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Original Article

Association of serum bile acids with metabolic syndrome in a Chinese population

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Abstract: Background: Metabolic syndrome is an important health issue worldwide. We aim to explore the association of serum bile acids with metabolic syndrome and its components in a Chinese population. Methods: A cross-sectional study with 5109 subjects was conducted. Metabolic syndrome was defined by the modified National Cholesterol Education Program Adult Treatment Panel III report. Blood pressure, liver enzymes, lipids profiles, glucose, uric acid, and bile acid and anthropometric measures were obtained. The odd ratios (ORs) of metabolic syndrome with bile acid were estimated using ordinal logistic regression. Results: The prevalence of metabolic syndrome and its components increased progressively with increase in bile acid quintiles. Bile acids were significantly associated with risk for metabolic syndrome in overall participants (OR 1.024, 95% CI 1.010-1.039) as well as in males (OR 1.034, 95% CI 1.016-1.052). However, in the females, the association was no longer statistically significant after adjusting for age, BMI and other related variables (OR 0.989, 95% CI 0.989-1.015). Conclusions: This study reveals a gender-specific association between bile acids and metabolic syndrome. Bile acids were significantly associated with risk for metabolic syndrome in male, but not in female.

Keywords: Bile acid, metabolic syndrome, association, gender-specific

Introduction

Metabolic syndrome is an important issue for global public health in the twenty-first century [1]. Multiple measurements showed that the prevalence of metabolic syndrome varies from 7.3% to 22.9% in different parts of China [2-5]. Due to the development of economy and urbanization in China, the prevalence of metabolic syndrome may increase in the next few decades [2, 3]. Metabolic syndrome includes complex components, such as central obesity, dyslipidemia, high blood pressure, and increased fasting blood sugar [6]. It is associated with increased risk of cardiovascular disease, type 2 diabetes mellitus and all-cause mortality [7, 8].

Bile acids are amphipathic molecules synthesized from cholesterol exclusively in parenchymal cells of the liver [9]. It has long been known to play central roles in the absorption of fat and fat-soluble vitamins as well as modulating cholesterol levels. Recent basic researches showed that bile acids were the ligands of the nuclear receptor farnesoid X receptor (FXR) and the cell surface receptor G protein-coupled bile acid receptor 5 (TGR5), which uncovered the regulatory function of bile acids in the control of gene expression [10, 11]. It is reported that FXR deletion led to elevation of circulating triglycerides and total cholesterol. In contrast, activation of FXR by bile acids or FXR agonists decreased liver and plasma triglycerides and cholesterol in mice [12]. Some studies suggested that FXR might be activated during the postprandial period to play a role in the regulation of glucose homeostasis [13, 14]. Moreover, Shaham *et al.* also reported that serum bile acid levels correlate with measures of insulin sensitivity [15]. All these findings indicated that bile acids played an important role in glucose, lipid and energy metabolism [16].

Unfortunately, few clinical studies have sought to reveal the association between bile acids

and metabolic syndrome or its components. Recent human clinical trials indicated that bile acid sequestrate colesevelam improved glycemic control and reduced LDL cholesterol levels in patients with type 2 diabetes [17]. On the contrary, Patti *et al.* reported that bile acid concentrations were inversely associated with 2-h post-meal glucose and triglyceride levels [18]. Therefore, further studies are highly needed to clarify the exact relationship between serum bile acids and metabolic syndrome.

In this study, we conducted a cross-sectional study to explore the association of serum bile acids with metabolic syndrome and its components in a Chinese population.

Methods

Subjects

The subjects of this study were recruited from adults who took their health checkups at the First Affiliated Hospital, College of Medicine, Zhejiang University from August 1 to December 31, 2014. We excluded subjects whose anthropometric data was not completed (n=327), or whose serum bile acids were not analyzed (n=983). Since bile acids could be influenced by liver cirrhosis, liver cancer, and hepatitis, we also excluded participates who had history of cancer, viral or autoimmune hepatitis, or unexplained abnormal liver functions in this study (n=718). Participant who was taking antihypertensive, antidiabetic, or lipid-lowering drugs was not excluded. A total of 5109 participants (3232 males and 1877 females) with a mean (standard deviation) age of 51.04 (9.93) years were included in the final analysis.

The study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. Because of the observational nature of the study, we verbally informed all participants about the study; written informed consent was not required. The subject information was anonymized at collection and anonymized prior to analysis. All methods were performed in accordance with the approved guidelines.

Clinical examinations

Clinical examinations were performed according to procedures described previously [19, 20]. Standing height, body weight and waist circumference were recorded for all participants. Body mass index (BMI) was calculated as the body weight (kg) divided by the standing height squared (m^2). Systolic and diastolic blood pressures were measured by standard clinical procedures.

Fasting blood samples were collected for the analysis of blood routine variables and biochemical variables without freezing. Blood routine variables including white blood cell count, hemoglobin and platelet count were analyzed by SYSMEX XT-1800 hematology autoanalyzer according to manufacturer's instructions. Biochemical variables included liver enzymes, lipids, glucose, uric acid, and bile acid were measured by a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan) using standard methods.

Diagnosis of metabolic syndrome

Metabolic syndrome was defined by the modified National Cholesterol Education Program Adult Treatment Panel III report. For a participant to be defined as having metabolic syndrome they must have three or more of the following factors: (1) central obesity, defined as waist circumference ≥90 cm for Chinese men and ≥80 cm for Chinese women; (2) raised triglyceride level, defined as triglycerides ≥1.7 mmol/L or specific treatment for this lipid abnormality; (3) reduced HDL cholesterol, defined as HDL cholesterol <1.03 mmol/L in males and <1.29 mmol/L in females; (4) elevated blood pressure, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and (5) raised fasting blood sugar, defined as fasting blood sugar ≥5.6 mmol/L, or previously diagnosed type 2 diabetes.

Statistical analysis

Data were managed and analyzed using SPSS software version 17.0 (SPSS, Inc., Chicago, IL). Continuous variables were compared using the student's *t*-test, and categorical variables were compared using the chi-squared test. A stepwise logistic regression analysis was performed to examine the relationship between metabolic syndrome and anthropometric or biochemical variables (probability to enter = 0.05 and probability to remove = 0.10). The odd ratios (ORs) of metabolic syndrome with bile acid were esti-

Table 1. Characteristics of participants according to the number of metabolic syndrome components

Number of metabolic syndrome components	Without metabolic syndrome			Metabolic syndrome		
	0	1	2	3	4	5
n (male/female)	692 (390/302)	1308 (774/534)	1323 (818/505)	1065 (734/331)	603 (432/171)	118 (84/34)
Age (years)	47.31±9.29	49.74±10.53	51.27±9.48	52.98±9.57	53.38±9.38	55.35±8.27
Body mass index (kg/m^2)	21.65±2.15	22.94±2.42	24.65±2.60	25.99±2.51	27.04±2.54	27.56±2.75
Waist circumference (cm)	76.97±6.92	80.87±7.70	86.55±7.72	90.91±7.20	94.19±6.75	96.38±7.28
Systolic blood pressure (mmHg)	114.33±9.14	123.91±15.91	130.20±16.81	137.33±16.24	143.68±14.25	145.36±14.47
Diastolic blood pressure (mmHg)	69.69±7.42	74.94±10.60	79.45±11.05	83.31±9.98	86.86±9.43	87.00±8.84
Alanine aminotransferase (IU/L)	18.62±7.95	19.95±8.93	22.11±9.45	24.91±9.72	26.74±10.06	26.97±9.68
Aspartate aminotransferase (IU/L)	20.47±4.88	20.75±5.63	21.02±5.30	21.76±5.55	22.21±5.61	21.86±7.04
Triglycerides (mmol/L)	0.94±0.32	1.16±0.66	1.64±1.08	2.21±1.65	2.76±1.52	3.04±1.63
Total cholesterol (mmol/L)	4.88±0.82	4.74±0.90	4.92±0.95	5.00±1.01	5.09±0.93	5.28±1.08
HDL cholesterol (mmol/L)	1.42±0.28	1.23±0.29	1.13±0.28	1.04±0.25	0.97±0.20	0.90±0.15
LDL cholesterol (mmol/L)	2.73±0.63	2.69±0.63	2.81±0.67	2.81±0.73	2.81±0.72	2.96±0.83
VLDL cholesterol (mmol/L)	0.73±0.34	0.82±0.40	0.98±0.48	1.15±0.54	1.30±0.54	1.42±0.65
Fasting blood sugar (mmol/L)	4.56±0.40	4.66±0.51	4.80±0.88	5.14±1.34	5.54±1.50	7.53±2.39
Uric acid (μmol/L)	306.48±76.56	325.44±84.35	339.05±84.65	364.06±89.10	375.38±85.59	381.29±106.74
Hemoglobin (g/L)	142.61±15.55	142.86±16.15	145.35±16.24	148.35±15.13	150.21±15.33	149.84±14.93
Platelet count (×10^9)	200.03±53.61	201.52±52.70	205.09±51.29	204.63±49.37	203.58±51.91	210.13±65.46
Bile acids (μmol/L)	4.30±2.87	4.53±3.28	4.93±3.71	5.14±3.80	5.54±5.19	5.33±4.76

Data are expressed as the mean ± standard deviation.

mated using ordinal logistic regression, and the number of metabolic syndrome components was ordinal dependent variable. The data were first adjusted for age and BMI and then for other covariates that might confound the relationship between the metabolic syndrome and bile acid. To explore the association between bile acids and metabolic syndrome, subjects were stratified into five groups according to quintiles of bile acid levels: quintile 1≤2.0 μmol/L; quintile 2, 2.1-3.0 μmol/L; quintile 3, 3.1-4.0 μmol/L; quintile 4, 4.1-6.0 μmol/L; and quintile 5, ≥6.1 μmol/L. Cochran Armitage trend test was used to show the trend of the prevalence. A *P*-value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of the study population

A total of 5109 participants were included in this study, 3232 were male and 1877 were female. The average age of study population was 51.04±9.93 years. Of the 5109 participants enrolled, 1553 (30.4%) were diagnosed as metabolic syndrome. The characteristics of all study participants are presented in **Table 1**. The participants with more metabolic syndrome components had greater BMI, waist circumference, higher systolic blood pressure, diastolic blood pressure, fasting blood sugar, as well as worse lipid profiles compared with the normal group. Moreover, there were significant differences in ALT, AST, uric acid, and bile acids among these groups.

Association of bile acids with prevalence of metabolic syndrome

To explore the association of bile acids with prevalence of metabolic syndrome, participants were stratified into quartiles according to their bile acid levels. Participates with higher levels of bile acids had higher BMI, waist circumference, systolic blood pressure, diastolic blood pressure, as well as worse lipid profiles compared with lower bile acids level groups (**Table 2**). The prevalence of each metabolic syndrome component was calculated by dividing the number of cases by the numbers of participants in each bile acid quintile. We found that the prevalence of metabolic syndrome and its components increased progressively with increase in bile acid quintiles (**Figure 1**). This observation indicated that participants with higher bile acid levels were more likely to have metabolic syndrome than those with lower levels.

Risk factors of metabolic syndrome

We analyzed the risk factors of metabolic syndrome by stepwise logistic regression analysis.

Table 2. Characteristics of participants according to serum bile acid quintiles

Variable	Serum bile acid levels (μmol/L)					*P* value
	Q1 (<2.0)	Q2 (2.0-3.0)	Q3 (3.0–4.0)	Q4 (4.0-6.0)	Q5 (≥6.0)	
n (male/female)	693/448	624/371	528/299	709/345	678/374	0.001
Age (years)	50.28±9.58	50.83±10.05	51.09±9.95	51.07±9.87	52.03±10.17	0.001
Body mass index (kg/m^2)	24.12±2.98	24.33±3.07	24.49±3.01	24.54±3.05	24.73±3.10	<0.001
Waist circumference (cm)	84.44±9.18	85.75±9.37	86.02±9.34	86.26±9.60	86.90±9.19	<0.001
Systolic blood pressure (mmHg)	128.00±18.31	129.22±18.07	130.18±17.70	130.94±17.17	131.25±17.13	<0.001
Diastolic blood pressure (mmHg)	77.76±11.66	78.14±11.70	79.15±11.24	79.85±11.15	79.40±10.96	<0.001
Alanine aminotransferase (IU/L)	21.66±9.46	22.08±9.60	22.33±9.33	22.75±9.97	22.88±9.85	0.020
Aspartate aminotransferase (IU/L)	20.76±5.23	20.89±5.25	20.87±4.99	21.44±5.56	21.96±6.21	<0.001
Triglycerides (mmol/L)	1.58±1.12	1.66±1.29	1.73±1.21	1.74±1.37	1.84±1.50	<0.001
Total cholesterol (mmol/L)	4.91±0.92	4.89±0.98	4.95±0.95	4.90±0.94	4.92±0.93	0.769
HDL cholesterol (mmol/L)	1.18±0.31	1.16±0.30	1.15±0.29	1.14±0.30	1.13±0.30	<0.001
LDL cholesterol (mmol/L)	2.77±0.68	2.79±0.71	2.82±0.67	2.76±0.68	2.73±0.67	0.062
VLDL cholesterol (mmol/L)	0.96±0.48	0.94±0.50	0.98±0.50	1.00±0.52	1.06±0.53	<0.001
Fasting blood sugar (mmol/L)	4.94±1.18	4.95±1.07	4.94±1.21	4.96±1.10	4.97±1.17	0.943
Uric acid (μmol/L)	338.37±92.30	339.69±87.54	342.45±85.13	344.75±87.45	343.35±86.63	0.421
Hemoglobin (g/L)	144.49±15.57	146.27±15.43	146.39±15.42	146.03±16.41	145.38±16.95	0.033
Platelet count (×10^9)	206.32±49.50	200.96±50.67	206.90±51.96	201.88±55.50	200.89±52.37	0.011

Data are expressed as the means (SD) or medians (IQR) depending on the data distribution. HDL, High-density lipoprotein; LDL, low-density lipoprotein.

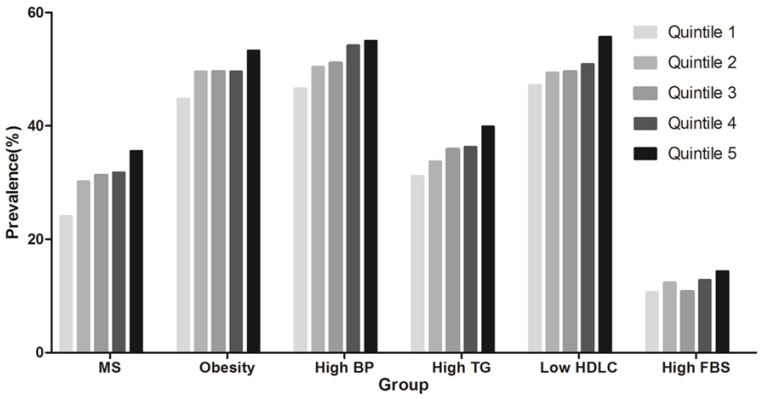

Figure 1. Morbidity of metabolic syndrome and its components according to quintiles of bile acid level. MS: metabolic syndrome; BP: blood pressure; TG: triglycerides; HDLC: high-density lipoprotein cholesterol; FBS: fasting blood sugar. *P* value for trend in metabolic syndrome, obesity, high blood pressure, high triglycerides and low high-density lipoprotein cholesterol group is less than 0.001; *P* value for trend in high fasting blood sugar group is 0.012.

As shown in **Table 3**, age, gender, systolic blood pressure, waist circumference, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood sugar, and alanine aminotransferase were associated with risk for metabolic syndrome in the overall participants. Bile acids was entered in the model but the *P* value was more than 0.05 (*P*=0.093). Interestingly, when we take the gender into consideration, bile acids was associated with metabolic syndrome in male group (*P*= 0.013) but was removed out of the model in female group.

We further performed ordinal logistic regression analysis to clarify whether bile acids is independently associated with risk for metabolic syndrome. The ordinal dependent variable was the number of metabolic syndrome components. We observed a gender-dependent association between bile acids and metabolic syndrome (**Table 4**). Bile acids were significantly and positively associated with risk for metabolic syndrome in overall participants as well as in males. However, in the females, the association was attenuated and no longer statistically significant after adjusting for age, BMI and other related variables.

Discussion

In this study, we found an association between bile acids and metabolic syndrome and its components. The bile acid levels increase with

Table 3. Stepwise logistic regression analysis of metabolic syndrome with anthropometric and biochemical variables

	Total			Male			Female		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.010	1.000-1.021	0.055		-*		1.021	1.001-1.041	0.040
Gender	18.319	13.885-24.168	<0.001		-			-	
Systolic blood pressure (mmHg)	1.050	1.044-1.057	<0.001	1.045	1.037-1.053	<0.001	1.062	1.05-1.074	<0.001
Waist circumference (cm)	1.290	1.266-1.314	<0.001	1.336	1.304-1.369	<0.001	1.231	1.197-1.267	<0.001
Triglycerides (mmol/L)	1.833	1.642-2.046	<0.001	1.636	1.496-1.788	<0.001	2.409	1.913-3.033	<0.001
Total cholesterol (mmol/L)	0.799	0.622-1.027	0.080		-			-	
HDL cholesterol (mmol/L)	0.021	0.013-0.035	<0.001	0.022	0.013-0.038	<0.001	0.018	0.009-0.037	<0.001
LDL cholesterol (mmol/L)	1.487	1.089-2.030	0.013		-			-	
Fasting blood sugar (mmol/L)	1.386	1.274-1.507	<0.001	1.365	1.246-1.496	<0.001	1.559	1.242-1.958	<0.001
Alanine aminotransferase (IU/L)	1.009	0.999-1.020	0.077		-			-	
Bile acids (μmol/L)	1.020	0.997-1.043	0.093	1.037	1.008-1.067	0.013		-	

The model was adjusted for all the characteristics mentioned in the **Table 1**. *The variable with *P*>0.10 did not remain in the final model.

Table 4. Ordinal logistic regression analysis of metabolic syndrome and bile acids

		OR	95% CI	*p*
Total	Model 1	1.048	1.035-1.062	<0.001
	Model 2	1.037	1.022-1.050	<0.001
	Model 3	1.024	1.010-1.039	<0.001
	Model 4	1.022	1.008-1.037	<0.001
Male	Model 1	1.049	1.023-1.070	<0.001
	Model 2	1.044	1.027-1.061	<0.001
	Model 3	1.034	1.016-1.052	<0.001
	Model 4	1.038	1.019-1.055	<0.001
Female	Model 1	1.049	1.030-1.064	<0.001
	Model 2	1.020	0.997-1.044	0.084
	Model 3	0.989	0.964-1.015	0.396
	Model 4	0.992	0.967-1.019	0.575

Model 1 was unadjusted. Model 2 was adjusted for age, and BMI. Model 3 was adjusted for age, BMI, waist circumference, systolic and diastolic blood pressure, triglycerides, HDL cholesterol, and fasting blood sugar. Model 4 was adjusted for age, BMI, as well as anthropometric and biochemical variables in the **Table 1**.

increasing in number of metabolic syndrome components. This association was independent of age, gender, BMI, and other variables associated with metabolic syndrome. In the subgroup analysis, a significant and positive association between bile acids and metabolic syndrome was observed in males in any model. However, the association was attenuated and no longer statistically significant after adjustment for BMI in females.

The present study showed higher serum bile acid levels, even within the normal range, were associated with an increased odds ratio of metabolic syndrome, and remained significant even after adjusting for confounding factors. The prevalence of metabolic syndrome and its components, such as elevated fasting blood sugar and raised triglycerides, increased progressively with increased bile acid levels (**Figure 1**). Bile acid metabolism is linked to the control of glucose and lipid metabolism and energy homeostasis [21]. FXR signaling mechanisms appear to play a dominated role in the association between bile acid and metabolic syndrome. Cholesterol 7-alpha hydroxylase (CYP7A1) is the first and rate-limiting enzyme in the pathway of bile acids synthesis. FXR has effects on CYP7A1 expression by induction of small heterodimer partner (SHP). The expression of SHP inhibit the transcriptional activity of hepatocyte nuclear factor 4α (HNF-4α) and liver-related homolog-1 (LRH-1), which resulted in inhibition of CYP7A1 gene transcription and then regulated the synthesis of bile acids [22]. Kok et al. found that FXR-deficient mice were showed elevated CYP7A1 mRNA expression and enlarged bile acid pool size [23]. So FXR plays a key role in negative feedback inhibition of bile acid synthesis. FXR also altered the transcription of several genes involved in fatty acid and triglyceride synthesis and lipoprotein metabolism. In mice, FXR reduces plasma triglyceride and cholesterol levels via repression of the lipogenic genes sterol regulatory element binding protein-1c (SREBP1c) [24]. Studies conducted in FXR (-/-) mice suggested that FXR deletion lead to hepatic lipid accumulation and elevation of circulating total cholesterol and total triglycerides

[25, 26]. On the contrary, activation of FXR by bile acids or FXR agonists results in hypolipidemia [12]. Duran-Sandoval *et al.* reported that hepatic FXR expression was decreased in streptozotocin-induced diabetic rats [27]. They also found that hepatic expressions of gluconeogenic genes altered in response to high carbohydrate refeeding in FXR(-/-) mice, indicating FXR as a modulator of hepatic glucose metabolism [28]. A more recent study showed that FXR activity is regulated by glucose fluxes in hepatocytes, this regulation was catalyzed by the glucose-sensing hexosamine biosynthetic pathway [29]. In our study, participates with higher levels of bile acids had greater BMI, waist circumference, higher systolic blood pressure, diastolic blood pressure, as well as worse lipid profiles. This may reflect the state of FXR inhibition, which increased bile acid synthesis and lipid metabolism. In addition, TGR5 signaling is also involved in bile acid regulation, energy expenditure and glucose metabolism [11, 16]. However, the mechanism in humans has not been studied, and needs further study.

Our study suggests that the association between bile acids and metabolic syndrome was no longer statistically significant in the females after adjustment for age and BMI. This phenomenon may be in related to the regulation of estrogen. Epidemiological studies have showed that the prevalence of metabolic syndrome becomes significantly higher among post-menopause women than pre-menopause women and men [30-32]. Estrogen seems to be an important protective factor in the development of abdominal obesity, T2DM and metabolic syndrome [33]. Study in mice suggested that the protective effects of estrogens on adipose tissue distribution, glucose hemostasis are mainly mediated by estrogen receptors (ER) [34]. Milona *et al.* reported that ERα interacted with FXR in an estradiol-dependent manner, and then altered bile acid homeostasis [35]. Recent studies of intrahepatic cholestasis of pregnancy (ICP) showed 17b-estradiol (E2) directly interacted with FXR through a non-classical E2/ERα transrepressive pathway and peroxisome proliferator-activated receptor-γ coactivator-1, thus repressed bile salt export pump expression and secretion of bile acids [36, 37]. But the mechanism between FXR and estrogen receptors is not very clear, and it is worthy to further clarify the interaction between these two receptors in metabolic syndrome.

The results in this study also suggest that the modulation of bile acids could be used as a therapeutic approach for the treatment of metabolic syndrome. Bile acid sequestrants, such as colesevelam, have been shown to be effective in improving both cholesterol and glucose in patients with type 2 diabetes mellitus [17]. FXR agonists were found to decrease plasma glucose, triglycerides, and cholesterol in mice [12], Clinical trials showed that obeticholic acid, a FXR agonist, could increase insulin sensitivity in type 2 diabetes patients [38], and improve the histological features in patients with non-alcoholic steatohepatitis [39]. This drug may be a promising therapy for the treatment of metabolic syndrome.

Our study has several limitations. First, the causal association between bile acids and metabolic syndrome could not be derived by this cross-sectional study. A prospective study of metabolic syndrome and bile acids should be conducted to figure out the causality. Second, the bile acid profiles were not available in this study. The hydrophobic bile acid chenodeoxycholic acid (CDCA) is the most efficacious ligand of FXR, followed by lithocholic acid (LCA), deoxycholic acid (DCA). A recent study suggested that the contribution of specific bile acid species, such as cholic acid (CA) and DCA, was altered in patients with type 2 diabetes mellitus [40]. Further studies are required to investigate the association of specific bile acid with metabolic syndrome.

In conclusion, this cross-sectional study reveals the gender-specific association between bile acids and metabolic syndrome. Future studies should be conducted to clarify the causality of bile acids and metabolic syndrome and its underlying regulatory mechanisms, which may help developing new therapeutic strategies.

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Disclosure of conflict of interest

None.

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