Observational Study

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Association between triglyceride glucose index and abnormal liver function in both urban and rural Chinese adult populations

Findings from two independent surveys

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Abstract

The purpose of this study was to investigate the association between triglyceride glucose (TyG) index and abnormal liver function both in urban and rural Chinese adult populations. The 5824 urban (Nanjing) and 20,269 rural (Hefei) Chinese adults, from random selected households provided clinical history, glucose, lipids, anthropometric, and blood pressure measurements. Liver functions were assessed using Alanine Aminotransferase (ALT). Linear regression was applied to examine the dose-response relationship between TyG index and ALT. Logistic regression was used to estimate the association between TyG index and abnormal liver and function. Cubic spline models were applied to investigate the dose-response association between TyG index and abnormal liver function. C-statistics was used to compare the discriminable capacity over triglyceride, glucose and TyG index. Linear dose-response relationship was identified between TyG index and ALT as 1.222 IU increase by 1 unit increase of TyG index (1.242 for urban population and 1.210 for rural population). The 6.0% of urban and 11.0% of rural Chinese adults were observed to have abnormal liver function. The linear association between TyG index and abnormal liver function was revealed as 2.044 (1.930 to 2.165) of odds ratio by in unit increase of TyG index (2.334 for urban population and 1.990 for rural population). Higher C-statistics was found for TyG index compared with fasting glucose and triglyceride both in Chinese urban and rural populations. This study suggested in both urban and rural Chinese adult populations, TyG index is associated with abnormal liver function. TyG index is a potential indicator to identify high-risk individuals with metabolic disorders, for example impaired liver function in Chinese population, especially in Chinese urban population.

Abbreviations: ALT = alanine aminotransferase, CAC = coronary artery calcification, IR = insulin resistance, OR = odds ratio, TyG index = triglyceride glucose index.

Keywords: Chinese, insulin resistance, liver function, triglyceride glucose index

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The authors declare that there are no conflicts of interest to disclose.

The data used to support the findings of this study are available from the corresponding author upon request.

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1. Introduction

It has been revealed by previous epidemiological studies that impaired liver function (evaluated by increased activity of liver enzyme, for example, alanine aminotransferase) is associated with progression of metabolic disorders.[1,2] Previous prospective studies demonstrates that Insulin resistance (IR) contributed to progression of many metabolic disorders like hypertension, central obesity, and dyslipidemia.[3–5] Recently, emerging researches also proposed that IR might also take a role in the development of impaired liver function.[1]

To quantify IR the gold standard is the hyperinsulinemic euglycemic clamp. Because it is a labor-intensive and costly procedure, this technique is not feasible in routine clinical settings.[6] Alternatively, the homeostasis model, assessment of insulin resistance (HOMA-IR) formula,[7] which is based on fasting glucose and insulin levels, is less invasive and labor-intensive. However, this method is much more variable than the clamp due to the wide range of "normal" values for fasting plasma insulin. Also, it cannot be used in patients with diabetes, where the normal homeostatic relationship between plasma glucose and insulin levels no longer exists.

The TyG index was first introduced as a surrogate marker for insulin resistance by Guerreo-Romero.[8] The TyG index has shown direct correlation with insulin resistance, as assessed by hyperinsulinemic euglycemic clamp or insulin-mediated glucose uptake.[9,10] In a Brazilian population, TyG index showed better performance for assessing insulin resistance than the HOMA-IR.[11] Therefore, the TyG index has shown direct correlation with IR and been proposed as a reliable and simple surrogate marker of IR in clinical practice.[12,13]

Consistent with these data, there is growing evidence to suggest that the TyG index is associated with metabolic disorders.[14–16] However the association between IR and impaired liver function in general Chinese adult populations are yet to be reported. In particular, few studies have examined the association between the TyG index as IR surrogate and abnormal liver function in Chinese adult population. Therefore, in the present study, we have investigated the relationship between the TyG index and abnormal liver function both in Chinese urban and rural adult populations via 2 independent surveys.

2. Methods

2.1. Data setting

Two independent surveys with one implemented in urban area and the other one was carried out in the rural area. The urban Chinese population data were derived from the Nanjing Community Cardiovascular Risk Survey, using random cluster sampling,[11] between 2011 and 2013 among the residents of 6 communities in Nanjing, Jiangsu Province, China. In each community, one street district or township was randomly selected. All households (n = 6445) in the selected street or town were included with only one participant aged ≥20 years selected from each household, without replacement. Overall, 5824 residents completed the survey and examination (response rate of 90%). The rural Chinese population data were derived from the Hefei Community Cardiovascular Risk Survey, using random cluster sampling,[11] between 2012 and 2013 among the residents of 10 rural towns in Hefei, Anhui Province, China. In each rural area, one township was randomly selected. All households (n = 22,032) in the selected town were included with only 1 participant aged ≥20 years selected from each household, without replacement. Overall, 20,269 residents completed the survey and examination (response rate of 92%).

2.2. Clinical measurements

In both surveys, questionnaires were completed, wherever possible, through face-to-face interviews by trained research staff. Questions included age, sex, ethnicity, education, and known diabetes.

In both surveys, blood pressure and body measurements including height, weight, and waist circumference were taken 3 times using a standardized methodology on the same day in the local clinical center and the mean of the 2 closest recordings was used. Height, weight, and waist circumference were measured by use of a metric scale and a vertical weight scale. Weight was measured in light indoor clothing without shoes to the nearest 10th of a kilogram. Height was measured without shoes to the nearest 10th of a centimeter. Waist circumference was measured at 1 cm above the navel at minimal respiration. In both studies all observers participated in a training session on the use of a standardized protocol for anthropometric measurement techniques.

An overnight-fasting venous blood specimen for measurement of serum glucose was collected by trained nurses using a vacuum tube containing sodium fluoride. The fasting time was verified prior to collecting the blood specimen. Participants who had not fasted for at least 10 hours did not have their blood drawn. Fasting blood specimens collected in Nanjing were processed at the examination center (Nanjing) for urban population and fasting blood specimens collected in Hefei rural population were shipped by air to Nanjing examination centre. Plasma glucose, alanine aminotransferase (ALT), creatinine, and lipid levels were measured by automated analyzer (Olympus AU600 autoanalyzer (Olympus Optical, Tokyo, Japan)). Type 2 diabetes was defined using WHO criteria or by self-report if previously diagnosed.[17] Hypertension was considered present if reported as having previously been diagnosed by a doctor or nurse.[18] Abnormal liver function was defined as ALT ≥ 40U/L.[19] TyG index was calculated as the ln [fasting triglyceride (mg/dl) ×fating glucose (mg/dl)/2] (14).

2.3. Statistical analysis

Continuous variables were characterized by their median and interquartile range, and differences across groups were tested using Kruskal–Wallis test. Categorical variables were characterized by percentages, and different across groups were tested using Chi-square test. Pearson correlation between Log 10 (ALT) (Normal transfer of ALT) and TyG index was evaluated in overall, urban and rural population, respectively. Multivariable linear regression was applied to examine the dose-response relationship between Log 10 (ALT) and TyG index and quantify the change of ALT by increase of TyG index with adjustment of covariables presented in Table 1. Multivariable Logistic regression model was used to evaluate the dose-response association between the TyG index and abnormal liver function and quantify the odds ratio (OR) by increase of TyG index after adjusting for covariables presented in Table 1.

C-statistics from multivariable Logistic regression model was used to compare the discrimination between glucose, triglyceride and TyG index. The 95% confidence interval of the C-statistics was obtained from 1000 bootstrap samples.

All analyses were performed using STATA (STATA/MP 15.0 StataCorp, College Station, TX). All *P* values were calculated using two-tailed tests and a *P* value < .05 was taken to indicate statistical significance.

The Institutional Review Board of Jiangsu Province Hospital on Integration of Chinese and Western Medicine Approved this Study (approval number 11–006). Signed, Informed consent was obtained from all participants.

3. Results

The characteristic of study participants by the liver function status (ALT < 40IU and ALT > = 40 IU) in both urban (Nanjing) and rural (Hefei) adult populations are presented in Table 1. The prevalence of abnormal liver function was more common in rural population comparing with urban population, as 6.0% and 11.0% for urban and rural adults, respectively. Both among urban and rural adults, the prevalence of male gender, current smoking, hypertension and type 2 diabetes was higher in participants with abnormal liver function comparing with those with normal liver function, respectively. Both in urban and rural populations, study participants with abnormal liver function

Table 1

Characteristics of participants in all and by liver function status.

	All	ALT < 40IU	ALT≥40IU	*P* value
Nanjing survey				
Participants, n	5,824	5,476 (94.0%)	348 (6.0%)	-
Age, years	52.0 (43.0 to 59.0)	52.0 (44.0 to 59.0)	51.0 (43.0 to 57.0)	<.0001
Women, n (%)	3,278 (56.3%)	3,119 (57.0)	159 (45.7)	<.0001
Current smoking, n (%)	1,571 (28.0%)	1,462 (27.7)	109 (32.3)	<.0001
Hypertension, n (%)	2,259 (38.8)	2,109 (38.5)	150 (43.1)	<.0001
Type 2 diabetes, n (%)	472 (8.1)	421 (7.7)	51 (14.7)	<.0001
Body mass index, kg/m^2	23.6 (21.4 to 26.1)	23.5 (21.3 to 25.9)	25.7 (23.1 to 28.1)	<.0001
Waist circumference, cm	80.0 (73.3 to 87.0)	80.0 (73.0 to 86.9)	86.1 (79.0 to 93.0)	<.0001
Systolic blood pressure, mmHg	128.0 (116.3 to 142.5)	128.0 (116.0 to 142.5)	128.0 (117.0 to 143.0)	<.0001
Diastolic blood pressure, mmHg	80.5 (73.5 to 88.5)	80.3 (73.0 to 88.5)	82.5 (75.0 to 90.0)	<.0001
Fasting glucose, mmol/L	5.4 (4.9 to 5.9)	5.4 (4.9 to 5.9)	5.6 (5.1 to 6.2)	<.0001
Triglyceride, mmol/L	1.2 (0.8 to 1.7)	1.1 (0.8 to 1.7)	1.6 (1.1 to 2.6)	<.0001
Total cholesterol, mmol/L	4.4 (3.9 to 4.9)	4.4 (3.9 to 4.9)	4.7 (4.0 to 5.2)	<.0001
High density lipoprotein cholesterol, mmol/L	1.3 (1.1 to 1.5)	1.3 (1.2 to 1.9)	1.3 (1.1 to 1.4)	.0436
Low density lipoprotein cholesterol, mmol/L	2.4 (2.0 to 2.9)	2.4 (2.0 to 2.8)	2.4 (2.0 to 2.9)	<.0001
Creatinine, mg/dl	1.0 (0.9 to 1.1)	88.0 (78.0 to 99.0)	94.0 (82.3 to 105.0)	<.0001
Alanine aminotransferase, IU	14.0 (9.0 to 22.0)	14.0 (8.0 to 20.0)	49.0 (43.0 to 61.0)	<.0001
Triglyceride glucose index	8.5 (8.1 to 9.0)	8.5 (8.1 to 8.9)	8.9 (8.5 to 9.5)	<.0001
Hefei Survey				
Participants, n	20,269	18,034 (89.0%)	2,235 (11.0%)	-
Age, years	51.0 (43.0 to 58.0)	51.0 (43.0 to 59.0)	49.0 (42.0 to 56.0)	<.0001
Women, n (%)	1,1905 (58.7)	10,899 (60.4)	1,006 (45.0)	<.0001
Current smoking, n (%)	4,687 (23.3)	4,009 (22.4)	678 (30.5)	<.0001
Hypertension, n (%)	9,228 (45.5)	8,146 (45.2)	1,082 (48.4)	<.0001
Type 2 diabetes, n (%)	1,832 (9.0)	1,540 (8.5)	292 (13.1)	<.0001
Body mass index, kg/m^2	24.1 (21.8 to 26.5)	24.0 (21.7 to 26.3)	25.2 (22.8 to 27.9)	<.0001
Waist circumference, cm	81.6 (74.3 to 88.7)	81.3 (74.0 to 88.2)	85.3 (77.1 to 92.3)	<.0001
Systolic blood pressure, mmHg	131.5 (119.5 to 147.9)	131.5 (119.0 to 147.5)	133.0 (121.5 to 148.5)	<.0001
Diastolic blood pressure, mmHg	82.5 (75.0 to 90.5)	82.0 (74.5 to 90.5)	84.5 (77.0 to 92.5)	<.0001
Fasting glucose, mmol/L	5.3 (4.8 to 5.2)	5.2 (4.8 to 5.8)	5.5 (5.1 to 6.1)	<.0001
Triglyceride, mmol/L	1.3 (0.9 to 1.8)	1.2 (0.9 to 1.8)	1.6 (1.1 to 2.3)	<.0001
Total cholesterol, mmol/L	4.6 (4.0 to 5.2)	4.6 (4.0 to 5.2)	4.7 (4.1 to 5.4)	<.0001
High density lipoprotein cholesterol, mmol/L	1.3 (1.1 to 1.5)	1.3 (1.2 to 1.9)	1.3 (1.1 to 1.5)	.0362
Low density lipoprotein cholesterol, mmol/L	2.6 (2.2 to 3.1)	2.6 (2.2 to 3.1)	2.6 (2.1 to 3.1)	<.0001
Creatinine, mg/dl	87.0 (77.0 to 97.0)	86.0 (77.0 to 96.0)	88.0 (78.0 to 99.0)	<.0001
Alanine aminotransferase, IU	19.0 (18.0 to 23.0)	17.0 (12.0 to 24.0)	50.0 (44.0 to 63.0)	<.0001
Triglyceride glucose index	8.6 (8.2 to 9.0)	8.5 (8.1 t0 9.0)	8.8 (8.5 to 9.3)	<.0001

Continuous variables were presented as median (interquartile range). Categorical variables were presented as n (%).

were more likely to have lower age and high-density lipoprotein, and higher levels of body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, triglyceride, total cholesterol, low-density lipoprotein, creatinine, alanine aminotransferase, and triglyceride glucose index.

The Pearson correlation coefficient was 0.517 between Log 10 (ALT) and TyG index in all participants (urban + rural). The Pearson correlation coefficient was 0.537 and 0.445 for Urban and rural population, respectively. A linear dose-response relationship between Log10 (ALT) and TyG index was revealed (*P* values for linear test >.05) in all participants (urban + rural) as presented in Figure 1. Similar linear relationships were revealed in the sensitivity analyses modelling the associations in urban population (Nanjing) (*P* values for linear test >.05) as shown as the middle panel of Figure 1 and in rural population (Hefei) (*P* values for linear test >.05) as shown as the right panel of Figure 1. After adjusting for covariables presented in Table 1, ALT increased 1.222 (95% confidence interval: 1.208 to 1.237) IU by 1 unit increase of TyG index in participants (urban + rural) in Table 2. ALT increased 1.242 (1.211 to 1.275) IU and 1.210 (1.194 to 1.227) IU by 1 unit increase of TyG index in urban and rural population, respectively (Table 2).

A linear relationship between TyG index and odds ratio of having abnormal liver function was found (*P* values for linear test >.05) in all participants (urban + rural) as presented in Figure 2. Relationship curves were derived from the natural cubic spline models with adjustment of covariates in Table 1. Similar linear relationships were revealed in the sensitivity analyses modelling the associations in urban population (Nanjing) (*P* values for linear test >.05) as shown as the middle panel of Figure 2 and in rural population (Hefei) (*P* values for linear test >.05) as shown as the right panel of Figure 2. After adjusting for covariables presented in Table 1, the odds ratio for having impaired liver function was 2.044 (1.930 to 2.165) by 1 unit increase of TyG index in participants (urban + rural) in Table 3. The odds ratio was 2.334 (2.024 to 2.690) and 1.990 (1.868 to 2.119) for urban and rural population, respectively in Table 3.

C-statistics for discriminating the status of having abnormal liver function by triglyceride, glucose and TyG index was presented in Table 4, respectively. In overall population (urban +

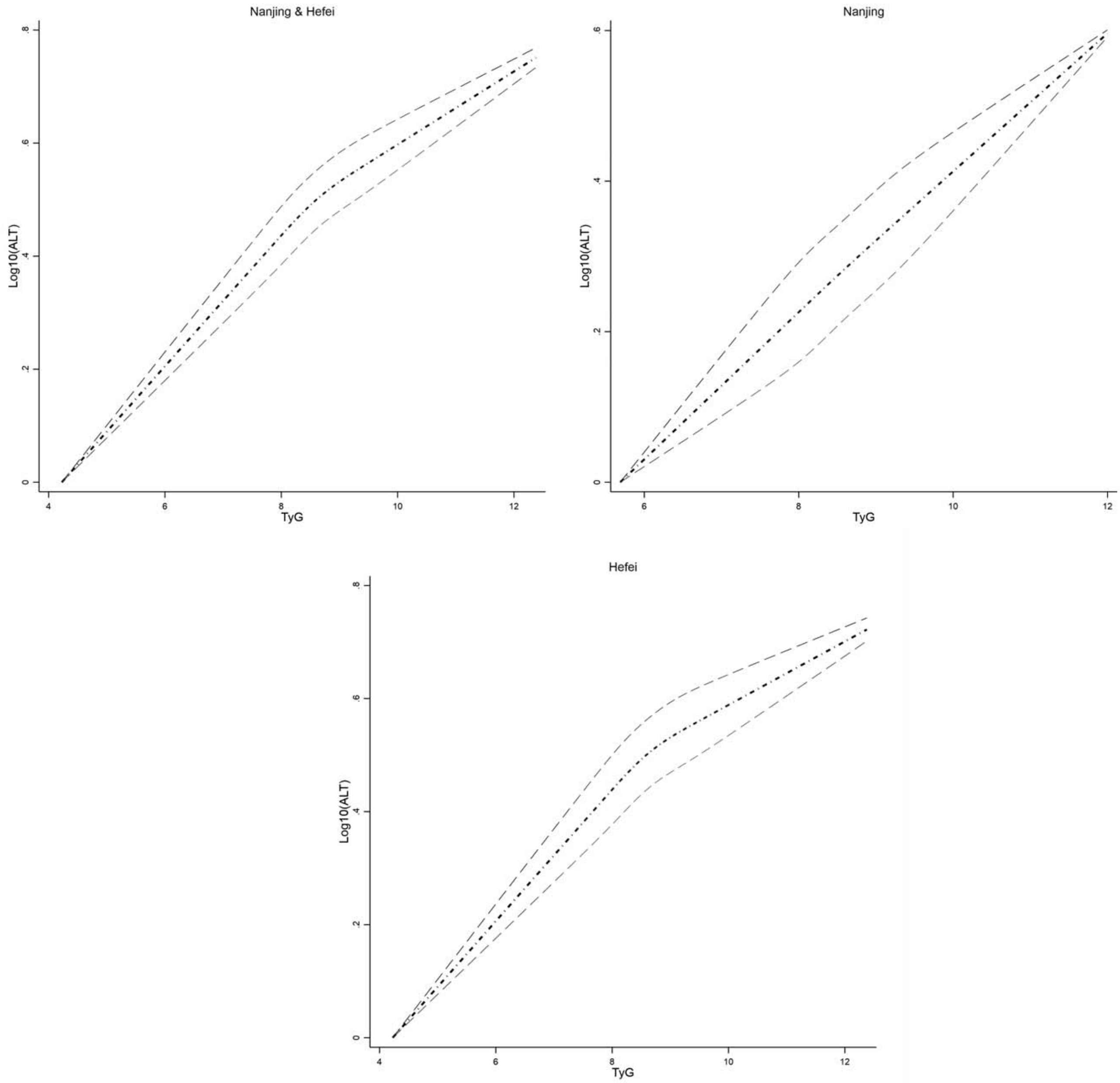

Figure 1. Dose-response relationship between TyG index and alanine aminotransferase. Alanine aminotransferase was transferred as log10 (alanine aminotransferase). Age, gender, smoking status, having hypertension, having type 2 diabetes, body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, creatinine were adjusted.

Table 2

C-statistics in predicting abnormal liver functions by 3 measurements (triglyceride, glucose, and TyG index).

	Abnormal Liver Function		
	TyG	Triglyceride	Glucose
Nanjing & Hefei	0.749 (0.739 to 0.760)	0.637 (0.626 to 0.648)	0.603 (0.592 to 0.614)
Nanjing	0.784 (0.755 to 0.813)	0.673 (0.644 to 0.702)	0.577 (0.545 to 0.608)
Hefei	0.742 (0.730 to 0.753)	0.628 (0.616 to 0.639)	0.612 (0.601 to 0.624)

Age, gender, smoking status, having hypertension, having type 2 diabetes, body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, creatinine were adjusted.

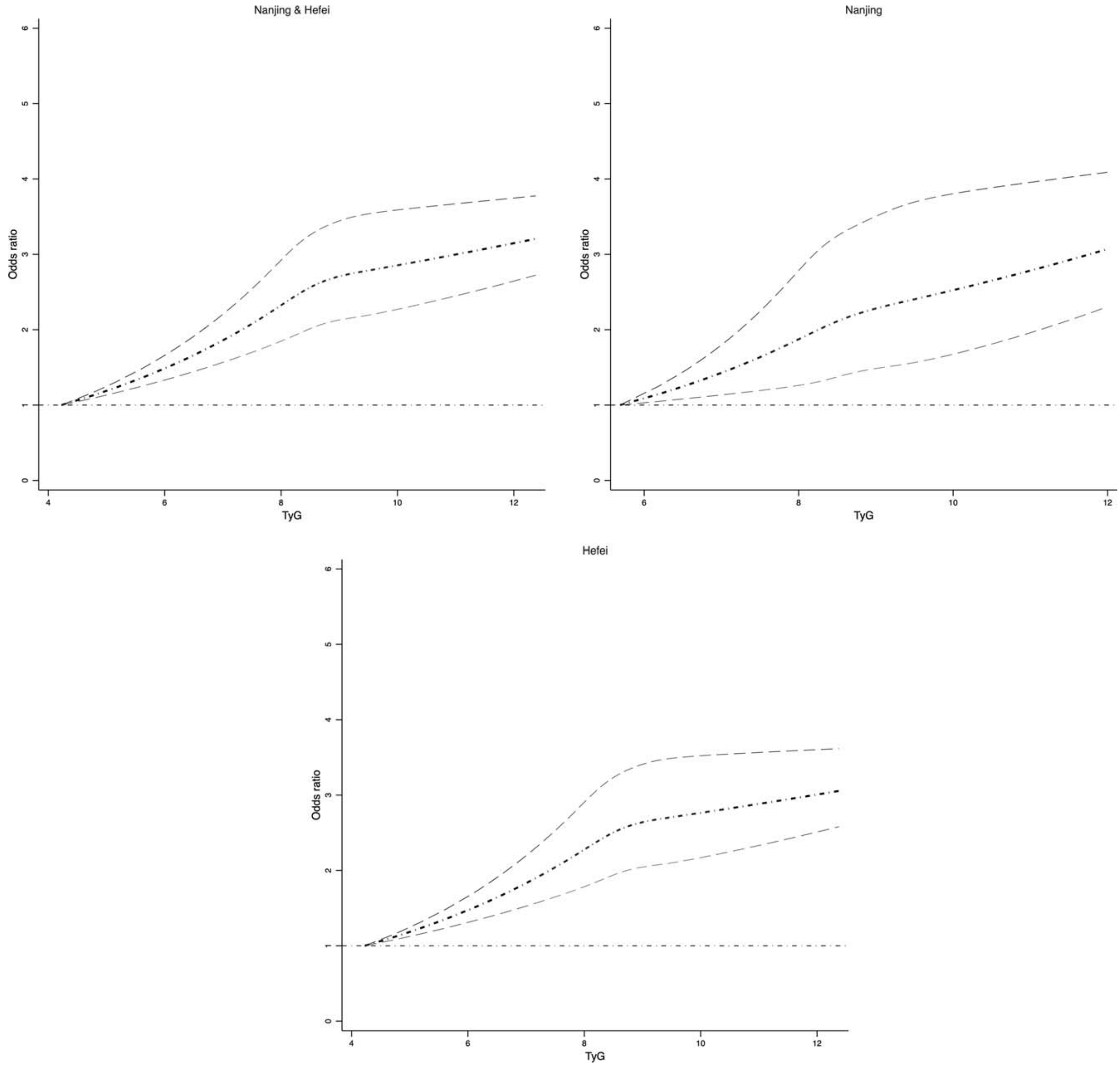

Figure 2. Association between TyG index and adjusted odds ratio for abnormal liver function. Age, gender, smoking status, having hypertension, having type 2 diabetes, body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, creatinine were adjusted.

Table 3

Adjusted regression coefficient between TyG index and alanine aminotransferase by 1 unit increase of TyG from multivariable linear regression models.

	Regression coefficient (95% CI)	10^ (Regression coefficient) (95%CI)
Nanjing & Hefei	0.087 (0.082 to 0.092)	1.222 (1.208 to 1.237)
Nanjing	0.094 (0.083 to 0.105)	1.242 (1.211 to 1.275)
Hefei	0.083 (0.077 to 0.089)	1.210 (1.194 to 1.227)

Age, gender, smoking status, having hypertension, having type 2 diabetes, body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, creatinine were adjusted.

Table 4

Adjusted odds ratio TyG index and alanine aminotransferase by 1 unit increase of TyG from multivariable Logistic regression models.

	*Adjusted Odds ratio (95% CI)	†Adjusted Odds ratio (95%CI)
Nanjing & Hefei	1.980 (1.870 to 2.095)	2.044 (1.930 to 2.165)
Nanjing	2.294 (1.991 to 2.642)	2.334 (2.024 to 2.690)
Hefei	1.922 (1.806 to 2.046)	1.990 (1.868 to 2.119)

* Age, gender, smoking status, having hypertension, having type 2 diabetes, body mass index, waist circumference, systolic and diastolic blood pressure were adjusted.

† Age, gender, smoking status, having hypertension, having type 2 diabetes, body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, creatinine were adjusted.

rural), higher C-statistics was revealed by TyG index comparing with triglyceride and glucose (both $P < .001$). Either in urban or rural population, C-statistics was higher for TyG index comparing with triglyceride and glucose (all $P < .001$).

4. Discussion

By 2 independent surveys in 2 provinces of China, we provide evidence that TyG index as the surrogate of insulin resistance may associate with abnormal liver function status, both in Chinese urban and rural populations. To our knowledge, this is the first study to identify TyG index measured in representative Chinese urban and rural adults as an independent risk factor of abnormal liver function. Increased levels of TyG index, a marker indicating the severity of IR was associated with a greater risk of having abnormal liver function, even after adjusting for potential confounders such as comorbidities, blood pressure and other lipid measurements.

Although TyG index is a good marker of insulin resistance severity, previous studies have paid more attentions on its association to the risk of progression of type 2 diabetes.[5,20,21] These have revealed significant relationships between the TyG index and risk of newly diagnosed diabetes in both overall and high-risk populations.[20,21] Some research also found significant relationships between TyG index and arterial stiffness,[22] subclinical atherosclerosis,[23] coronary artery calcification (CAC),[5] and cardiac autonomic neuropathy,[9] which all indicate that the TyG index is a marker for insulin resistance severity, which in turn contributed to the development and prognosis of metabolic diseases. Notably, this study identified the TyG index, a commonly used marker of insulin resistance severity,[24] as a novel risk factor for abnormal liver function both in Chinese urban and rural adult populations. Although the TyG index has not previously been examined in the association with the risk of having abnormal liver function, these findings are consistent with prior studies showing an increased level of measures of glucose and cardiovascular risk factors (for example, elevated fasting glucose, C-reaction protein) among those with higher levels of the TyG index. Taken together, all these findings suggest that higher level of TyG index, which could result from impaired insulin and metabolism status, could be related to the development of abnormal liver function both in Chinese urban and rural populations.

In previous studies, insulin resistance traditionally measured by HOMA-IR was documented to be associated with parameters of metabolic disorders such as body mass index, impaired fasting glucose, and triglyceride, et al among patients with abnormal liver function.[23,24] Both among urban and rural Chinese adults it was observed that more severe insulin resistance measured by TyG index was associated with higher risk of having abnormal liver function after adjusting for potential confounders. Moreover, this study also revealed that TyG index could be a more discriminable marker in terms of abnormal liver function than glucose or triglyceride, especially in Chinese adult urban population. This study suggest that TyG index could be a tool to screen adults (especially urban adults) at high risk of IR related impaired liver function based on the quantified association results derived from this study

Several mechanisms may contribute to the findings of this study.

Impaired liver function might result from an altered systemic balance between and adipokines and inflammatory factors, as both the acute-phase inflammatory reactant, C-reaction protein, and the proinflammatory cytokines, such as TNF-α and IL-6 were previously found to be associated with insulin resistance.[25] On the other hand, a decreased adiponectin level was found to be associated with higher level of TyG index.[25] Adiponectin, the only adipokine inversely associated with metabolic disorders including insulin resistance, is a signaling protein that is predominantly synthesized and secreted by adipose tissue and is one of the most abundant plasma proteins in humans.[23]

In this study, both in urban and rural populations, ALT increased with the increase of TyG index, and odds ratio of having impaired liver function increased with the increase of TyG index. It is also found ALT increased higher in urban population than those in rural population, and the odds ratio of having impaired liver function is higher in urban population than those in rural population, even after adjusting demographical variables, body mass index, blood pressure, comorbidities, and lipid profiles. This might be explained by the diet status and physical activity as previous studies suggest that low-calorie diet and high level of physical activity are more common in rural population comparing with those in urban population.[26] However, the diet and lifestyle measurements were not available in this study.

The main limitation of the present study is the use of cross-sectional data in 2 independent surveys, whereby TyG index and abnormal liver function were assessed at the same time. It is difficult to make causal inference between TyG index and impaired liver function. Further analysis of longitudinal data would be the next step in examining these relationships. Another limitation of this study is that the data were not collected within the same survey, although the data do appear to be comparable. Furthermore, the infection of hepatitis B could alter the liver function of participants, although the infection of hepatitis B is very common in China. However, the information of the status of hepatitis B infection B was not accessible in this study. Finally, future external validation studies with further adjustment for more confounders, alongside a meta-analysis are needed to better determine whether TyG index does have the potential to be used as a simple screening tool in clinical practice.

5. Conclusion

In conclusion, both in the urban and rural Chinese population, TyG index was found to be associated with abnormal liver function. TyG index has the potential as a proxy marker for the severity of insulin resistance to identify adults at high risk of impaired liver function, especially in Chinese adult urban population.

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