Clinical Rheumatology (2019) 38:3227–3233
https://doi.org/10.1007/s10067-019-04671-6

ORIGINAL ARTICLE

Association between three non-insulin-based indexes of insulin resistance and hyperuricemia

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Received: 4 March 2019 / Revised: 17 June 2019 / Accepted: 1 July 2019 / Published online: 12 July 2019

Abstract

Objective The association between hyperuricemia and insulin resistance (IR) has been demonstrated by many studies, but the traditional IR indexes are too impractical to be used in clinical practice for the recognition of the IR state in individuals with hyperuricemia. Therefore, we aimed to further investigate the association between hyperuricemia and three non-insulin-based IR indexes in this large-scale cross-sectional study.

Methods A total of 174,695 adults without self-reported use of antihyperuricemic agents, hypoglycemic agents, or lipid-lowering drugs were included in the current analysis. The triglyceride to high-density lipoprotein cholesterol ratio (TG/HDLc), the product of fasting triglycerides and glucose (TyG), and metabolic score for IR (METS-IR) were calculated. Then, logistic regression analyses were applied to explore their association with hyperuricemia.

Results The TG/HDLc, TyG, and METS-IR all had positive correlations with uric acid level. However, only TG/HDLc and TyG were significantly associated with hyperuricemia in both sexes and body mass index (BMI) classification (the ORs of the highest quartile for each were 6.751 and 1.505 in females and 6.487 and 1.646 in males, respectively). The AUC values of TG/HDLc and TyG to discriminate hyperuricemia were also statistically significant in both sexes and BMI classification (all greater than 0.7).

Conclusions TG/HDLc and TyG are strongly associated with hyperuricemia regardless of BMI classification. These two obtainable and cost-effective non-insulin-based IR indexes could be potential monitors during the management of hyperuricemia and prevention of its IR-driven comorbidities.

Key Points

- *In this large-scale study, we identified TG/HDLc and TyG as indicators for identification of IR in patients with hyperuricemia.*
- *These simple and practical IR indicators are of substantial clinical importance for implementing preventive strategies against IR-driven comorbidities of hyperuricemia.*

Keywords Hyperuricemia · Insulin resistance · METS-IR · TG/HDLc · TyG index

Introduction

Uric acid (UA) is the metabolic end product of purine degradation, and UA crystals are incriminated in the pathogenesis of gout and kidney stones [1]. Apart from gout and renal disease, hyperuricemia has also been shown to be closely related to a variety of metabolic diseases and cardiovascular disease (CVD) [2]. Insulin resistance (IR) has a critical and central role in the development of many CVD risk factors, including type 2 diabetes, hypertension, and atherogenic dyslipidemia [3, 4]. The bidirectional relationship between hyperuricemia and IR is the most accepted mechanism of hyperuricemia involvement in the pathophysiology of metabolic derangement [5, 6]. In addition, several longitudinal studies have even shown that hyperuricemia might contribute first to IR and play a causative role in cardiometabolic diseases [7, 8].

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Therefore, early recognition of IR in individuals with hyperuricemia and targeted treatment of IR may be of substantial clinical importance for the management of hyperuricemia and prevention of its IR-driven comorbidities.

The currently used tools for assessing the degree of IR are hyperinsulinemic/euglycemic clamp (HEC) and homeostasis model assessment for IR (HOMA-IR) index. However, they are either invasive and impractical or not accurate enough and less reproducible [9]. In recent years, some non-insulin-based IR indexes, such as triglycerides-to-high-density lipoprotein cholesterol ratio (TG/HDLc), the product of fasting triglycerides and glucose (TyG), and metabolic score for IR (METS-IR), have been developed to compensate for the shortcomings of traditional IR indicators. The aforementioned three indicators can be calculated by simple routine biochemical tests and are suitable for large clinical and epidemiological studies.

To our knowledge, no studies have specifically focused on assessing the connection between these three non-insulin-based IR indexes and hyperuricemia. Thus, we performed this large-scale cross-sectional study to investigate the association between the three non-insulin-based IR indexes and hyperuricemia.

Methods

Participants

This study was based on the data of subjects who received routine physical examinations between November 2015 and May 2018 in Eastern China. Considering the effects that some diseases and drugs may have on biochemical indicators, individuals who were pregnant or lactating; had gout, renal dysfunction, urinary tract infection, or other serious diseases; or were on antihyperuricemic agents, hypoglycemic agents, or lipid-lowering drugs were excluded. Finally, a total of 174,695 adults were included in this study. The study was approved by the ethics committee of Hangzhou Aeronautical Sanatorium of the Chinese Air Force.

Collection of clinical data

Basic medical history and medication use were collected. Height and weight were measured with participants barefoot and in light clothing. Waist circumference (WC) and hip circumference (HC) were measured by well-trained examiners. Systolic and diastolic blood pressures (SBP/DBP) were measured 3 times on the right arm after at least 5 min of rest using an automatic blood pressure monitor (HEM-1000, OMRON). The blood samples of participants were collected after a minimum of 8 h of overnight fasting. Serum levels of fasting plasma glucose (FPG), plasma uric acid (UA), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDLc), HDLc, and serum creatinine (Scr) were measured by a biochemical autoanalyzer.

Definitions

Body mass index (BMI) was calculated as weight divided by the square of height, and elevated BMI was defined as a BMI ≥ 24 kg/m^2 and normal BMI was defined as a BMI = 18.5–23.9 kg/m^2 [10]. Hyperuricemia diagnosis was made at serum UA ≥ 420 μmol/L for men and postmenopausal women and ≥ 360 μmol/L for premenopausal women [11]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation [12]. Non-insulin-based IR indexes were calculated using the following formulas: TG/HDLc = TG divided by HDLc [13]; TyG = $\log_e$[fasting TG (mg/dL)*FPG(mg/dL)/2] [14]; METS-IR = $\log_e$[(2*FPG) + TG]*BMI)/($\log_e$[HDLc]) [15]; and $e \approx 2.71828183$.

Statistical analysis

Data are expressed as numbers (percentage) or means ± SD. Statistical analysis was performed using SPSS 18.0 (SPSS Inc.). Categorical variables were compared using the chi-squared test, and *t* test or ANOVA was used to test the differences in continuous data. Partial correlation was applied to examine the correlation between UA levels and the three non-insulin-based IR indexes and was adjusted for age. After adjustment for age, smoking status, WC, and eGFR, logistic regression analyses were used to explore the association between the three non-insulin-based IR indexes and hyperuricemia. Because the cut points to establish IR of TG/HDLc, TyG, and METS-IR are still inconsistent in different races, these indexes were divided into four quartiles and the lowest quartile was used as a reference when perform logistic regression analysis. Receiver-operating characteristic (ROC) analyses and the area under ROC curves (AUC) were then used to assess the ability of TG/HDLc, TyG, and METS-IR to discriminate hyperuricemia. A p value<0.05 was considered to indicate statistical significance.

Results

The clinical characteristics of the 174,695 participants (69,533 females and 105,162 males) are summarized in Table 1. The mean age was 45.0 ± 12.2 years. The prevalence of hyperuricemia was 17.5% in total, 11.9% in females, and 21.3% in males. Regardless of sex, the biochemical indicators (FPG, UA, and lipid parameters) and the three non-insulin-based IR indexes were significantly higher, while BMI, WC, HDLc, and eGFR were dramatically lower, in the hyperuricemia group. There were no significant differences in age, SBP,

Table 1 Clinical characteristics of the participants by sex and hyperuricemia status

Variable	Total		Male		Female	
	Non-HUA	HUA	Non-HUA	HUA	Non-HUA	HUA
No., *n* (%)	144,063	30,632 (17.5)	82,781	22,381 (21.3)	61,282	8,251 (11.9)
Age, years	45.1 ± 11.8	45.1 ± 12.7*	45.4 ± 12.6	45.2 ± 12.5*	41.2 ± 10.7	46.0 ± 12.8
BMI (kg/m^2)	23.8 ± 3.2	23.0 ± 3.2	24.6 ± 3.2	24.5 ± 3.1	22.5 ± 3.0	21.7 ± 2.8
WC (cm)	80.2 ± 9.9	77.2 ± 10.1	83.7 ± 8.8	83.5 ± 8.6	73.5 ± 8.3	71.4 ± 7.6
SBP (mmHg)	123.6 ± 13.2	120.9 ± 16.8	127.3 ± 16.0	127.2 ± 15.9*	119.0 ± 18.3	115.1 ± 15.5
DBP (mm Hg)	76.4 ± 11.5	74.4 ± 11.5	79.0 ± 11.2	79.1 ± 11.1*	71.7 ± 10.7	70.2 ± 10.2
FPG (mmol/L)	5.67 ± 1.2	5.81 ± 1.11	5.70 ± 1.22	5.79 ± 1.09	5.62 ± 1.16	5.79 ± 1.13
TC (mmol/L)	4.70 ± 0.88	4.91 ± 0.93	4.71 ± 0.88	4.96 ± 0.94	4.66 ± 0.87	4.87 ± 0.92
TG (mmol/L)	1.33 ± 1.04	2.07 ± 1.70	1.37 ± 1.08	2.12 ± 1.75	1.24 ± 0.95	1.97 ± 1.62
HDLc (mmol/L)	1.54 ± 0.34	1.35 ± 0.28	1.52 ± 0.34	1.36 ± 0.28	1.57 ± 0.35	1.37 ± 0.28
LDLc (mmol/L)	2.65 ± 0.75	2.76 ± 0.78	2.67 ± 0.75	2.78 ± 0.79	2.62 ± 0.75	2.75 ± 0.78
UA (μmol/L)	303.6 ± 61.1	455.0 ± 59.5	309.0 ± 62.4	464.2 ± 59.1	290.2 ± 55.9	436.0 ± 59.4
eGFR (mL/min/1.73 m^2)	70.6 ± 17.8	67.2 ± 18.5	71.5 ± 19.3	69.3 ± 15.3	68.7 ± 15.6	66.9 ± 16.7
TG/HDLc	0.99 ± 1.11	1.71 ± 1.89	1.03 ± 1.13	1.76 ± 1.99	0.91 ± 1.07	1.60 ± 1.73
TyG	8.52 ± 0.59	8.96 ± 0.63	8.56 ± 0.59	8.98 ± 0.63	8.46 ± 0.57	8.91 ± 0.63
METS-IR	31.4 ± 10.3	33.1 ± 9.5	32.9 ± 10.1	35.6 ± 9.1	28.8 ± 10.2	30.6 ± 9.3

The asterisk represents no significant difference between the two groups

HUA, hyperuricemia; *UA*, plasma uric acid; *BMI*, body mass index; *WC*, waist circumference; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *TC*, total cholesterol; *TG*, triglyceride; *HDLc*, high-density lipoprotein cholesterol; *LDLc*, low-density lipoprotein cholesterol; *eGFR*, estimated glomerular filtration rate; *TyG*, triglyceride and glucose index; *METS-IR*, metabolic score for insulin resistance

or DBP in males with and without hyperuricemia; nonhyperuricemic females had higher SBP and DBP than hyperuricemic females.

The UA level was significantly elevated from the bottom to top quartiles of TG/HDLc, TyG, and METS-IR (Fig. 1). The partial correlations between the three non-insulin-based IR indexes and UA levels are shown in Table 2. After controlling for age, the UA level had positive correlations with TG/HDLc, TyG, and METS-IR in both sexes ($r = 0.291$, 0.415, and 0.153 in females; 0.294, 0.410, and 0.177 in males, respectively; all $p < 0.001$). In addition, there were also a significant correlation between these three non-insulin-based IR indicators in both sexes. The proportion of hyperuricemic subjects showed a significant increasing trend with ascending quartiles of TG/HDLc, TyG, and METS-IR (all $p < 0.001$) (Fig. 1).

The multivariate analysis for the association between hyperuricemia and the three non-insulin-based IR indexes are shown in Table 3. Regardless of sex and BMI classification, TG/HDLc and TyG were significantly associated with hyperuricemia; the ORs for hyperuricemia in the highest quartile of the TG/HDLc and TyG were 6.751 (95%CI 5.852–7.788) and 1.505 (95%CI 1.311–1.727) in females and 6.487 (95%CI 5.612–7.499) and 1.646 (95%CI 1.431–1.893) in males, respectively, and all $p < 0.001$. Among women, METS-IR was not significantly associated with hyperuricemia; among men, only the ORs for hyperuricemia in the highest quartile were statistically significant (1.121 (95%CI 1.030–1.221), $p = 0.008$), but after BMI was classified this significant disappeared.

The AUC values of TG/HDLc, TyG, and METS-IR to discriminate hyperuricemia are shown in Table 4. TG/HDLc and TyG all had significant discriminative ability for hyperuricemia in both sexes and BMI classification; for women, the AUC values were 0.728 (95%CI 0.723–0.733) and 0.711 (95%CI 0.706–0.716), respectively; for men, the AUC values were 0.713 (95%CI 0.708–0.717) and 0.701 (95%CI 0.696–0.705), respectively. However, METS-IR had a weaker ability to identify hyperuricemia; the AUC values were 0.566 (95%CI 0.560–0.572) in females and 0.600 (95%CI 0.595–0.605) in males.

Discussion

Although the significant intercorrelation between hyperuricemia and IR has been well demonstrated by many experimental and epidemiologic studies [5, 16], this study is the first to evaluate associations between hyperuricemia and simple IR indexes simultaneously. We found that TG/HDLc and TyG, simple and inexpensive surrogates of IR, were significantly associated with hyperuricemia in both sexes and BMI classification. These results not only further confirm the close

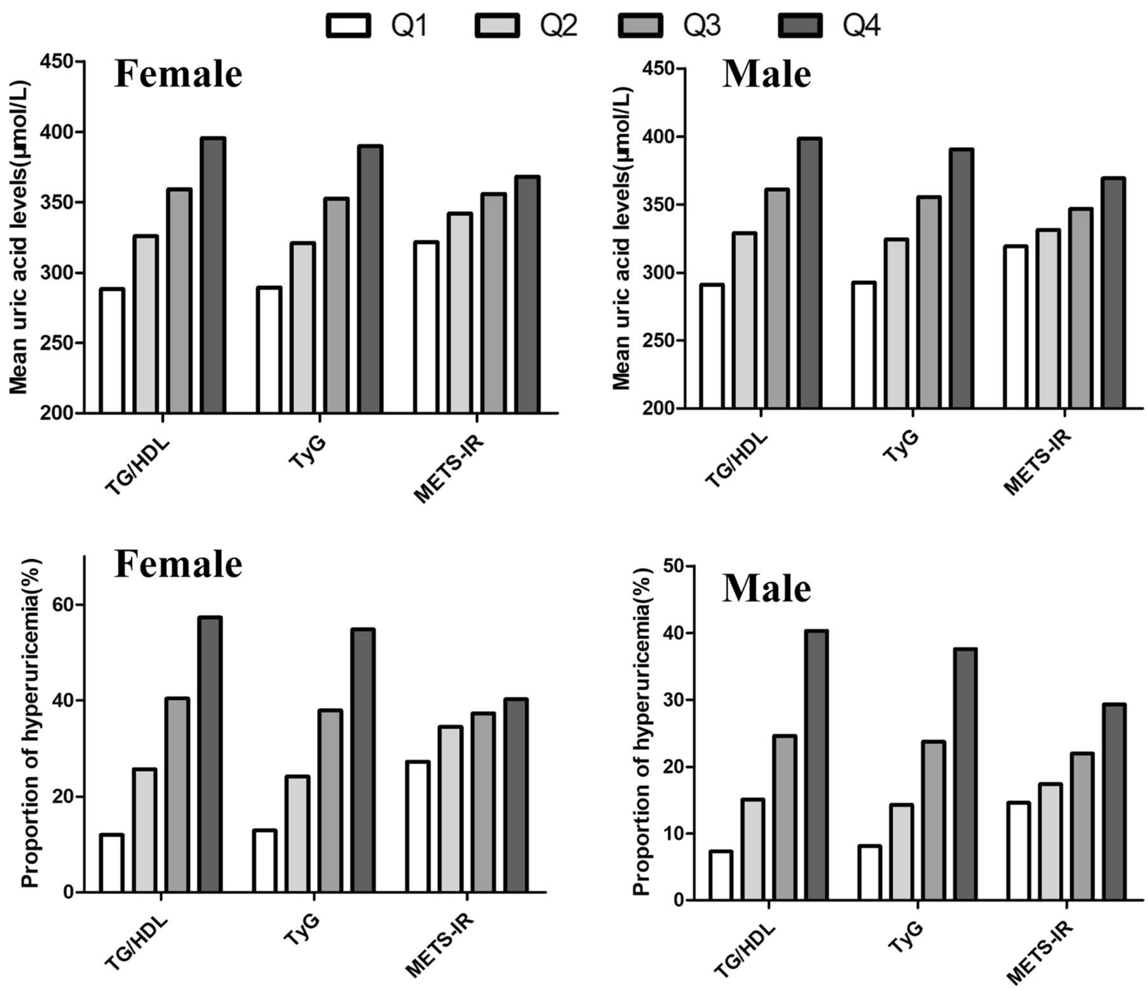

Fig. 1 The serum uric acid level and proportion of hyperuricemia by quartiles of TG/HDLc, TyG, and METS-IR. The uric acid level and proportion of hyperuricemia all showed a significant trend with stepwise increase across ascending quartiles of TG/HDLc, TyG, and METS-IR (all $p < 0.001$). TyG, triglyceride and glucose index; METS-IR, metabolic score for insulin resistance

correlation between IR and hyperuricemia but also provide simpler and more economical options for distinguishing the IR status in hyperuricemic patients in clinical practice.

The HEC technique, which requires intravenous administration of exogenous insulin or glucose, is the gold standard for estimating IR. However, HEC is not appropriate in clinical and epidemiological studies because it is a costly, time-consuming, invasive, and unphysiological method [17]. In clinical research, the most widely used methods to assess IR are HOMA-IR or quantitative insulin sensitivity check index (QUICKI), which mainly require the value of insulin [18]. However, the insulin assay is susceptible to factors such as the choice of kit, calibration setup in kits, and conversions between units (mIU/L to pmol/L). One study found that the value of HOMA2-IR estimated by 11 insulin kits varied by up to twofold [19]. In addition, the price of insulin assays is also a problem that needs to be considered in large sample clinical practice. Therefore, researchers are always looking for simpler, more economical and accurate IR indicators.

IR is often accompanied by dyslipidemia, such as hypertriglyceridemia and low HDLc levels [20], but the discriminatory power of TG or HDLc alone is poor. Therefore, TG/HDLc has become a potential surrogate marker of IR, which has been proven in several studies [21, 22]. The same type of dyslipidemia is also common in patients with hyperuricemia [23]. The mechanism of dyslipidemia and hyperuricemia is requirement of large amounts of free fatty acids (FFAs) for triglyceride synthesis, which are associated with the de novo synthesis of purines and thus accelerated UA production [24]. Hyperuricemia then affects lipid metabolism through decreased glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity, inflammation, reduced adiponectin production, and deposition of ectopic fat [25, 26]. Due to the aforementioned mechanism, although TG/HDLc is the simplest of the three indicators, it had the strongest correlation with hyperuricemia in this study.

The TyG index was first reported to be a useful surrogate of IR in 2008 [14]. A series of subsequent studies demonstrated

Table 2 Partial correlations coefficients between the three indexes and UA level

Variable	UA	TG/HDLc	TyG	METS-IR
Total				
UA	–	0.293	0.413	0.170
TG/HDLc	0.293	–	0.733	0.261
TyG	0.413	0.733	–	0.301
METS-IR	0.170	0.261	0.301	–
Male				
UA	–	0.294	0.410	0.178
TG/HDLc	0.294	–	0.733	0.275
TyG	0.410	0.733	–	0.318
METS-IR	0.178	0.275	0.318	–
Female				
UA	–	0.291	0.415	0.153
TG/HDLc	0.291	–	0.733	0.244
TyG	0.415	0.733	–	0.274
METS-IR	0.153	00.244	0.274	–

All adjusted for age; *UA*, plasma uric acid; *TG*, triglyceride; *HDLc*, high-density lipoprotein cholesterol; *TyG*, triglyceride and glucose index; *METS-IR*, metabolic score for insulin resistance; all $P < 0.001$

the strong association between TyG and IR, type 2 diabetes mellitus (T2DM), hypertension, and other cardiometabolic diseases [27, 28]. However, there are still very few studies on the correlation between TyG and hyperuricemia. In this study, we verified that TyG was significantly associated with hyperuricemia. Although TyG outperformed the other two indices with the highest correlation coefficient with UA level ($r = 0.413$), its strength of association with hyperuricemia was not stronger than that of TG/HDLc after multiple regression analysis. This result may be related to the inverted U-shaped relationship between FPG and UA level [29, 30]. Hyperinsulinemia may increase the UA level by increasing UA production and/or reducing UA excretion [31]. However, when FPG rises to a certain threshold, elevated urine glucose levels lead to competitive inhibition of reabsorption of UA and increase the excretion of UA [32].

METS-IR, which combines FPG, lipid profile, and BMI, is a novel score to evaluate IR. Bello-Chavolla et al. suggested that METS-IR had better diagnostic performance of incident T2DM than that of TyG and TG/HDLc in Mexican subjects, which is mainly attributed to the addition of anthropometric indicators to the calculation formula of METS-IR [15]. Another study based on the Chinese population found that METS-IR's ability to identify metabolic unhealth was not as good as that of TyG [33]. In the present study, its strength of association with hyperuricemia was the weakest among the three indicators in males and was not statistically significant in females. In addition, its AUC for hyperuricemia was also the smallest and was less than 0.7 in both sexes. The contradiction may result from the drawback of BMI, which has a weak capacity to distinguish muscle and fat, especially for Asian individuals [34]. Our recent research also showed that the association between hyperuricemia and adiposity indices incorporating WC and lipid parameters were stronger than that of indices that simply standardized BMI [35].

The main limitation of this study is that this cross-sectional study design cannot show a causal association between hyperuricemia and IR. Although the causal association between these factors is still under debate [2], several experimental and clinical studies have suggested that UA-lowering therapy can improve IR or hypertension [36, 37]. If the causative role of hyperuricemia is true, active and effective management of hyperuricemia and coexisting IR may prevent the occurrence of IR-driven comorbidities. Another limitation of this study is

Table 3 Odds ratios (OR) and 95% CI for hyperuricemia of the toppest quartile of non-insulin-based IR indexes (reference to the lowest quartile)

Variable	Total		Elevated BMI		Normal BMI	
	OR (95%CI)	*P* values	OR (95%CI)	*P* values	OR (95%CI)	*P* values
TG/HDLc						
Female	6.751 (5.852–7.788)	< 0.001	5.278 (3.792–7.346)	< 0.001	6.247 (5.288–7.380)	< 0.001
Male	6.487 (5.612–7.499)	< 0.001	6.235 (5.082–7.650)	< 0.001	5.919 (4.733–7.403)	< 0.001
TyG						
Female	1.505 (1.311–1.727)	< 0.001	1.905 (1.403–2.587)	< 0.001	1.465 (1.250–1.717)	< 0.001
Male	1.646 (1.431–1.893)	< 0.001	1.564 (1.294–1.889)	< 0.001	1.671 (1.348–2.071)	< 0.001
METS-IR						
Female	1.068 (0.972–1.172)	0.169	1.059 (0.992–1.131)	0.085	1.088 (0.936–1.264)	0.273
Male	1.121 (1.030–1.221)	0.008	1.029 (0.936–1.132)	0.552	1.085 (0.938–1.254)	0.271

Elevated BMI was defined as a BMI ≥ 24 kg/m^2. Normal BMI was defined as a BMI = 18.5–23.9 kg/m^2

BMI, body mass index; *CI*, confidence interval; *TG*, triglyceride; *HDLc*, high-density lipoprotein cholesterol; *TyG*, triglyceride and glucose index; *METS-IR*, metabolic score for insulin resistance

Table 4 The AUC with its 95% CI of the three non-insulin-based IR indexes for discriminating hyperuricemia

Variable	Total	Elevated BMI	Normal BMI
TG/HDLc			
Women	0.719 (0.713–0.724)	0.738 (0.727–0.749)	0.7220 (.716–0.727)
Men	0.713 (0.708–0.717)	0.732 (0.726–0.739)	0.721 (0.714–0.728)
TyG			
Women	0.705 (0.700–0.711)	0.722 (0.711–0.733)	0.704 (0.698–0.710)
Men	0.701 (0.696–0.705)	0.717 (.711–0.723)	0.706 (0.699–0.714)
METS-IR			
Women	0.591 (0.584–0.597)	0.664 (0.652–0.676)	0.616 (0.609–0.622)
Men	0.600 (0.595–0.605)	0.655 (0.649–0.662)	0.647 (0.639–0.655)

Elevated BMI was defined as a BMI ≥ 24 kg/m^2. Normal BMI was defined as a BMI = 18.5–23.9 kg/m^2; all $P < 0.001$

BMI, body mass index; *AUC*, area under the receiver-operating characteristic curve; *CI*, confidence interval; *TG*, triglyceride; *HDLc*, high-density lipoprotein cholesterol; *TyG*, triglyceride and glucose index; *METS-IR*, metabolic score for insulin resistance

that we cannot assess how consistent METS-IR was with HOMA-IR in East Asian subjects because the insulin assay was not included in routine physical examinations. Whether the poor performance of METS-IR among the three indicators is related to this limitation remains to be further studied. Third, the lack of similar research makes it impossible to fully compare the results.

In conclusion, the present large-scale cross-sectional study showed that TG/HDLc and TyG were significantly associated with hyperuricemia in both sexes. The clinical practical significance of these findings is that the two obtainable and cost-effective non-insulin-based IR indexes could be potential monitors in hyperuricemia management and help develop prevention and intervention strategies against IR-driven comorbidities of hyperuricemia.

Acknowledgments In the preparation and implementation of this study, we get a lot of selfless help. All of our authors thank all those who have helped us.

Funding This work was supported by the National Natural Science Foundation of China (grant number 81671595).

Compliance with ethical standards

This study was approved by the ethics committee of Hangzhou Aeronautical Sanatorium of the Chinese Air Force.

Disclosures None.

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