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Usefulness of metabolic score for insulin resistance index in estimating the risk of mildly reduced estimate glomerular filtration rate: a cross-sectional study of rural population in China

Pengbo Wang ,[1] Qiyu Li,[1] Xiaofan Guo,[1] Ying Zhou,[1] Zhao Li ,[1] Hongmei Yang,[1] Shasha Yu,[1] Guozhe Sun,[1] Liqiang Zheng ,[2] Yingxian Sun ,[1] Xingang Zhang [1]

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[1]Department of Cardiology, The First Hospital of China Medical University, Shenyang, Liaoning, China
[2]Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China

Correspondence to
Dr Xingang Zhang;
zhangxingang80@aliyun.com

ABSTRACT

Objectives This study aimed to reveal the association between metabolic score for insulin resistance (MetS-IR) and the risk of mildly decreased estimated glomerular filtration rate (eGFR), and explore the evaluation effect of MetS-IR on the progress of eGFR decline.

Study design A cross-sectional study.

Setting and participants A total of 11 956 rural participants (aged ≥35 years) from northeastern China were enrolled in the study. After excluding the subjects whose data were not integrated or who met the exclusion criteria, we finally obtained 11 042 participants in the present study.

Main outcome measures Mildly decreased eGFR was defined as 60–90 mL/min/1.73 m^2.

Results The prevalence of mildly decreased eGFR in the general population was 36.9%. After adjustment of covariates, each SD increment of MetS-IR could bring 26.3% additional risk of mildly decreased eGFR (OR: 1.263, 95% CI: 1.066 to 1.497, p=0.007). When MetS-IR was classified into four levels by quartile, we observed participants in the top level had 3.032-fold risk of mildly decreased eGFR (OR: 3.032, 95% CI: 1.841 to 4.991, p<0.001) compared with those from the bottom level. Further, we found the participants with higher MetS-IR score were more likely to aggravate into a worse renal state which presented as higher risk of accelerated decline of eGFR, by additional 28.3% risk in whole participants (OR: 1.283, 95% CI: 1.150 to 1.430, p<0.001) and 41.9% in men (OR: 1.419, 95% CI: 1.183 to 1.701, p<0.001).

Conclusion High MetS-IR was associated with high risk of mildly reduced eGFR and often accompanied by a high risk of accelerated decline in eGFR. Hence, we believed MetS-IR was a suitable indicator to evaluate the risk of early-stage renal dysfunction.

Strengths and limitations of this study

- ► The present study was a large-scale population study which guaranteed the stability of our conclusion, and focused on the rural population for the first time.
- ► We conducted multiple logistic regression and ordinal logistic regression to describe the association between metabolic score for insulin resistance (MetS-IR) and mildly reduced estimated glomerular filtration rate.
- ► The regression models in our study contained multitype variables such as risk factors, anthropometrics and biochemical parameters for adjustment to make our results more accurate and credible.
- ► This was a cross-sectional study which could not clarify the causal relationship, and thus we still need prospective cohort studies to confirm our results.
- ► MetS-IR does not have a validated cut-off value, leading us to use quartiles to compare the differences among multiple levels of MetS-IR which could bring some bias.

INTRODUCTION

Chronic kidney disease (CKD) is a syndrome of reduced renal function and related systemic metabolic disorders; the incidence of CKD is increasing globally.[1] End-stage renal disease (ESRD) and other CKD-related complications have greatly reduced quality of life of patients, so it is an important public health issue worldwide that should be addressed to prevent complications from leading to CKD in time.[2] BUN (blood urea nitrogen), Scr (serum creatinine) and estimated glomerular filtration rate (eGFR) are usually used to evaluate renal function. BUN is the decomposition product of protein in the human body. Normally, it can be filtered out of the body through the kidney and maintained in a stable

range, but the patients with CKD usually present elevated BUN levels due to deficient renal function. Meanwhile, the BUN levels can be greatly affected by various factors such as the consumption of hormone drugs, heart failure and obesity. Creatinine is the product of muscle metabolism in the human body which is mainly excreted through the kidney as well. Under renal dysfunction conditions, creatinine cannot be discharged through glomerular filtration, leading to the level of creatinine in blood increasing in serum. However, Scr levels are also affected by age, race, gender and body mass index (BMI). Considering that BUN and Scr are affected by various factors, we thus used eGFR to evaluate the renal function of patients with CKD. eGFR is an indicator of renal function which is calculated based on Scr and combined with other factors such as gender and weight. eGFR fully corrects the impact of other factors on Scr and could more comprehensively reflect the overall situation of patients compared with Scr and BUN. A research revealed the prevalence of CKD in China was 29.9%, but only 13% of people had decreased eGFR which was defined as below 60 mL/min/1.73 m^2, indicating a large number of patients with kidney damage might have mildly reduced or even normal eGFR.[3] The boundary range of eGFR between 60 and 90 mL/min/1.73 m^2 was defined as random mildly reduced eGFR. The population in this borderline had significantly higher risk of CKD than the healthy ones, and the outcome they eventually had also got worse progressively with decreasing eGFR even if without CKD.[2 4] However, patients with this borderline eGFR lacked obvious clinical symptoms and were often ignored in the early stage of the disease, so we tried to identify an independent CKD risk factor to assess the risk of mild eGFR reduction in the population, so that we could detect and intervene in this abnormal population as soon as possible, delay the occurrence of renal damage and improve the adverse prognosis.

Insulin resistance (IR) existed in the early stage of various chronic diseases such as hypertension, metabolic syndrome, diabetes mellitus (DM) and even ESRD.[5] With the development of these diseases, IR was often involved in metabolic changes and even metabolic syndrome, thus metabolic syndrome was also named as IR syndrome.[6 7] Additionally, various studies suggested that obesity status or metabolic syndrome had a significant association with mildly decreased eGFR.[8–10] Taken together, we believed IR and metabolic changes often coexist in the early stage of chronic disease.

Among the variable methods to assess IR, the gold standard method is hyperinsulinaemic/euglycaemic clamp (HEC),[11] but this invasive method is unsuitable to a large-scale population. In view of this limitation, insulin-based IR indexes such as the Matsuda Index[12] and Homeostasis Model Assessment for IR (HOMA-IR) Index[13] have been proposed, but the changes and fluctuations of insulin levels in human body lead to poor accuracy and stability of these indexes. In recent years, some non-insulin indicators which combined various serum biochemical indexes to evaluate IR level have gained more attention, such as triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C), triglyceride-glucose index (TyG) and the metabolic score for IR (MetS-IR). These indicators were easy to measure and calculate, so they have been widely used in epidemic studies and compared with traditional insulin indexes. Some studies indicated TyG could predict coronary artery calcification progression and coronary atherosclerosis better than HOMA-IR,[14 15] and even had better evaluation effect than HEC method in men.[16] Some research also believed MetS-IR could effectively identify the early hypertensive population,[17] especially for patients with dyslipidaemia.[18] Compared with HEC method, MetS-IR was more effective in predicting the risk of type 2 diabetes[19] and ischaemic heart disease.[20] Taken together, increasing evidence suggested that it was suitable for these novel indicators to replace the traditional insulin indexes to evaluate the IR level. Among the above three indicators, MetS-IR involved more lipid types and evaluated metabolic status more comprehensively which could represent metabolic status and IR status, respectively, leading to MetS-IR being recognised as a validated index for the estimation of IR in a Chinese population[17 21–24] and able to evaluate IR states in a more stable and accurate way than the others which was also confirmed by some chronic disease studies.[19 25 26] Hence, we speculated that MetS-IR might be an independent risk factor for random mildly reduced eGFR. In this study, we tried to use MetS-IR to evaluate the risk of random mildly reduced eGFR and describe the trend of eGFR change, so that we could achieve the early detection of people with mild eGFR reduction and delay the transition progress of them into CKD.

METHOD

Study population and data collection

We conducted a cross-sectional study from July 2012 to August 2013 in the rural regions of Liaoning Province in northeastern China, and tried to describe the characteristics of cardiovascular disease (CVD) and metabolic disease.[27–29] The detailed sampling protocol was introduced in the previous researches,[27 30] thus we performed a brief introduction here. To make our study population more representative, we set a multistage, stratified, random-cluster sampling protocol (figure 1). Eventually, we obtained 26 villages from 3 cities of Liaoning Province, and enrolled 14 016 natural individuals (aged ≥35 years) who could be healthy or have some diseases such as hypertension, DM or CVDs in our study. Among them, 2060 subjects met the exclusion criteria such as pregnancy, cancer, mental disorders or failed to complete related research, thus we finally had 11 956 participants involved in our study with a response rate of 85.3%. In the present study, we tried to reveal the association between the metabolic status which was presented by MetS-IR and early-stage renal dysfunction (eGFR ≤60 mL/min/1.73 m^2). According to the criteria of the present study, we

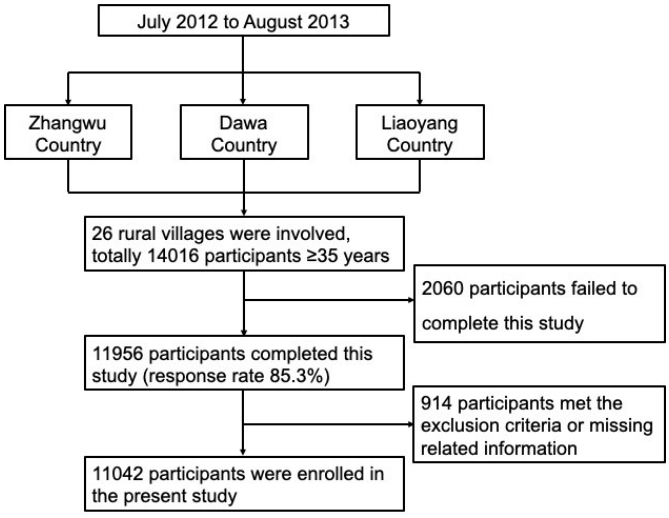

Figure 1 Flow chart of our selected study population protocol. We randomly selected 26 villages from 3 countries in northeastern China, from July 2012 to August 2013. In total, 14 016 participants were enrolled in our study. After excluding people who did not meet the research criteria such as cancer, pregnancy and missing related information, we finally got a study population with 11 042 subjects.

excluded 442 participants who had missing related information such as renal function parameters and 472 subjects with eGFR ≤60 mL/min/1.73 m^2. Eventually, we obtained a target population of 11 042 for the present study.

We established a cardiologists team to conduct outpatient face-to-face interviews with participants and complete paper-version standard questionnaires to collect data. Before the project, we conducted a training course about project-related knowledge and ethical content. Only the staff who pass the related test could be authorised to conduct subsequent research.

Lifestyle risk factors

Information such as age, gender, race or exercise situations was obtained from the questionnaire during the interview. Meanwhile, we also asked the participants whether they were currently smoking or drinking. The race was classified as Han or others. Family income was divided into three groups as ¥≤5000, ¥5000–¥20 000 and ¥>20 000 per year. Education level was assessed to three categories: primary school or below, middle school, high school or above. Physical activity level was considered to combine occupational workload and leisure-time exercise, then reclassified into three levels as low, moderate and high level. In terms of diet, we collected information on meat and vegetable intake for every participant per week, and divided each variable into four groups: merely, below 250 g, 250–500 g, above 500 g for meat intake; and merely, below 1 kg, 1–2 kg, above 2 kg for vegetable intake, respectively. All participants were asked whether they had a history of CVD and nephrosis.

Anthropometric, biochemical and blood pressure measurements

Height and weight were measured when participants were standing and wearing lightweight clothes without shoes. Meanwhile, the waist circumference (WC) was measured in the umbilicus level at the end of a normal expiration. The measurement results were accurate to 0.1 kg and 0.1 cm, respectively.

All participants were instructed to fast for at least 12 hours in advance and blood samples were collected from them the next morning. The blood samples were added to vacutainer tubes containing anticoagulant and obtained plasma by centrifuged. Fasting plasma glucose (FPG), serum uric acid (SUA), Scr, BUN, TG, plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C and other biochemical indicators were obtained by enzymatic analysis on an Olympus AU640 automated analyser (Olympus, Kobe, Japan). All laboratory equipment was calibrated and repeat samples were done using blind method.

Following the American Heart Association protocol,[31] the participants rested for at least 5 min, sat in a quiet room and kept naked in the upper arm which was at the same level as the heart; then, using an automatic electronic sphygmomanometer (HEM-741C; Omron, Tokyo, Japan), their systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured for three times, 2 min apart between each time. The average of the three measurements were taken for subsequent analysis.

Definition

According to JNC7(7th Joint National Committee) criterion, we defined hypertension as blood pressure ≥140/90 mm Hg (SBP/DBP), or under medication treatment for hypertension in last 2 weeks.[32] Diabetes was defined as FPG ≥7.0 mmol/L or a previous diagnosis of diabetes.[33] Hyperuricaemia was diagnosed when the SUA concentration ≥357 µmol/L for women and ≥417 µmol/L for men.[34] As for eGFR, we chose formulas including creatinine level raised by CKD-EPI(The Chronic Kidney Disease Epidemiology),[35] mildly decreased eGFR was defined as 60–90 mL/min/1.73 m^2. The BMI was calculated with weight (kg)/height^2 (m^2). The MetS-IR was calculated using the following formula: MetS-IR=BMI (kg/m^2)×Ln(2×FPG (mg/dL)+TG (mg/dL))/Ln(HDL-C (mg/dL)).[19] Meanwhile, we categorised MetS-IR by its quartiles as the following: quartile 1 was MetS-IR ≤31.32, quartile 2 was 31.33<MetS-IR≤35.83, quartile 3 was 35.84<MetS-IR≤41.28, and quartile 4 was MetS-IR ≥41.29.

Statistical analysis

Overall, the data were normally distributed, so we described the characteristic by mean value±SD (M±SD) or frequency and percentage for continuous and categorical variables, respectively. The differences between continuous variables were compared by one-way analysis of variance and χ^2 test analysis for categorical variables. We convert the variable MetS-IR into four levels by quartile, and the lowest level was

set as the reference. We conducted multivariable logistic regression model to calculate ORs and 95% CIs so that we could assess the association between MetS-IR and random mildly reduced eGFR. Meanwhile, we divided participants with random mildly reduced eGFR into three states, and further executed parallel test to judge whether these were progressive states. Then, we set an ordinal multicategorical logistic regression to assess the relationship between the severity or progress of the eGFR decline and MetS-IR level. P<0.05 under two-tailed condition was considered as having significant differences.

Patient and public involvement

There were no patients involved in the setting of study questions or outcome measurements, nor in the design or implementation of the study. Participants or patients were not asked to make suggestions on the interpretation or recording of the results. There is no plan to disseminate research results to research participants.

RESULTS

Baseline characteristics of study population

We involved a total of 11 042 participants in the present cross-sectional study. Table 1 shows their gender-specific characteristics including general information, risk factors and serum biochemistry indicator. In both genders, the participants in random mildly reduced eGFR group were older and had a higher prevalence of hypertension, dyslipidaemia, DM and hyperuricaemia than the control group. Meanwhile the subjects with reduced eGFR were lacking of physical activities and they had a larger WC and greater degree of IR manifested as a higher MetS-IR. Additionally, with regard to the gender of the population with mildly reduced eGFR, the male participants were older and more likely to drink or smoke; thus, they had a higher prevalence of hypertension and hyperuricaemia. However, a higher proportion of female participants had a history of CVD and nephrosis compared with men.

The normal group is defined as subjects with eGFR >90 mL/min/1.73 m^2, and mildly decreased eGFR group is defined as 60–90 mL/min/1.73 m^2.

Data are presented as mean (SD) or %, as appropriate.

Prevalence of random mildly reduced eGFR

As the result shown in figure 2, overall, the prevalence of random mildly reduced eGFR was 36.9%, and women had a significantly higher prevalence than men (41.1% vs 31.8%, p<0.001). Meanwhile, we classified the population into four groups by quartile of MetS-IR and found the prevalence of mildly reduced eGFR was increasing from 31.7% to 41.5% with the increased MetS-IR level in general participants. We also found the same tendency in gender-specific participants (26.7%–37.0% for male and 36.3%–45.7% for female, p<0.001 for both genders).

Association between MetS-IR and random mildly reduced eGFR

Multivariable logistic regression was conducted to analyse the association between MetS-IR and the risk of random mildly reduced eGFR. Meanwhile, we set an adjustment model to exclude the influence by covariates including age, gender, CVD history, nephrosis history, race, education level, family income condition, physical activity, hypertension, DM, hyperuricaemia, current smoking or drinking, WC and some serum biochemistry indicators like BUN, TC, LDL-C and AST/ALT ratio(Aspartate aminotransferase /Alanine aminotransferase ratio). The results were summarised in table 2.

Based on the categorical variable, the participants with higher MetS-IR level tended to exhibit a higher likelihood of reducing eGFR mildly in the general population, especially in the top group, participants had 3.032-fold more risk of eGFR reducing mildly than those in quartile 1. In the female population, we got the same tendency as the general population; moreover, the female population in the top group had a higher risk of eGFR reducing mildly by 3.637-fold. However, the tendency in male participants presented an 'inverse U shape' which the participants in quartile 3 had the highest risk, which was 2.920-fold more risk than the reference, different from the 'linear shape' risk in general and female population. Thus, as a continuous variable, every SD increment of MetS-IR brought a significant extra increased risk of having early-stage renal dysfunction by 26.3% and 55.1% in general and female participants, respectively.

Relationship between MetS-IR level and condition alteration of eGFR

We also conducted multivariable ordinal logistic regression to assess the effect of MetS-IR alteration on the progress of eGFR decline. According to eGFR level, we further divided early-stage renal dysfunction into the following three states: state 1 (eGFR: 80–89 mL/min/1.73 m^2), state 2 (70–79 mL/min/1.73 m^2) and state 3 (60–69 mL/min/1.73 m^2). The results were shown in table 3. After adjusting with the same model as in the previous regression analysis, we found each SD increment would brought 28.3%, 41.9% and 19.1% extra risk of increased eGFR decline in general, male and female participants, respectively. Meanwhile, as a categorical variable, our results indicated the subjects in quartiles 3 and 4 in general or female population and quartile 4 in male population had a significant association between MetS-IR level and the progress of eGFR decline. Especially, we accidentally noticed that the male population in the top level of MetS-IR had higher risk of eGFR state alteration, that reached 3.146-fold, compared with the reference.

DISCUSSION

This study revealed for the first time the relationship between IR and eGFR in the rural population of northeastern China. Our results indicated that people with higher MetS-IR tended to show a higher risk of early-stage renal dysfunction. Moreover, we also observed that high MetS-IR score was usually accompanied by a higher risk of accelerating decline of eGFR, especially in male

Table 1 Baseline characteristics of study population

Variable	Male (n=5126)			Female (5916)			
	Normal n=3497	Mildly reduced eGFR n=1629	P value	Normal n=3466	Mildly reduced eGFR n=2450	P value	P value
Age (years)	55.60±8.74	61.64±10.44	<0.001	49.16±8.60	58.35±9.46	<0.001	<0.001
Race			<0.001			<0.001	0.788
Han	93.9	96.5		93.2	97.1		
Others	6.1	3.5		6.8	2.9		
Currently smoking	61.4	49.4	<0.001	14.7	18.0	<0.001	<0.001
Currently drinking	50.5	35.8	<0.001	3.1	2.5	0.206	<0.001
Education			<0.001			<0.001	<0.001
Low	35.8	53.5		47.5	68.1		
Moderate	51.9	36.7		43.2	26.0		
High	12.3	9.8		9.3	5.9		
Income (¥)			<0.001			<0.001	0.017
≤5000	10.7	17.7		8.6	14.9		
5000–20 000	54.3	52.9		56.0	54.8		
>20 000	35.9	29.5		35.4	30.3		
Physical activity			<0.001			<0.001	<0.001
Low	22.0	44.4		34.3	52.6		
Moderate	19.4	18.8		21.0	16.9		
High	58.7	36.8		44.7	30.4		
Meat intake			0.001			<0.001	<0.001
Merely	12.6	15.2		23.2	27.2		
Below250	21.6	24.6		28.0	30.5		
250–500 g	31.1	29.8		28.2	25.8		
Above500g	34.7	30.4		20.5	16.5		
Vegetable intake			0.016			<0.001	0.008
Merely	2.0	1.5		2.2	1.6		
Below1kg	8.0	6.6		7.9	6.8		
1–2 kg	51.6	49.4		55.5	51.8		
Above2kg	38.4	42.5		34.4	39.8		
Hypertension	45.7	61.5	<0.001	40.4	49.8	<0.001	<0.001
Diabetes	9.0	11.1	0.018	8.5	13.1	<0.001	0.200
Hyperuricaemia	11.4	19.0	<0.001	3.1	11.3	<0.001	<0.001
CVD history	7.7	15.7	<0.001	15.1	23.0	<0.001	<0.001
Nephrosis history	5.4	17.6	<0.001	5.9	30.3	<0.001	<0.001
SUA (μmol/L)	323.36±78.40	350.60±83.75	<0.001	236.07±57.50	276.95±66.43	<0.001	<0.001
BUN (mmol/L)	5.70±1.44	6.14±2.06	<0.001	4.97±1.87	5.57±2.39	<0.001	<0.001
Scr (μmol/L)	73.84±8.93	88.86±8.70	<0.001	58.26±8.36	72.52±5.95	<0.001	<0.001
eGFR (mL/min/1.73 m^2)	101.99±11.14	80.8±7.23	<0.001	103.00±10.67	79.63±7.35	<0.001	<0.001
AST/ALT ratio	1.09±0.53	1.14±0.55	0.001	1.20±0.62	1.18±0.47	0.363	<0.001
FPG (mmol/L)	5.91±1.74	6.01±1.42	0.033	5.73±1.58	6.00±1.56	<0.001	0.002
TC (mmol/L)	5.11±1.00	5.28±1.07	<0.001	5.07±1.05	5.56±1.10	<0.001	<0.001
TG (mmol/L)	1.65±1.37	1.64±1.26	0.823	1.47±1.26	1.78±1.34	<0.001	0.058

Continued

Table 1 Continued

Variable	Male (n=5126) Normal n=3497	Male (n=5126) Mildly reduced eGFR n=1629	Male (n=5126) P value	Female (5916) Normal n=3466	Female (5916) Mildly reduced eGFR n=2450	Female (5916) P value	P value
HDL-C (mmol/L)	1.45±0.44	1.32±0.36	<0.001	1.45±0.35	1.36±0.31	<0.001	0.821
LDL-C (mmol/L)	2.84±0.77	2.95±0.82	<0.001	2.87±0.82	3.08±0.83	<0.001	<0.001
Mean SBP (mm Hg)	140.97±21.47	148.16±23.57	<0.001	137.87±23.46	142.13±23.98	<0.001	<0.001
Mean DBP (mm Hg)	83.18±11.58	84.59±12.00	<0.001	79.78±11.24	81.44±11.51	<0.001	<0.001
Mean WC (cm)	83.40±9.61	84.45±9.84	<0.001	80.68±9.55	81.84±9.85	<0.001	<0.001
BMI (kg/m^2)	24.67±3.58	24.85±3.45	0.087	24.92±3.78	24.75±3.70	<0.001	0.076
MetS-IR	36.46±7.72	37.59±7.33	<0.001	36.29±7.23	37.21±7.21	<0.001	0.305

AST/ALT ratio, Aspartate aminotransferase/Alanine aminotransferase ratio; BMI, body mass index; BUN, blood urea nitrogen; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS-IR, metabolic score for insulin resistance; SBP, systolic blood pressure; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

population. These results suggested that we should pay more attention to the renal function of patients with high MetS-IR. Furthermore, the patients with high MetS-IR scores and who were already had random mildly reduced eGFR should be given attention as soon as possible to avoid the eventual development of renal failure.

Some epidemiology studies have found that IR and hyperinsulinaemia were involved in the development of chronic renal dysfunction and ESRD,[5 36] even in the early-stage of CKD population who presented with mildly reduced GFR.[37] IR states could effectively evaluate eGFR levels and predict the risk of complications in patients with renal failure.[38 39] Meanwhile, some studies revealed various potential mechanisms between the IR and development of CKD. They believed IR or hyperinsulinaemia could change the structure and function of vascular system, such as endothelial injury and increased vascular permeability, resulting in glomerular ultrafiltration and excessive mesangial proliferation which eventually led to the decrease of eGFR.[40–42] On the other side, some studies also observed increased IR states could be regulated via overactivated inflammatory response in the patients with CKD.[43–47] These results suggested there might be an internal relationship between IR and mildly decreased eGFR. For now, there were few studies focused on the mild decline of eGFR, but some results from CKD could indirectly confirm our conclusion. For example, some studies had found that IR could affect the level of eGFR, which was also a risk factor for renal insufficiency, and could even predict the deterioration of renal function in patients with stage 3 CKD.[48 49] Meanwhile, IR could also be detected in patients with type 1 DM with mildly decreased GFR.[50] A 10-year follow-up cohort study that enrolled 6065 participants in South Korea found that patients would have a higher risk of CKD or lower GFR level if they had metabolic syndrome or high IR condition.[51] Another population genomic study found that the corresponding GFR level of patients would be significantly decreased once the gene sites related to IR were mutant.[52] The above researches have confirmed the strong relationship between IR and renal function; combining with our results, we believed that MetS-IR as a novel and stable index of IR could well evaluate the state of mildly decreased eGFR. However, some studies on obese people have come to different conclusions. Taner *et al* conducted a 30-month follow-up study involving 76 obese patients but they did not observe significant differences in eGFR levels between different IR states.[53] Meanwhile, whether the patients have kidney disease or not, their IR levels were almost approximate. In addition, a cross-sectional study involving 380 obese participants also

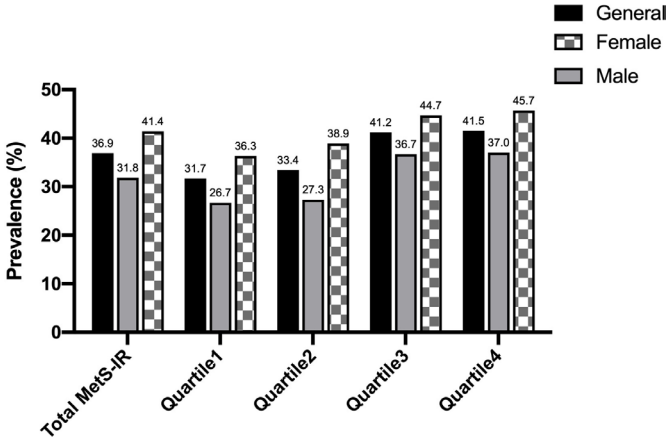

Figure 2 The prevalence of mildly decreased eGFR. Prevalence of mildly decreased eGFR in total population and different genders was increasing with the increased MetS-IR quartile, macroscopically. Meanwhile, the prevalence in male participants was significantly lower than that in female participants. eGFR, estimated glomerular filtration rate; MetS-IR, metabolic score for insulin resistance.

Table 2 Association between MetS-IR and mildly reduced eGFR

Variable MetS-IR	Full model adjusted					
	Total population		Male		Female	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Continuous						
Per SD increase	1.263 (1.066 to 1.497)	0.007	1.003 (0.756 to 1.330)	0.984	1.551 (1.243 to 1.935)	<0.001
Categorical						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.404 (0.948 to 2.080)	0.091	1.422 (0.792 to 2.553)	0.239	1.424 (0.826 to 2.454)	0.203
Quartile 3	2.710 (1.766 to 4.158)	<0.001	2.920 (1.470 to 5.804)	0.002	2.709 (1.537 to 4.774)	0.001
Quartile 4	3.032 (1.841 to 4.991)	<0.001	2.756 (1.223 to 6.211)	0.014	3.637 (1.889 to 7.002)	<0.001

eGFR, estimated glomerular filtration rate; MetS-IR, metabolic score for insulin resistance.

denied the correlation between metabolic syndrome or IR and the risk of CKD. Moreover, they believed that the level of renal function would only be affected stably by obesity.[54] We speculated that this difference may be due to the various characteristics of the study population. Obesity played an important role in the development of CKD, but the traditional indexes of IR did not consider obesity, so they may not be suitable for evaluation in obese people. MetS-IR combined BMI and IR level, this consideration coincided with the above study that obesity affected the risk of CKD. On the other hand, our study just focused on the population with mildly declined eGFR, but their research covered all conditions of GFR and IR level which could ignore the relationship within the subgroup participants. Next, we found that metabolic syndrome in rural areas of northeastern China was prevalent.[55] Compared with traditional indicators, MetS-IR considered metabolic status of the population to overall evaluate the degree of IR. Finally, the above two studies were small scale, which might lead to the poor stability of the results, so our results based on a large-scale population could be more accurate.

Additionally, we unexpectedly found that the relationship between increased MetS-IR and the risk of mild eGFR reduction in male participants was an 'inverted U shape'. This phenomenon seems to be inconsistent with some previous results.[56 57] These two studies also observed the relationship between IR and eGFR, but the risk curves were presented as 'U shape' which was different from ours. We analysed the differences might be brought by our research objectives. To evaluate the state of pre-renal failure state, we set the event as a slightly decreased eGFR, leading to our study not containing low eGFR population. Second, we had different category methods which we simply grouped according to the quartile, while the above research divided the population according to the percentage. These two classification methods have their own advantages and suitable population, which made our results different from the description of population characteristics. Finally, we further compared and found that we have different research populations. We obtained the conclusion from the male adult population, and the above two studies were carried out in the adolescent population (aged <18 years). It was generally believed that the

Table 3 Association between MetS-IR and alterations of renal function

Variable MetS-IR	Full model adjusted					
	Total population		Male		Female	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Continuous						
Per SD increase	1.283 (1.150 to 1.430)	<0.001	1.419 (1.183 to 1.701)	<0.001	1.191 (1.039 to 1.368)	0.013
Categorical						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.097 (0.368 to 1.336)	0.353	0.987 (0.731 to 1.404)	0.939	1.141 (0.888 to 1.467)	0.304
Quartile 3	1.471 (1.178 to 1.835)	0.001	1.416 (0.973 to 2.061)	0.069	1.470 (1.114 to 1.941)	0.006
Quartile 4	1.844 (1.409 to 2.413)	<0.001	2.014 (1.288 to 3.146)	0.002	1.616 (1.149 to 2.275)	0.006

MetS-IR, metabolic score for insulin resistance.

adolescent population has better compensatory function. Except for the too high or too low level of IR or eGFR, the disease risk of the rest of the population was low and stable. Therefore, it presented a 'U-shaped' disease risk curve, while the adult population gradually showed an irreversible process with the development of the disease. Therefore, the high-risk population or boundary population was easier to further develop and deteriorate into renal failure state, resulting in our results presenting survivor bias, thus we got an 'inverted U-shaped' risk curve. To confirm our speculation, we further divided the slightly decreased eGFR level into three states of gradual aggravation, and evaluated the ability of MetS-IR to describe the progress of eGFR by multivariable ordinal regression. The results showed that high level of MetS-IR was significantly associated with deterioration of eGFR, and the highest risk was 3.146 times. Some studies also found IR level could affect the progress of eGFR decline; the patients with renal dysfunction with lower HOMA-IR had slower development of CKD.[58 59] Therefore, we believed that the higher the MetS-IR in men, the greater the decline of eGFR and the higher the risk of further deterioration of kidney disease. In this study, the renal function of male population with high MetS-IR could rapidly develop into renal failure or even death, which reduced the number of people with mildly decreased eGFR, resulting in survivor bias, and eventually led to an 'inverted U-shaped' risk curve.

Besides, we noticed the SEs of MetS-IR were crossed between two subgroups in men and we believed that these were caused by the characteristics of the subgroups. In the subsequent analysis, we found that the male subjects with higher MetS-IR score usually had a higher risk and deterioration rate of declining eGFR, which were more likely to develop into renal dysfunction from early renal failure. Therefore, it would cause survivor bias in the subgroup of male population with high MetS-IR, leading to the SEs of MetS-IR in this subgroup getting lower than others and eventually even presented an 'inverted U-shaped' risk curve. Although it seemed that the difference was not obvious, there was indeed a significant difference of MetS-IR in random mildly reduced eGFR subgroup compared with the normal participants. Meanwhile, this phenomenon also showed a limitation of our research which MetS-IR still had no validated cut-off value. Hence, it was impossible for us to define a clear abnormal population according to the MetS-IR level, that we could only compare the relative level differences of MetS-IR among different patients, and we failed to simply evaluate the absolute degree of a person's IR state through the person's own Mets-IR score. To avoid the impact of this problem in the present study, we only suggested that patients with a higher MetS-IR score may have a higher risk of having early-stage renal dysfunction and accelerated trend of eGFR decline than the patients with lower MetS-IR score, and we did not try to use this index to directly evaluate the level of renal function instead of eGFR. Therefore, we suggested that more attention be paid to the renal function of patients with high MetS-IR score, to detect the patients in the early stage of CKD in time which is presented by random mildly reduced eGFR.

In this study, we had strength to support our conclusion. First of all, a large-scale population guaranteed our results were more stable. In addition, MetS-IR was more suitable for the high prevalence of metabolic syndrome in rural areas of northeastern China, which made our results more accurate. Finally, we focused on mildly declined eGFR, which was an important risk factor of renal failure. Our results were conducive to the early prevention of kidney disease. Our study also had some limitations. First, this study was a cross-sectional study, which determined that our results had a weak evidence-based efficacy and therefore we could not draw a clear causal association between MetS-IR and early-stage renal dysfunction. Moreover, our study defined random mildly reduced eGFR or early-stage renal dysfunction by only one-time measurement of eGFR, because this definition was not comprehensive and perfect. Besides, our research paid more attention to the rural population in northeastern China, which was different from the urban population in terms of lifestyles, health awareness and medical investment, leading to the distribution of different eGFR levels being unbalanced, and this survivor bias was particularly obvious in the male population. Most of the studies were conducted on patients with CKD, the people with random mildly reduced eGFR did not receive much attention. The concept of MetS-IR was raised in recent years and the related studies were limited, resulting in the representative cut-off value that has not been obtained. However, we could evaluate the effect of MetS-IR indirectly by comparing it with HOMA-IR which was recognised as the gold standard for IR. A research that enrolled different indicators contained HOMA-IR and MetS-IR to evaluate IR levels and observe their similar tendency under various pathological conditions, which indicated MetS-IR had the same evaluation effect as HOMA-IR.[60] Therefore, we believed it was appropriate to use quartiles instead of an unvalidated cut-off value to divide participants into different IR subgroups in our study. Meanwhile, we also could not sufficiently compare and improve our findings with other related studies which focused on MetS-IR. We still need large-scale, less biased, high-level evidence-based studies to confirm the relationship between MetS-IR and early-stage renal dysfunction.

In summary, our results revealed the association between MetS-IR and the risk of mildly reduced eGFR. Furthermore, high MetS-IR scores were often accompanied by a high risk of accelerated decline in eGFR. Hence, we believed MetS-IR was a suitable indicator to evaluate the risk of early-stage renal dysfunction in rural population.

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ORCID iDs
Pengbo Wang http://orcid.org/0000-0001-7405-7905
Zhao Li http://orcid.org/0000-0003-2281-8332
Liqiang Zheng http://orcid.org/0000-0003-0101-9398
Yingxian Sun http://orcid.org/0000-0002-1961-899X
Xingang Zhang http://orcid.org/0000-0001-8811-1634

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