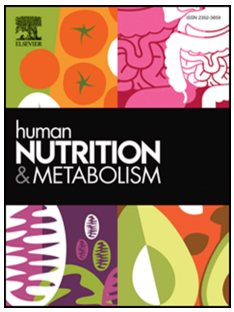

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Sex-specific association of blood triglyceride and uric acid with body shapes in Chinese adults

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ABSTRACT

Background:

Abnormal metabolic syndrome, adipose distribution and different body shapes caused by obesity are associated with the levels of blood biochemical indexes. However, the sex-specific relationship between body shapes and blood biochemical indexes is poorly investigated.

Research design and methods:

A cross-sectional study was conducted on 1828 subjects matched by age and sex. The scatter plot and restricted cubic spline were used to analyze the correlation between variables. Logistic regression was used to explore the relationship between body shapes and the risk of abnormal blood biochemical indexes level.

Results:

Compared with the non-obesity group, the compound obesity group had a higher risk of abnormal Glu and TG levels independent of sex. Besides, the sex-specific association showed that the risk of abnormal TG levels was higher in males with peripheral obesity but in females with central obesity. Meanwhile, female subjects with peripheral obesity had a higher risk of abnormal UA levels.

Conclusions:

This study showed that obese subjects had a higher risk of abnormal UA and TG compared to non-obese subjects, and there were sex differences in this relationship, suggesting that future studies exploring the relationship between body shapes and blood biochemical indexes also need to consider the potential role of sex.

Keywords: obesity, adipose distribution, blood biochemical index, cross-sectional study, sex difference

1. Introduction

The increase of high-energy food intake and the decline of exercise lead to the dramatic increase of obesity in the Chinese population[1]. At present, body mass index (BMI) is a commonly used criterion for obesity in China[2], that is, BMI ≥ 24.0 kg/m^2 is overweight, and BMI ≥ 28.0 kg/m^2 is obesity. A national survey conducted in China estimated that in the past five years, 34.3% of adults (≥ 18 years old) was overweight, and 16.4% was obesity[3]. However, these data only indicated the high prevalence of obesity in the Chinese adults but ignored the diversity of obesity.

The criteria for diagnosing obesity vary around the world, and the parameters applied for measuring adult obesity include BMI, waist circumference (WC), body fat percentage (BFR) and waist-hip ratio (WHR), etc. However, each of these diagnostic indicators has its own limitation, for example, BMI is a relatively good indicator for obesity, but not for adipose distribution. Therefore, a combination of multiple parameters might be wise for the scientific assessment of adult obesity.

The WC is one of the comprehensive indicators of the total amount of adipose and its distribution. The previous study found a positive correlation between WC and the prevalence of abdominal obesity[4], and the combined use of WC with BMI is a sensitive predictor of the risk for premature death[5]. WC is a comprehensive indicator reflecting the degree of visceral adipose distribution, indicating that WC could be a

compensation for BMI's insensitivity to measuring adipose distribution. Therefore, it is recommended to subdivide the diversity of obesity by combining BMI and WC to reflect the degree of obesity and adipose distribution and comprehensively describe the body shapes.

Obesity is a metabolic syndrome caused by excessive calorie intake and accumulation of adipose in the body. As a major threat to human life quality, obesity is closely related to chronic diseases, such as diabetes, dyslipidemia, kidney dysfunction and hypertension[6]. Some studies had shown that visceral adipose is an independent risk predictor for cardiovascular diseases and is often closely related to inflammatory responses in endocrine and metabolic activities[7], and ectopic adipose deposition may lead to atherosclerosis[8]. These results suggest that the diversity of obesity caused by adipose accumulation at different sites may lead to various disease risks. Abnormal fluctuations in blood biochemical indexes usually occur early in multiple chronic diseases. And these indexes could be used to predict disease risks, such as abnormal fasting blood glucose levels represents an increased risk of diabetes, disruption of purine metabolism leads to hyperuricemia, and abnormal total cholesterol (TC) and triglyceride (TG) levels are characteristics of dyslipidemia. Therefore, exploring the relationship between body shapes and blood biochemical indexes is beneficial for monitoring the progress and risk of obesity, thus avoiding the occurrence of diseases associated with abnormalities in these indexes level.

The role of sex in the diversity of obesity has been demonstrated by multiple studies [9, 10], showing that when BMI levels (total adipose) were comparable or females were

postmenopausal, more fatty tissue was accumulated around the abdomen in females. These results suggest that the description of obesity diversity should take sex as the influencing factor to be considered. And there are sex differences in many blood biochemical indexes, such as the regulation of glucose metabolism[11], the physiological regulation of urate homeostasis[12], and blood lipid metabolism[13]. To prevent obesity-related diseases efficiently, it is significant to explore the sex-specific relationship between body shape and blood biochemical indexes. Hence, we conducted a cross-sectional study to explore the association between body shapes and blood biochemical indexes in Chinese adults.

2. Materials and methods

2.1 Study population

A total of 1828 participants, including 914 males and 914 females matched by sex and age (± 2 years old), were recruited from Beijing and Suzhou city in China. The study protocol was approved by the Committee on Medical Ethics of Capital Medical University (No. 2012SY23), and the study procedures followed the ethical standards of the Helsinki Declaration of 1975. Informed consent was signed by all participants.

2.2 Demographic characteristics and anthropometric measures

Participants underwent a general information survey and physical examination. Information on demographic characteristics including age and sex was collected by using a self-administered questionnaire. Anthropometric indices include height, weight, WC and hip circumference (HC). These measurements were measured by trained nurses in community medical service centers. BFR was determined by

INBODY S10 (InBody Japan, Tokyo, Japan). BMI was calculated as weight (kg)/height (m^2), and WHR was calculated as WC (cm)/HC (cm).

2.3 Biochemical measurements

The fasting venous blood (5 mL) was collected from all the participants in the morning. After centrifuging at 1500g for 15 min, the blood was separated and used for blood biochemical index measurement. The ILAB600 clinical chemistry analyzer (Instrumentation Laboratory, Lexington, WI, USA) was applied for blood glucose (Glu), total protein (TP), albumin (ALB), uric acid (UA), total cholesterol (TC) and triglyceride (TG) levels measurement.

2.4 Criteria for body fat distribution assessment

In this study, according to the recommended Chinese criteria of body weight for adults[2], BMI ≥ 24.0 was defined as overweight. And abdominal obesity was defined as waist circumference (WC) ≥ 90 cm in males and ≥ 85 cm in females. Therefore, in this study, obesity was divided into (1) compound obesity (high BMI, high WC), (2) peripheral obesity (high BMI, low WC), (3) central obesity (low BMI, high WC), (4) non-obesity (low BMI, low WC) by combining BMI and WC assessment.

2.5 *Criteria for blood biochemical indexes*

The fasting blood glucose (Glu) was defined as Glu ≤ 7.0 mmol/L within the normal range[14]. The blood total protein (TP) was defined as 60 g/L ≤ TP ≤ 80 g/L within the normal range. The blood albumin (ALB) was defined as 35 g/L ≤ ALB ≤ 51 g/L within the normal range[15]. The blood uric acid (UA) was defined as 149 μmol/L ≤ UA ≤ 416 μmol/L in males and 89 μmol/L ≤ UA ≤ 357 μmol/L in females within the

normal range. The blood total cholesterol (TC) was defined as 2.83 ≤ TC ≤ 5.20 mmol/L within the normal range. The blood triglyceride (TG) was defined as 0.45 ≤ TG ≤ 1.69 mmol/L within the normal range. According to whether these blood biochemical indexes were within the normal range, the normal range is defined as '0', and the abnormal range is defined as '1'.

2.6 *Statistical Analysis*

The data were statistically analyzed by SPSS 26.0 software (Chicago, IL, USA). The figures were drawn with R 4.2.1 language. Continuous variables were represented as mean ± standard deviation (SD). The correlation between anthropometric indices and blood biochemical indexes was analyzed by Pearson correlation analysis and restricted cubic spline. The t-test was used to compare the differences between groups, and the analysis of variance (ANOVA) was used to compare the differences among multiple groups. Binary logistic regression was applied to ascertain the correlation of body shapes with the risk of abnormal blood biochemical indexes (Glu, TP, ALB, UA, TC and TG) levels. The power was analyzed by using G*power 3.1 software. $P < 0.05$ was statistically significant.

3. Results

3.1 Anthropometric and blood biochemical indexes of the participants

The age, anthropometric indices and blood biochemical indexes of the participants were shown in **Table 1**. The age of the participants ranged from 18 to 85 years, with an average age of 48.80 ± 11.15 years. Males had higher BMI, WC, WHR and BFR levels than females ($P < 0.001$). Males had higher blood Glu, TP, ALB, UA, TC and

TG levels than females ($P < 0.05$).

Table 1. Anthropometric and blood biochemical indexes of the participants

Variable	Male (*n* = 914)	Female (*n* = 914)	Total (*n* = 1828)	*P-value*
Age	49.10 ± 11.16	48.49 ± 11.14	48.80 ± 11.15	0.609
Anthropometric indices				
BMI (kg/m^2)	25.34 ± 3.55	23.57 ± 3.31	24.46 ± 3.54	**0.000**
WC (cm)	92.34 ± 10.88	84.66 ± 8.79	88.50 ± 10.61	**0.000**
WHR	0.94 ± 0.07	0.91 ± 0.05	0.92 ± 0.06	**0.000**
BFR	25.49 ± 5.84	32.50 ± 5.61	28.99 ± 6.72	**0.000**
Blood biochemical indexes				
Glu (mmol/L)	6.19 ± 1.43	5.89 ± 0.94	6.04 ± 1.22	**0.000**
TP (g/L)	72.19 ± 4.00	71.42 ± 4.03	71.81 ± 4.03	**0.000**
ALB (g/L)	47.19 ± 2.71	46.34 ± 2.91	46.76 ±2.84	**0.000**
UA (μmol/L)	362.82 ± 98.18	312.92 ± 96.04	337.87 ± 100.24	**0.000**
TC (mmol/L)	5.37 ± 1.04	5.23 ± 1.01	5.30 ± 1.02	**0.003**
TG (mmol/L)	1.76 ± 1.23	1.43 ± 0.89	1.60 ± 1.08	**0.000**

Data were expressed as means ± SD. The age, anthropometric indices and blood biochemical indexes were compared by using t-tests. $P < 0.05$ was considered statistically significant. BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; BFR, body fat ratio; Glu, glucose; TP, total protein; ALB, albumin; UA, uric acid; TC, total cholesterol; TG, triglyceride.

3.2 Association between anthropometric indices and blood biochemical indexes

The sex-specific correlation between anthropometric indices and blood biochemical indexes was shown in **Figure 1**. Blood UA, TC and TG were positively correlated with the BMI or WC regardless of sex. The positive association between blood Glu and WC was only shown in females. There was no correlation between blood TP and ALB levels with anthropometric indices in the participants ($P > 0.05$).

In **Figure 2**, the restricted cubic spline showed a dose-response relationship between anthropometric indices and the risk of abnormal blood biochemical indexes level. The risk of abnormal Glu, ALB, UA, TC and TG levels is positively correlated with BMI

or WC in dose-response relationships. In addition, only the risk of abnormal blood TG levels showed a nonlinear relationship with WC and BMI, respectively. The dose-response relationship between biochemical blood indexes (Glu and TG) and anthropometric indices (BMI and WC) was sex-specific (*P*-Sex < 0.05).

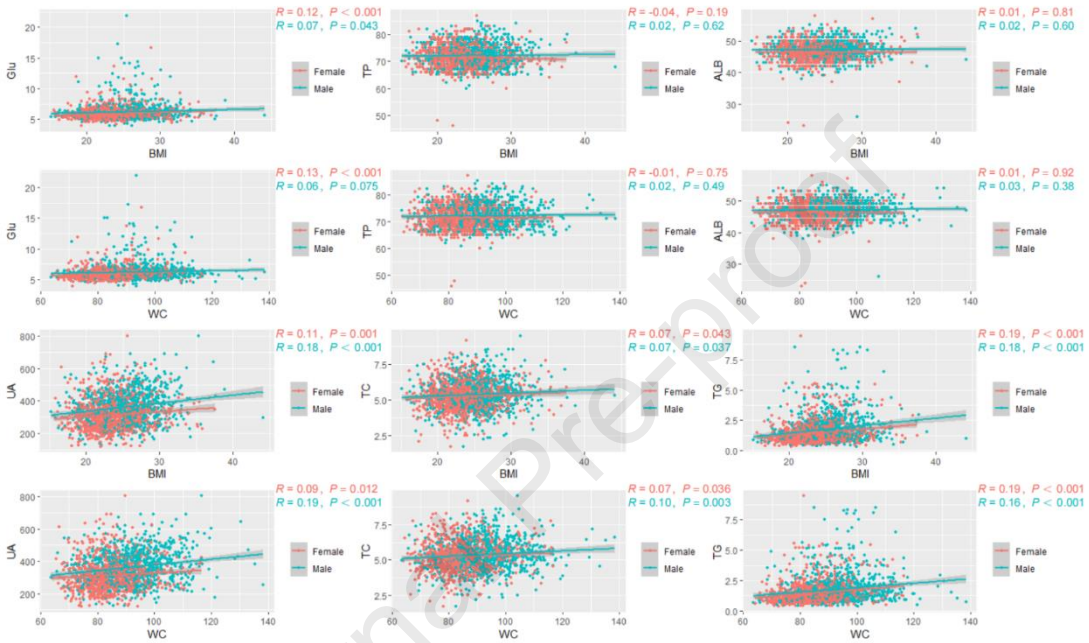

Figure 1. The scatterplot with the linear best-fit line of the association between anthropometric indices and blood biochemical indexes. The solid lines indicate a linear fit between anthropometric indices (BMI or WC) and blood biochemical indexes (Glu, TP, ALB, UA, TC, and TG) level, fitted using Pearson correlation analysis. The shaded area represents the 95% confidence interval. $P < 0.05$ was considered statistically different. BMI, body mass index; WC, waist circumference; Glu, glucose; TP, total protein; ALB, albumin; UA, uric acid; TC, total cholesterol; TG, triglyceride.

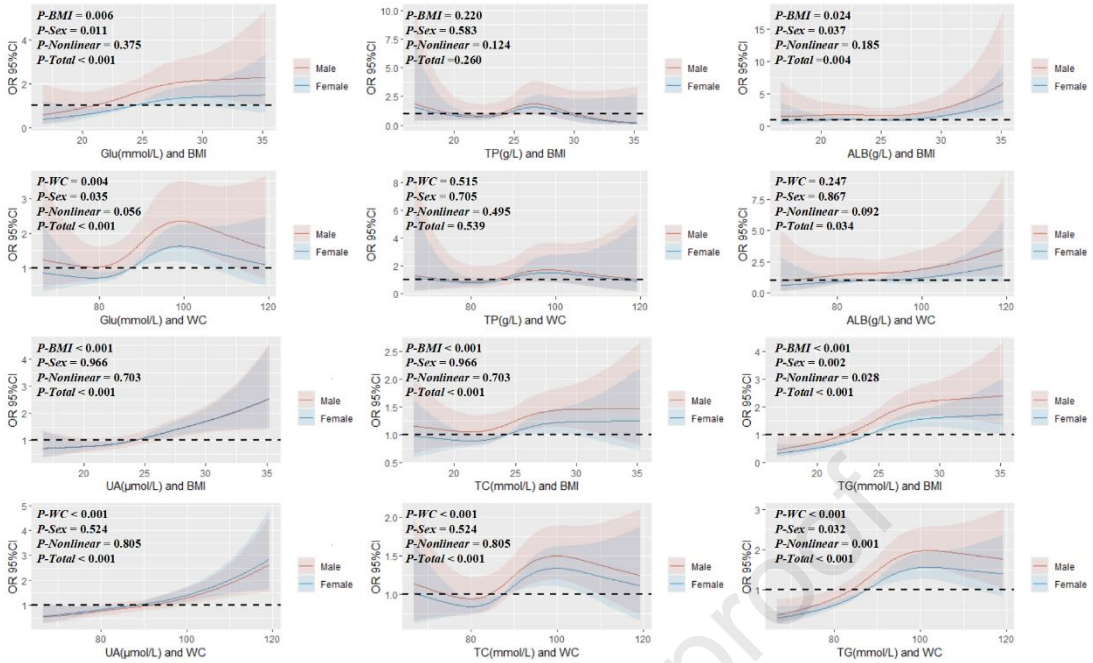

Figure 2. The restricted cubic spline of the association between anthropometric indices and blood biochemical indexes. The solid lines indicate estimates of the risk of abnormal blood Glu, TP, ALB, UA, TC and TG levels across the continuous level of anthropometric indices (BMI or WC), fitted using logistic regression analysis. The shaded areas indicate the 95% confidence intervals. $P < 0.05$ was considered statistically different. BMI, body mass index; WC, waist circumference; Glu, glucose; TP, total protein; ALB, albumin; UA, uric acid; TC, total cholesterol; TG, triglyceride.

3.3 The distribution of body shapes according to the sex

The body shapes were shown in **Figure 3**, including compound obesity (high BMI, high WC), peripheral obesity (high BMI, low WC), central obesity (low BMI, high WC) and non-obesity (low BMI, low WC). For males, the percentage was 52.8% (n = 483), 12.1% (n = 111), 3.7% (n =34), and 31.3% (n = 286), respectively. While for females, the percentage was 34.5% (n = 315), 4.0% (n = 37), 10.1% (n = 92), and 51.4% (n = 470), respectively. The distribution of body shapes according to sex was statistically significant ($P < 0.05$). The prevalence of compound obesity and peripheral obesity in males are higher than that in females.

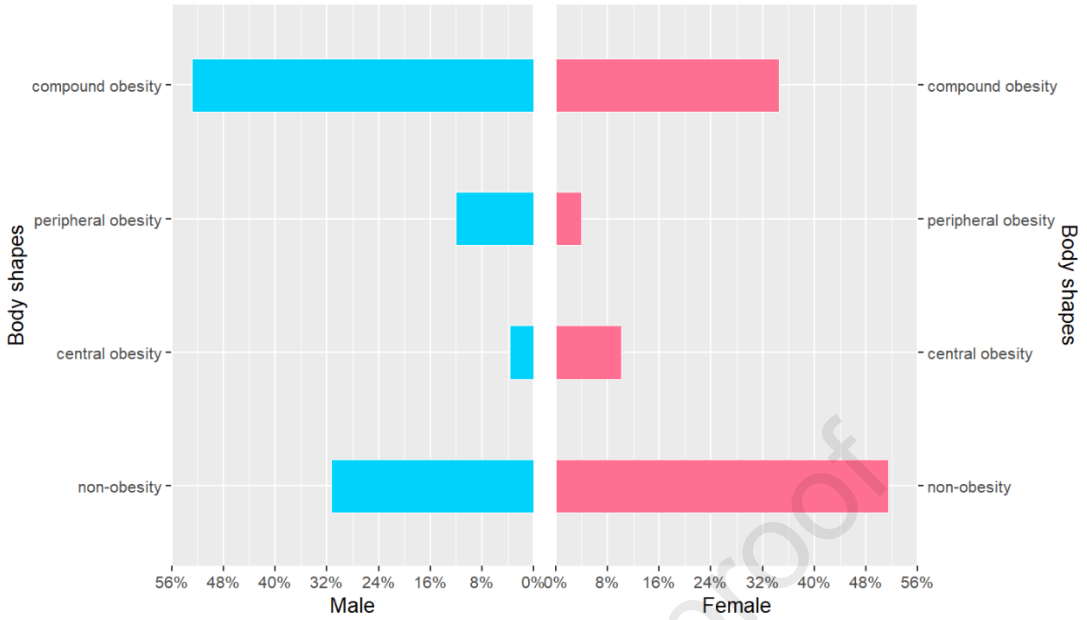

Figure 3. The distribution of participants with different body shapes according to sex. Data were expressed as percentages.

3.4 The sex-differences in blood biochemical indexes according to body shapes

As shown in **Figure 4**, the blood Glu, UA, TC and TG levels of compound obesity were higher than those of non-obesity in males. But for females, the blood Glu, UA and TG levels of compound obese subjects were higher than those of the non-obesity ones. There was no body shapes difference in blood TC levels among females. Moreover, in terms of blood lipid parameters, the TC and TG levels of male subjects with compound obesity were significantly higher than that of male subjects with peripheral obesity. In addition, the UA level of compound obesity male subjects was significantly higher than that of subjects with the other three types of obesity, while that of the non-obesity male subjects was significantly lower than that of female subjects with compound obesity and peripheral obesity. No statistical difference was found in the blood TP and ALB levels between body shapes according to sex.

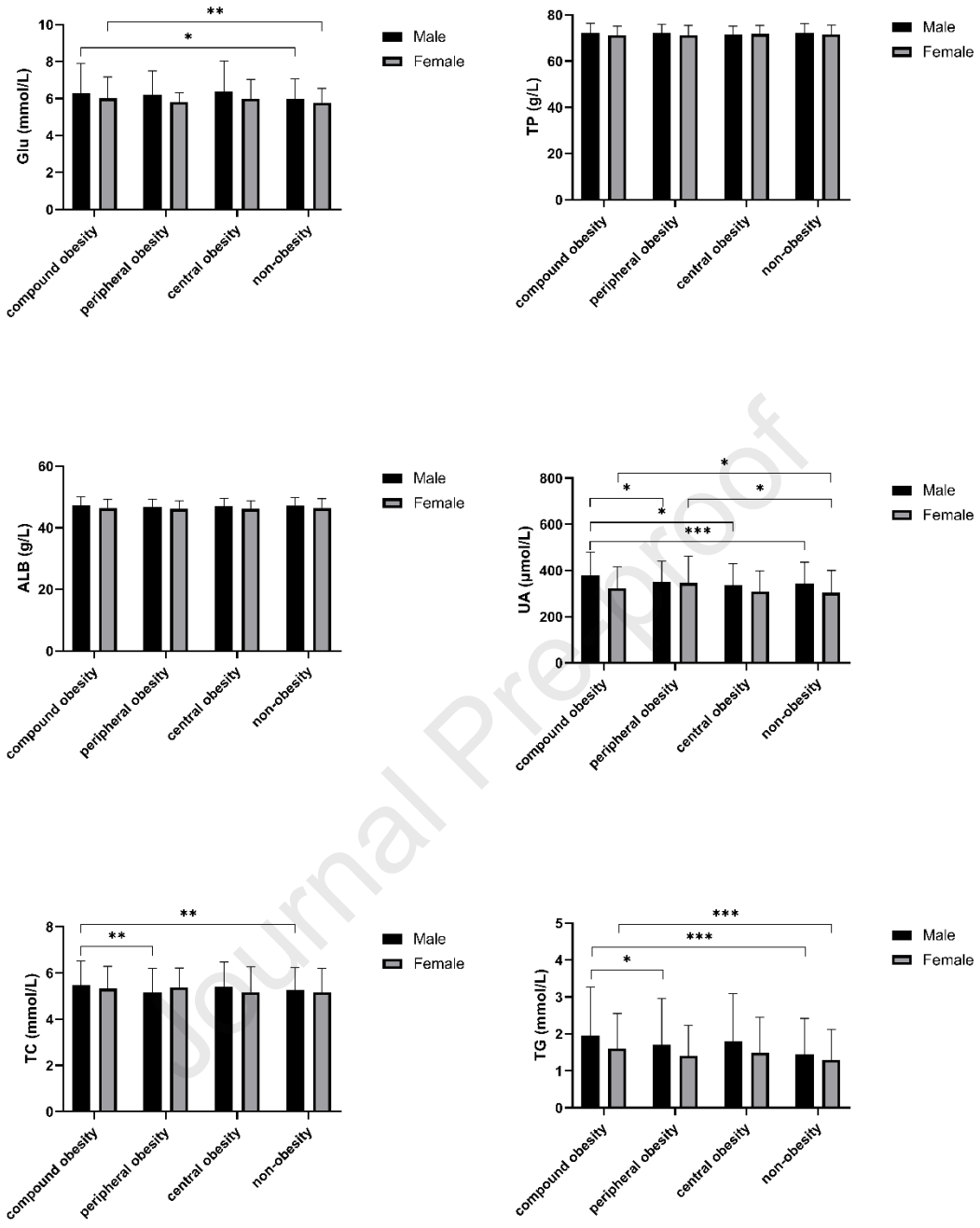

Figure 4: The difference in blood biochemical indexes of body shapes according to sex. Data were expressed as means ± SD. Differences in blood biochemical indexes by body shape were compared by using analysis of variance (ANOVA). $P < 0.05$ was considered statistically different. BMI, body mass index; WC, waist circumference; Glu, glucose; TP, total protein; ALB, albumin; UA, uric acid; TC, total cholesterol; TG, triglyceride.

3.5 Sex-specific association between body shapes and the level of abnormal blood biochemical indexes

The sex-specific association between body shapes and the level of abnormal blood

biochemical indexes was shown in **Figure 5**. Compared with the non-obese subjects, the compound obese subjects were more likely to have the risk of abnormal blood Glu levels. For the UA level, the subjects with peripheral obesity showed a higher risk of abnormal blood UA level than female non-obese subjects (*OR* = 2.715, *95%CI:* 1.367 – 5.392, *P* = 0.004), while the risk of compound obesity was higher than male non-obese subjects. Compared with the non-obese subjects, males with compound obesity and peripheral obesity had a higher risk of abnormal blood TG level, while females with compound obesity and central obesity had a higher risk of abnormal blood TG level. No statistical difference was found among participants with different body shapes in TP and ALB.

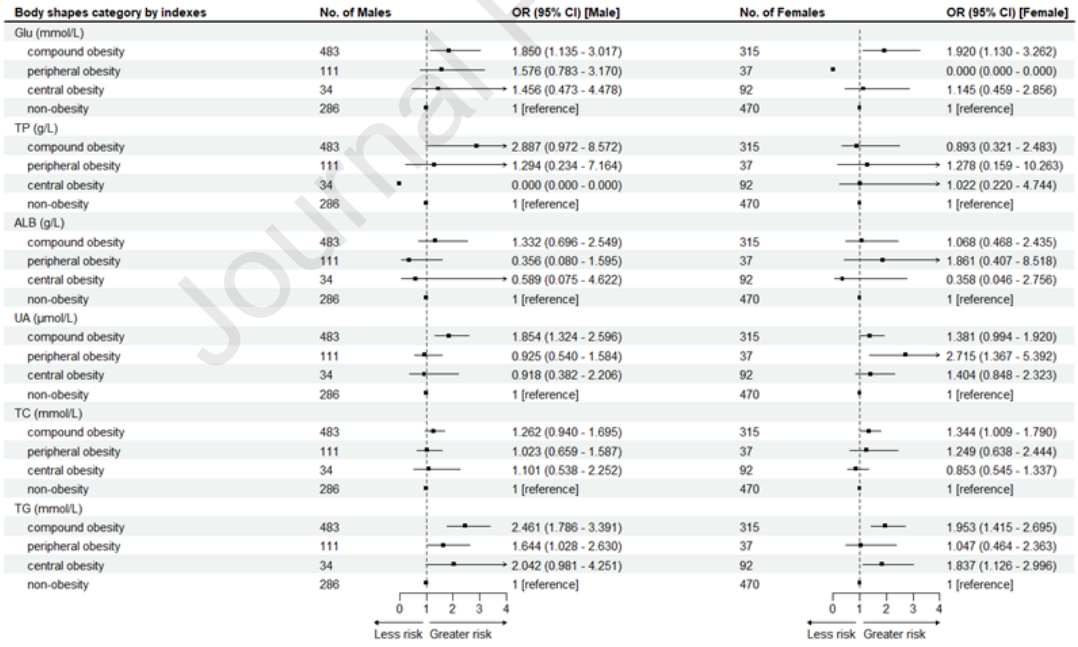

Figure 5: Sex-specific association between body shapes and the risk of abnormal blood biochemical indexes level. The sex-specific association between body shapes and the risk of abnormal blood biochemical indexes level was determined by logistic regression. $P < 0.05$ was considered statistically different. Glu, glucose; TP, total protein; ALB, albumin; UA, uric acid; TC, total cholesterol; TG, triglyceride; OR, odds ratio; CI, confidence interval.

4. Discussion

In the present study, we explored the relationship between blood Glu, TP, ALB, UA,

TC and TG levels with body shapes (different types of obesity) according to sex. Consistent with the previous study[16], we found a sex-specific association between the anthropometric indices and blood biochemical indexes, showing that males had higher anthropometric indices and blood biochemical indexes level than females (**Table 1**), which was possibly due to the hormonal differences in males and females[17]. Moreover, the difference in the dietary pattern might also contribute to this sex discrepancy in anthropometric indices and blood biochemical index levels[18], as Y Kang et al. found that sex factors may influence the relationship between dietary patterns and metabolic syndrome[19]. The study reported that sex plays an important role in modifying the relationship between BMI and visceral adipose tissue[20], suggesting that it is necessary to consider the factor of sex when assessing body adipose distribution by BMI. These data indicated that sex is a potential impactor on the relation between blood biochemical indexes and body shapes in adults.

When using BMI or WC as the criterion for determining obesity, we found that males had higher BMI or WC levels than females. However, when assessing obesity by BMI and WC jointly, we found that more females were central obesity (low BMI, high WC) and non-obesity (low BMI, low WC), while more males were peripheral obesity (high BMI, low WC) and compound obesity (high BMI, high WC) (**Figure 3**), suggesting that the overall obesity rate in males is higher than that in females. These results were consistent with the findings of a national survey conducted on the Chinese population[21], which reported that the number of obese males was 1.3 times higher than obese females (48 million males *vs.* 37 million females). The sex difference in

obesity diversity suggests that, even with the same BMI, males are more likely to have subcutaneous adipose accumulation (peripheral obesity) as compared with females. In contrast, females are prone to visceral adipose accumulation (central obesity)[9]. The previous study reported the impact of estrogen on the accumulation of abdominal adipose in females [22]. Combined with the current study that the average age of females is 48.49 years old, therefore we speculate that the dramatic reduction in estrogen levels in females at perimenopause promotes the accumulation of abdominal adipose.

The positive correlation between anthropometric indices (BMI and WC) and diabetes mellitus has been demonstrated in several population-based studies[23, 24]. Consistently, we found that the subjects with higher blood Glu levels (**Figure 1**) and higher risk of abnormal Glu levels (**Figure 2**) displayed a sex-independent increase in WC and BMI levels. Data from the clinical study suggests that visceral adipose tissue produces diabetes-risk substances[25], such as TNF-α, IL-6 and IL-1, which might be attributable to the increased risk of diabetes[26]. Compared with the subjects with non-obesity, the subjects with compound obesity (generalized obesity and visceral adipose accumulation) are at an increased risk for abnormal Glu level, while this increase in the risk of abnormal Glu level was not found in the subjects with central obesity (visceral adipose accumulation) (**Figure 5**). We, therefore, speculate that generalized obesity (high BMI) may underlie the pathology of visceral adipose tissue (central obesity) that exacerbates diabetes.

Serum uric acid (UA) is the product of purine metabolism, which is closely related to

energy supply and metabolic regulation in the body. Kazuko et al. found that, as a determinant of BMI changes, the UA level could be used to predict weight gain[27], suggesting that the degree of adipose tissue accumulation is positively correlated with serum UA level[28]. This result is in line with our findings in middle-aged Chinese adults (**Figure 1**). Some studies have elucidated the mechanism from the perspective of the production and excretion of UA[29]. Adipose accumulation provides the body with excess free fatty acids, accelerating the *de novo* synthesis of purines from NADPH production in the pentose phosphate pathway[30, 31], resulting in increased UA production. And the metabolic activity of adipose tissue may cause insulin resistance by increasing the release of various adipocyte cytokines, including leptin and adiponectin[32], which further increases the renal tubule reabsorption of UA and leads to decreased excretion[33]. We found that peripheral obesity (subcutaneous adipose tissue) was associated with the risk of abnormal UA levels only in females compared to the non-obese subjects (*OR* = 2.715, *95%CI*: 1.367-5.392). These results suggest that peripheral obesity (excessive accumulation of subcutaneous adipose tissue) significantly affects circulating UA levels in females.

Total cholesterol (TC) and triglyceride (TG) are important components of the lipid profile. Our study found that the influence of body shapes on TG is sex-dependent. Compared with non-obese subjects, not only the subject with compound obesity displayed a higher risk of abnormal TG levels, but also peripheral obesity had a higher abnormal TG level risk in males, while central obesity was in females. Estrogen could reduce the biosynthesis of lipid in the liver by maintaining acetyl-CoA

carboxylase (ACC) phosphorylation and promoting the oxidation of free fatty acids (FA)[34]. Estrogen also act directly on the hepatic cells to reduce TG levels through the estrogen receptor (ER)[35]. These results suggest that the decline in estrogen level in women after menopause will increase TG production through regulating lipid metabolism in liver. Data from population-based studies have also shown that blood estrogen levels are negatively correlated with triglyceride level, and this effect is more pronounced in the subjects with obesity[36]. Julieta et al. found that the lipid metabolism-related gene and protein expression is affected by sex[37], which is expressed in a hormone-responsive way. This may be the physiological basis for the increased risk of abnormal TG levels in males due to peripheral obesity (subcutaneous adipose accumulation) but not in females. In females with central obesity, the amount of visceral adipose tissue was positively correlated with blood TG level[38, 39], indicating the possible sex-dependent impact of the compound and central obesity on the risk of abnormal TG level.

This study found that peripheral obesity was associated with blood TG level in the males, while central obesity was associated with blood TG level in the females. In addition, peripheral obesity is associated with blood UA level in the females. Clinically, for the male obesity patients with peripheral obesity, and female subjects with abdominal obesity (especially after the menopause), blood TG level should be taken as a routine monitoring index. Peripheral obesity in females may lead to elevated blood UA level and increase the risk of gout, so regular monitoring of blood UA level and appropriate dietary and exercise interventions are recommended.

According to the type and gender characteristics of obesity, it is crucial to develop personalized intervention programs for preventing obesity-related metabolic abnormalities.

There are several limitations in this study. Firstly, the small sample size of this study resulted in a further smaller sample size for each group after stratifying the participants according to different body shapes, which made it impossible for us to conduct further statistical analysis to compare peripheral obesity with blood Glu in females and central obesity with blood TP in males. Secondly, the cross-sectional design of the study fails to explain the causal relationship between sex, blood biochemical indexes and body shapes. Thirdly, the potential impact of confounding factors such as lifestyle and dietary intake habits on the outcome were not considered during data analysis. Therefore, a longitudinal population-based study and accurate measurement of body fat distribution is needed in the future to further explore the relation between body size and blood biochemical markers over time in male and female subjects.

5. Conclusion

Participants with compound obesity had a higher risk of abnormal circulating Glu and TG levels independent of sex than non-obese participants. There was a sex-specific difference in blood UA and TG between the subjects with central obesity and peripheral obesity. Specifically, peripheral obesity in males while central obesity in females was associated with blood TG levels. Peripheral obesity in females was associated with blood UA levels. The risk of abnormal blood biochemical indexes

also differs between males and females with different body shapes, suggesting that future studies exploring the relationship between body shapes and blood biochemical indexes also need to consider the potential role of sex.

Conflicts of Interest

The authors declare that there is no potential conflict of interest.

Author's Contributions

Xixiang Wang: Methodology, Formal analysis, Visualization, Writing - Original Draft. Jingjing Xu: Methodology, Writing - Original Draft. Yiyao Gu: Investigation. Jie Mu: Investigation. Xiaojun Ma: Investigation. Lu Liu: Investigation. Yu Liu: Investigation. Zhi Duan: Investigation. Shaobo Zhou: Writing – Review & Editing. Ying Wang: Conceptualization, Supervision, Writing - Review & Editing, Funding acquisition. Linhong Yuan: Conceptualization, Supervision, Writing - Review & Editing, Funding acquisition.

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Highlights

- When BMI is similar, female is prone to central obesity, and male is peripheral obesity.
- There exists sex-differences in the relationship between blood TG and UA with body shapes.
- The risk of abnormal TG levels is higher in peripheral obese males and central obese females.
- Peripheral obese females have higher risk of abnormal UA levels, which is not observed in peripheral obese males.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: