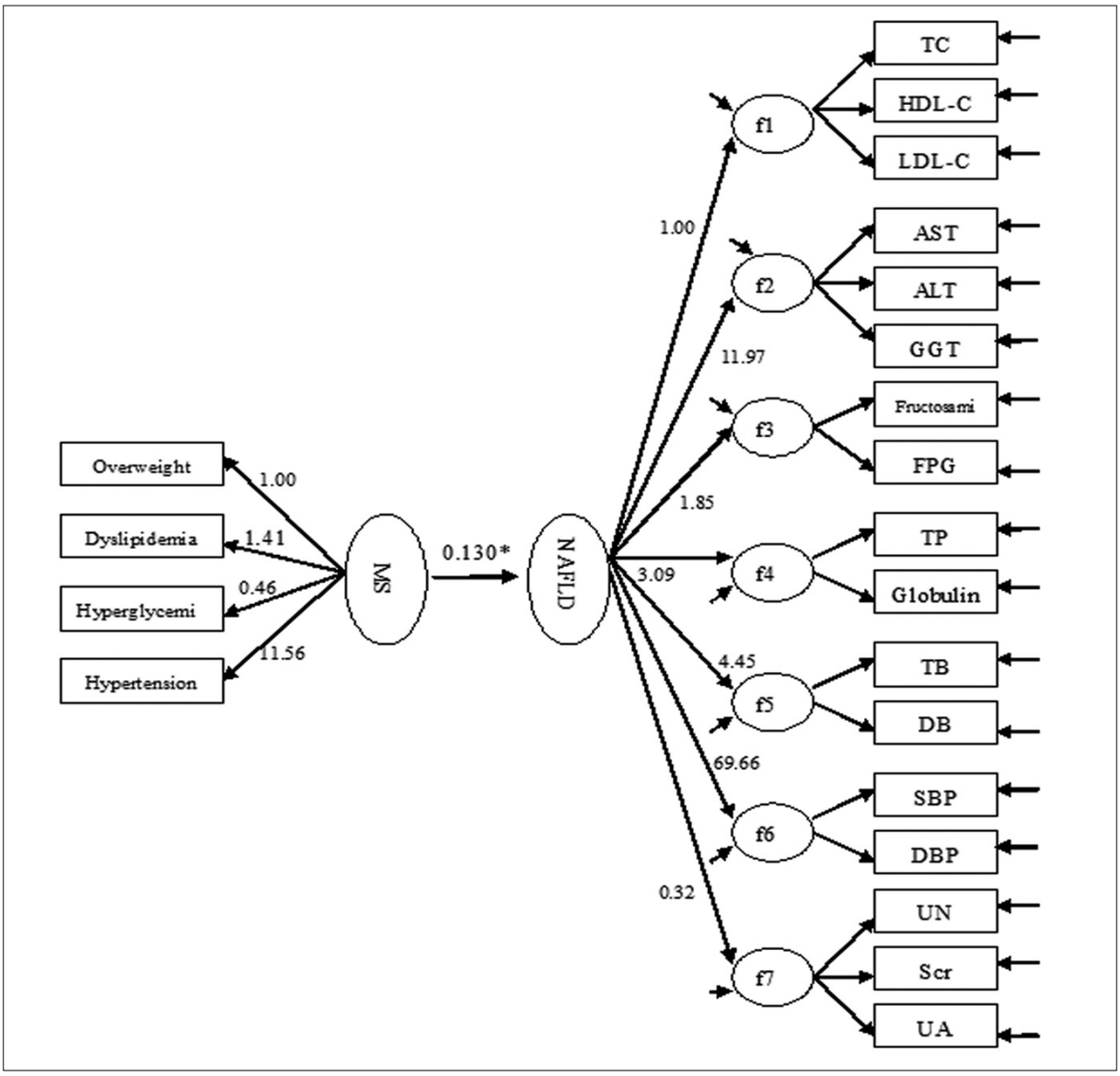

Figure 1. Structural equation model of the relationship between nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome (MS) latent construct. Ellipse stands for the latent variable, and rectangle stands for observed variables. Right half is the CFA model of NAFLD. Lipid factor (f1) has been identified to have the highest factor loading in the CFA of NAFLD and is therefore designated as the metric for the CFA (1.0). Left half is the CFA model of MS. BMI (body mass index) has been identified to have the highest factor loading in the EFA of MS; therefore, overweight is designated as the metric for the CFA (1.0). Single arrow represents causal relationship. Numbers on the arrow lines show the path coefficient. *, $p < 0.05$. TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase; FPG, fasting plasma glucose; TP, total protein; TB, total bilirubin; DB, direct bilirubin; SBP, systolic blood pressure; DBP, diastolic blood pressure; UN, urea nitrogen; Scr, serum creatinine; UA, uric acid.

risk factor of NAFLD. These findings shed new light on the association between MS and elevated NAFLD risk, and assisted in designing more targeted treatments and preventive interventions for NAFLD. These findings were of both theoretical and clinical significance.

The second-order CFA of NAFLD showed that the observed variables (biochemical variables) appeared to load onto seven latent factors, which were further clustered together under an unobserved NAFLD factor. Among the seven latent factors, enzymology and blood pressure

were more important in NAFLD than the other factors, which were in concordance with previous studies concerning the pathophysiology of NAFLD[34,35]. It suggested that altered ALT, AST and GGT and hypertensions might play important roles in NAFLD.

The study provided evidence that an unobserved factor linked to the co-occurrence of MS features, which included overweight, hyperglycemia, hypertension and dyslipidemia. Among the 4 MS features, Hypertension component showed the highest loading. These observations were in agreement with a previous finding demonstrating the presence of a latent factor that underlies the clustering of the MS features[36].

NAFLD and other diseases such as MS may coexist, because they share common risk factors[37]. Increasing studies have shown that the risk factors shared by MS and NAFLD, such as obesity, diabetes, dyslipidemia, and insulin resistance, play important roles in the development of MS and NAFLD[5,37]. In concordance with these observations, the blood pressure factor showed high loading in both the MS and NAFLD latent constructs in the present study, supporting that MS and NAFLD may have common risk factors and similar potential pathways. Moreover, increased ALT concentration has been shown to be associated with insulin resistance and NAFLD grading in subjects with NAFLD[38], indicating that the enzymological variables might mediate the role of these risk factors in NAFLD.

It has been demonstrated that MS is associated with NAFLD[10]. Other studies on the relationship between MS and NAFLD have considered NAFLD an additional feature of MS[10,11]. Our results extended these findings to establishment of the latent causal constructs between NAFLD and MS, indicating that MS, as a single latent factor, might be a risk factor of NAFLD. MS might act as a single latent factor to promote hepatic steatosis. Thus, early detection, prevention, and screening of MS and its components might help identify individuals at high risk of NAFLD and other associated liver diseases, including liver cirrhosis and cancer.

This study had several strengths. First, a second-order CFA was performed to analyze the latent relationships between the observed variables of NAFLD. Second, SEM with continuous latent factors was utilized to analyze the relationships between MS and NAFLD. However, our study also had several limitations. MS in our study was defined according to the NCEP-ATPIII definition. Since diagnostic disconcordance remains between different definitions of MS[40-42], our findings may not be appropriate for other definitions of MS. Besides, this was cross-sectional study on a Chinese population, further prospective studies were warranted to determine the directionality of the causal relationship between MS and NAFLD.

Conclusions

Collectively, we found that MS was closely associated with increased risk of NAFLD in a Chinese population, indicating that MS and its components may play an important role in the development of NAFLD. The study suggested that preventive and therapeutic interventions targeting MS and its components might reduce the incidence of NAFLD in non-obese healthy individuals without explainable risk factors.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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