Metabolic Score for Insulin Resistance, a novel score to evaluate insulin sensitivity, is associated with the urinary albumin-to-creatinine ratio in Chinese adults: A cross-sectional REACTION study

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Keywords
Metabolic score for insulin resistance, Sex, Urinary albumin-to-creatinine ratio

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J Diabetes Investig 2022; 13: 1222–1234

doi: 10.1111/jdi.13782

ABSTRACT

Aims/Introduction: The Metabolic Score for Insulin Resistance (METS-IR) is a novel non-insulin-based metabolic index used as a substitution marker of insulin resistance. However, whether METS-IR is associated with the urinary albumin-to-creatinine ratio (UACR) is not well known. Therefore, we explored the associations between METS-IR and UACR, and compared the discriminative ability of METS-IR and its components for elevated UACR.

Materials and Methods: This study included 37,290 participants. METS-IR was calculated as follows: (Ln[2 × fasting blood glucose + fasting triglyceride level] × body mass index) / (Ln [high-density lipoprotein cholesterol]). Participants were divided into four groups on the basis of METS-IR: <25%, 25–49%, 50–74% and ≥75%. Logistic regression analyses were carried out to determine the associations between METS-IR versus its components (fasting blood glucose, triglyceride level, body mass index and high-density lipoprotein cholesterol) with UACR.

Results: Participants with the highest quartile METS-IR presented a more significant trend toward elevated UACR than toward its components (odds ratio 1.260, 95% confidence interval 1.152–1.378, P < 0.001 in all participants; odds ratio 1.321, 95% confidence interval 1.104–1.579, P = 0.002 in men; odds ratio 1.201, 95% confidence interval 1.083–1.330, P < 0.001 in women). There were significant associations between METS-IR and UACR in younger participants (aged <65 years for women and aged 55–64 years for men). Increased METS-IR was significantly associated with UACR in men with fasting blood glucose ≥5.6 or postprandial blood glucose ≥7.8 mmol/L and systolic blood pressure ≥120 or diastolic blood pressure ≥80 mmHg. The relationships were significant in women with diabetes and hypertension.

Conclusions: Increased METS-IR was significantly associated with elevated UACR, its discriminative power for elevated UACR was superior to that of its components.

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Received 19 November 2021; revised 11 February 2022; accepted 24 February 2022

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INTRODUCTION

Increased urinary albumin-to-creatinine ratio (UACR) has been regarded a marker of early kidney dysfunction and an independent factor for cardiovascular disease (CVD) risk. An elevated UACR is more closely associated with increased CVD risk than with the estimated glomerular filtration rate (eGFR) in patients with diabetes. In addition, elevated fasting blood glucose (FBG) level, hyperlipidemia and obesity are not only associated with CVD, but also with chronic kidney disease. Compelling evidence confirmed that dyslipidemia, including high levels of low-density lipoprotein cholesterol, total cholesterol (TC) and triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C), is the cornerstone of arteriolosclerosis, and is an important risk factor for the progression of chronic kidney disease and CVD. Furthermore, both diabetes and albuminuria are risk factors for CVD, and the morbidity of microalbuminuria remarkably increased in people with diabetes.

Insulin resistance (IR) plays roles in the pathophysiology of dyslipidemia, type 2 diabetes mellitus and microalbuminuria. Many studies found that IR is a major risk factor for CVD events and has strong relationships with other risk factors for CVD (inflammation, dyslipidemia and hypertension) through various pathophysiological mechanisms. The routine assessment of IR probably holds great significance in preventing a global pandemic and reducing the socioeconomic burden. The homeostatic model assessment of the IR index has been widely used for IR evaluation in clinical practice. However, this index has limitations, including variability depending on the utilized technique, low practicality and invasiveness.

Compared with other non-insulin-based IR indices, the novel surrogate of IR, namely, the Metabolic Score for IR (METS-IR), shows a higher concordance with the euglycemic–hyperinsulinemic clamp and its components, including the TG, HDL-C and FBG levels, and body mass index (BMI), and has strong predictive abilities for CVD risk. IR is a key factor connecting CVD and increased UACR. However, information is limited on the association of METS-IR with UACR. Therefore, the current study evaluated the association between METS-IR and UACR, and compared it with the associations between FBG level, BMI and HDL-C level with UACR in the Chinese population.

MATERIALS AND METHODS

Participants

The present study was a substudy of the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal study (REACTION study), which was designed to investigate the association of prediabetes and type 2 diabetes mellitus with the risk of cancer among Chinese adults. The REACTION study was carried out with individuals aged ≥40 years in centers across mainland China from 2011 to 2012. A total of 47,808 participants were included in this study. We excluded participants diagnosed with primary kidney disease at baseline, who used lipid-lowering drugs or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, had missing and incomplete clinical or demographic data, or used hypoglycemic drugs and insulin. Finally, 37,290 participants (10,909 men and 26,381 women) were included in the present study. The flowchart describing the enrolment of the participants in this study is presented in Figure 1.

Social, clinical and biological parameters

All participants were administered a detailed questionnaire on their lifestyle, medical history and medication use, and subsequently underwent anthropometric assessments according to standardized procedures. Medical history included history of type 2 diabetes mellitus, hypertension, kidney disease, CVD (including stroke, myocardial infarction and coronary artery disease) and drug use. Smoking habits were categorized as a history of never smoking, currently smoking (frequently: smoking ≥1 cigarettes daily; occasionally: smoking <7 cigarettes weekly) or formerly smoking (had already quit smoking for at least half a year). Drinking habits were categorized as a history of never drinking, currently drinking (frequently: drinking more than once a week; occasionally: drinking less than once a week) or formerly drinking (had already quit drinking for at least half a year).

Height (cm), weight (kg) and waist circumference (cm) were measured by trained nurses. BMI was calculated as the ratio of the bodyweight in kilograms and the squared body height in meters (kg/m²). Blood pressure (BP) and resting heart rate were measured sequentially three times with 1-min intervals each. The three measurement results of diastolic BP (DBP) and systolic BP (SBP) were averaged for analysis.

Blood samples were collected by venipuncture after a 10-h overnight fast. A 75-g oral glucose tolerance test was then carried out. Biochemical parameters included FBG, 2-h post-load blood glucose (PGB), TC, low-density lipoprotein cholesterol, HDL-C, TG, aspartate transaminase, gamma-glutamyl transferase, alanine transaminase (ALT), serum creatinine and glycosylated hemoglobin. The biological parameters were assayed by quality control procedures. The eGFR (mL/min/1.73 m²) was calculated according to the following formula: 186 × (serum creatinine × 0.011)⁻¹·₁₅⁴ × (age)⁻⁰·₂⁰₃ × (0.742 if female) × 1.233, where serum creatinine was presented in μmol/L. The procedure used the Modification of Diet in Renal Disease, which was recalibrated for the Chinese population.

Definition of variables

According to the self-reported questionnaires, history of hypertension and history of diabetes were defined as documented hypertension at baseline and documented diabetes at baseline, respectively. Urinary albumin and creatinine concentrations were determined in the first-void sterile urine specimens collected early in the morning. UACR was defined as the ratio of the urinary albumin concentration to the urinary creatinine concentration.
concentration, which was divided into two groups: UACR ≥30 mg/g or UACR <30 mg/g. METS-IR was calculated using the following formula: \((\ln[2 \times FBG\text{(mg/dL)}] + TG0\text{(mg/dL)} ] \times BMI) / (\ln[HDL-C\text{(mg/dL)}])^3\). The METS-IR index was divided by quartiles.

Statistical analysis

All statistical analyses were carried out using SPSS 24.0 (IBM, Chicago, IL, USA). We used one-way analysis of variance to compare the distinctions among the continuous variables of the four groups. The least significant distinction was compared using the multiple comparison test, and continuous variables were expressed as means ± standard deviations. Continuous variables with non-normal distributions were expressed as medians (interquartile range). Categorical variables were described as percentages (%). The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to explore the associations between METS-IR and UACR through logistic regression analyses. Model 1 was a non-adjusted model. Model 2 was adjusted for center, age and sex. Model 3 was further adjusted for education status, smoking habits, drinking habits and previous diagnosis of CVD. Model 4 was further adjusted for history of diabetes and hypertension, and use of hypotensive drugs. Model 5 was further adjusted for eGFR, waist circumference, SBP, DBP, low-density lipoprotein cholesterol, TC, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, glycosylated hemoglobin and resting heart rate. The relationships between METS-IR and UACR were also explored in subgroups that were stratified by age (<55, 55–64 and ≥65 years), eGFR (<60, 60–90 and ≥90 mL/min/1.73 m²), blood glucose (BG) status (normal: FBG <5.6 and PBG <7.8; prediabetes: 5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1; and diabetes: FBG ≥ 7.0 or PBG ≥ 11.1, mmol/L) and BP status (normal BP: SBP <120 and DBP <80; prehypertension: 80 ≤ DBP < 90 or 120 ≤ SBP < 140; and hypertension: DBP ≥90 or SBP ≥140, mmHg). The present study also investigated the interactions between METS-IR and the stratified variables among participants with increased risk of UACR. Two-tailed \(P < 0.05\) was considered statistically significant.

RESULTS

Clinical characteristics of the participants

Among the 37,290 participants included in the present study, 10,909 were men and 26,381 were women (Table 1). The characteristics of the study participants, who were divided into four groups on the basis of the quartiles of the METS-IR index, are as follows. The mean age of the Q4 group was 58.72 ± 9.13 years. The mean ages of the Q1, Q2 and Q3 groups were 56.77 ± 9.29, 57.49 ± 8.01 and 58.30 ± 9.13 years. The proportions of men and women were the highest in the
Table 1 | Characteristics of the study subjects by Metabolic Score for Insulin Resistance quartiles

| Variable               | METS-IR   |
|------------------------|-----------|
|                        | Q1 (n = 9,322) | Q2 (n = 9,323) | Q3 (n = 9,323) | Q4 (n = 9,322) | P value |
| Age (year)             | 56.77 ± 9.29 | 57.49 ± 8.01 | 58.30 ± 9.13 | 58.72 ± 9.13 | <0.001 |
| Male sex, n (%)        | 2,107 (19.3) | 2,336 (21.4) | 2,923 (26.8) | 3,543 (32.5) | <0.001 |
| Female sex, n (%)      | 7,215 (77.3) | 6,987 (62.6) | 6,400 (24.3) | 5,779 (21.9) | <0.001 |
| WC (cm)                | 76.37 ± 7.89 | 83.05 ± 7.13 | 87.77 ± 7.24 | 94.23 ± 8.51 | <0.001 |
| Triglycerides (mmol/L) | 0.96 (0.76–1.25) | 1.23 (0.92–1.63) | 1.51 (1.10–2.05) | 1.93 (1.35–2.80) | <0.001 |
| BMI (kg/m²)            | 20.62 ± 1.73 | 23.31 ± 1.50 | 25.24 ± 1.74 | 28.45 ± 3.74 | <0.001 |
| TC (mmol/L)            | 4.88 ± 1.24 | 5.10 ± 1.13 | 5.06 ± 1.14 | 5.12 ± 1.07 | <0.001 |
| LDL-C (mmol/L)         | 2.93 ± 0.87 | 3.06 ± 0.90 | 3.04 ± 0.89 | 2.82 ± 0.92 | <0.001 |
| HDL-C (mmol/L)         | 1.60 ± 0.34 | 1.38 ± 0.28 | 1.24 ± 0.26 | 1.08 ± 0.26 | <0.001 |
| UACR (mg/g)            | 8.28 (5.65–16.47) | 9.39 (5.57–17.68) | 10.07 (5.85–19.07) | 11.56 (6.21–21.52) | <0.001 |
| ALT (U/L)              | 15.16 ± 12.62 | 16.34 ± 12.26 | 18.83 ± 13.79 | 21.90 ± 16.72 | <0.001 |
| AST (U/L)              | 21.68 ± 10.57 | 21.28 ± 11.29 | 22.15 ± 12.41 | 23.12 ± 13.37 | <0.001 |
| SBP (mmHg)             | 122.17 ± 19.30 | 128.17 ± 20.31 | 133.07 ± 20.95 | 137.51 ± 20.93 | <0.001 |
| DBP (mmHg)             | 72.79 ± 10.68 | 75.89 ± 10.88 | 78.51 ± 11.09 | 81.03 ± 11.29 | <0.001 |
| RHR (bpm)              | 78.81 ± 12.60 | 78.45 ± 12.35 | 78.66 ± 12.13 | 79.12 ± 12.25 | <0.001 |
| HbA1c (%)              | 5.7 (5.5–6) | 5.8 (5.5–6.1) | 5.9 (5.6–6.2) | 6 (5.7–6.4) | <0.001 |
| GGT (U/L)              | 22.84 ± 35.30 | 25.91 ± 31.99 | 30.96 ± 42.74 | 35.38 ± 40.05 | <0.001 |
| FBG (mmol/L)           | 5.29 ± 0.78 | 5.55 ± 1.07 | 5.82 ± 1.34 | 6.25 ± 1.74 | <0.001 |
| eGFR (mL/min/1.73 m²)  | 119.29 ± 21.73 | 119.84 ± 22.87 | 119.98 ± 24.84 | 122.11 ± 29.62 | <0.001 |
| High-school education, n (%) | 6,830 (73.3) | 4,717 (50.6) | 4,428 (47.5) | 3,938 (42.2) | <0.001 |
| Current smoker, n (%)  | 1,110 (12.0) | 1,096 (11.8) | 1,325 (14.2) | 1,631 (17.5) | <0.001 |
| Former smoker, n (%)   | 902 (9.68) | 980 (10.51) | 1,286 (13.8) | 1,547 (16.6) | <0.001 |
| Current alcohol drinker, n (%) | 2,170 (23.3) | 2,195 (23.5) | 2,420 (26.0) | 2,513 (27.0) | <0.001 |
| Former alcohol drinker, n (%) | 2,041 (21.9) | 2,045 (22.0) | 2,318 (24.9) | 2,432 (26.1) | <0.001 |
| History of hypertension, n (%) | 757 (0.08) | 1,246 (13.4) | 1,839 (19.7) | 2,511 (27.0) | <0.001 |
| History of diabetes, n (%) | 85 (0.91) | 145 (1.56) | 238 (2.55) | 366 (3.93) | <0.001 |
| Previous MI, n (%)     | 6 (0.06) | 16 (0.17) | 25 (0.27) | 56 (0.60) | <0.001 |
| Previous stroke, n (%) | 68 (0.73) | 83 (0.89) | 95 (1.02) | 137 (1.47) | <0.001 |
| Previous CAD, n (%)    | 201 (2.16) | 223 (2.39) | 332 (3.56) | 431 (4.62) | <0.001 |
| Taking hypertension drugs, n (%) | 103 (1.10) | 148 (1.59) | 181 (1.94) | 242 (2.60) | <0.001 |

Data were mean ± standard deviation or median (interquartile range) for skewed variables or numbers (proportions) for categorical variables. Statistical significant differences (P < 0.05) between two different groups separately are illustrated by † and §. ALT, alanine transaminase; AST, aspartate transaminase; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; GGT, gamma-glutamyl transferase; HbA1c, glycylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; METS-IR, Metabolic Score for Insulin Resistance; MI, myocardial infarction; RHR, resting heart rate; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio. *Q1 versus Q2; ‡Q1 versus Q3; §Q1 versus Q4; ¶Q2 versus Q3; ††Q2 versus Q4; †††Q3 versus Q4.

The highest and lowest quartile METS-IR groups, respectively (men: Q1, 19.3%; Q2, 21.4%; Q3, 26.8%; Q4, 32.5%; women: Q1, 27.3%; Q2, 26.5%; Q3, 24.3%; Q4, 21.9%). The highest quartile METS-IR group was characterized by significantly higher waist circumference, BMI, UACR, SBP, DBP, resting heart rate, TC, TG, alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, FBG and glycosylated hemoglobin levels. Furthermore, the eGFR and HDL-C levels were lower, because METS-IR was higher.

Association between UACR and METS-IR quartiles
As presented in Table 2, only the highest quartile METS-IR group had a positive relationship with UACR after adjusting for confounding factors among all participants (odds ratio [OR] 1.260, 95% confidence interval [CI] 1.152–1.378, P < 0.001).

As shown in Table 3, in the non-adjusted model, Q1–Q4 were all associated with UACR; however, after adjusting for various confounding factors, only the highest quartile of METS-IR was associated with UACR in model 5 (for men: OR 1.321, 95% CI 1.104–1.579, P = 0.002; for women: OR 1.201, 95% CI 1.083–1.330, P < 0.001). The association in men was more significant than that in women.
## Table 2 | Association of the Metabolic Score for Insulin Resistance index and its components with urinary albumin-to-creatinine ratio in total participants

| METS-IR | Model 1 | OR (95% CI) | P-value | Model 2 | OR (95% CI) | P-value | Model 3 | OR (95% CI) | P-value | Model 4 | OR (95% CI) | P-value | Model 5 | OR (95% CI) | P-value |
|---------|---------|------------|---------|---------|------------|---------|---------|------------|---------|---------|------------|---------|---------|------------|---------|
| **METS-IR** | | | | | | | | | | | | | | | |
| Q1 (17.75–31.63) | Reference | | | | | | | | | | | | | | |
| Q2 (31.64–36.03) | 1.180 (1.075–1.296) | 0.001 | | | | | | | | | | | | | |
| Q3 (36.04–41.03) | 1.310 (1.195–1.435) | <0.001 | | | | | | | | | | | | | |
| Q4 (41.04–137.55) | 1.787 (1.637–1.951) | <0.001 | | | | | | | | | | | | | |
| **TG (mmol/L)** | | | | | | | | | | | | | | | |
| <1.7 | Reference | | | | | | | | | | | | | | |
| ≥1.7, <2.3 | 1.443 (1.331–1.564) | <0.001 | | | | | | | | | | | | | |
| ≥2.3 | 1.702 (1.574–1.840) | <0.001 | | | | | | | | | | | | | |
| **FBG (mmol/L)** | | | | | | | | | | | | | | | |
| <5.6 | Reference | | | | | | | | | | | | | | |
| ≥5.6, <7.0 | 1.235 (1.156–1.321) | <0.001 | | | | | | | | | | | | | |
| ≥7.0 | 1.602 (1.506–1.705) | <0.001 | | | | | | | | | | | | | |
| **BMI (kg/m²)** | | | | | | | | | | | | | | | |
| <18.5 | Reference | | | | | | | | | | | | | | |
| ≥18.5, <24 | 0.986 (0.812–1.197) | 0.887 | | | | | | | | | | | | | |
| ≥24, <28 | 1.108 (0.912–1.345) | 0.303 | | | | | | | | | | | | | |
| ≥28 | 1.447 (1.182–1.771) | <0.001 | | | | | | | | | | | | | |
| **HDL (mmol/L)** | | | | | | | | | | | | | | | |
| ≥1 | Reference | | | | | | | | | | | | | | |
| <1 | 1.291 (1.192–1.397) | <0.001 | | | | | | | | | | | | | |

Model 1: Unadjusted. Model 2: Adjusted for center, age and sex. Model 3: Further education status, smoking habits, drinking habits and cardiovascular disease status. Model 4: Further diabetes history, hypertension history and hypotensive drugs. Model 5: Further estimated glomerular filtration rate, low-density lipoprotein cholesterol, total cholesterol, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, glycosylated hemoglobin, systolic blood pressure, diastolic blood pressure, waist circumference and heart rate. BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; METS-IR, Metabolic Score for Insulin Resistance; OR, odds ratio; TG, triglycerides; UACR, urinary albumin-to-creatinine ratio.
Table 3 | Association of the Metabolic Score for Insulin Resistance index and its components with urinary albumin-to-creatinine ratio by sex

| METS-IR                | Model 1                          | Model 2                          | Model 3                          | Model 4                          | Model 5                          |
|------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                        | OR (95% CI)                      | P-value                          | OR (95% CI)                      | P-value                          | OR (95% CI)                      | P-value                          |
| **Men**                |                                  |                                  |                                  |                                  |                                  |                                  |
| Q1 (18.98–32.95)       | Reference                         |                                  |                                  |                                  |                                  |                                  |
| Q2 (22.96–37.78)       | 1.129 (0.910–1.400)              | 0.270                            | 1.165 (0.935–1.452)              | 0.175                            | 1.131 (0.930–1.376)              | 0.218                            |
| Q3 (7.79–42.71)        | 1.348 (1.155–1.573)              | <0.001                           | 1.389 (1.131–1.707)              | <0.001                           | 1.365 (1.166–1.598)              | <0.001                           |
| Q4 (42.72–115.22)      | 1.878 (1.559–2.263)              | <0.001                           | 2.092 (1.722–2.540)              | <0.001                           | 1.745 (1.525–1.970)              | <0.001                           |
| **TG (mmol/L)**        |                                  |                                  |                                  |                                  |                                  |                                  |
| <1.7                   |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥1.7, <2.3             | 1.182 (0.998–1.401)              | 0.053                            | 1.175 (0.988–1.398)              | 0.068                            | 1.173 (0.985–1.398)              | 0.074                            |
| ≥2.3                   | 1.667 (1.426–1.949)              | <0.001                           | 1.531 (1.319–1.777)              | <0.001                           | 1.547 (1.323–1.808)              | <0.001                           |
| **FBG (mmol/L)**       |                                  |                                  |                                  |                                  |                                  |                                  |
| <5.6                   |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥5.6, <7.0             | 1.359 (1.184–1.560)              | <0.001                           | 1.051 (1.008–1.326)              | <0.001                           | 1.033 (1.025–1.041)              | <0.001                           |
| ≥7.0                   | 1.696 (1.529–1.882)              | <0.001                           | 1.187 (1.065–1.324)              | <0.001                           | 1.353 (1.170–1.563)              | <0.001                           |
| **BMI (kg/m²)**        |                                  |                                  |                                  |                                  |                                  |                                  |
| <18.5                  |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥18.5, <24             | 0.912 (0.621–1.340)              | 0.640                            | 1.026 (0.694–1.516)              | 0.899                            | 1.023 (0.687–1.522)              | 0.911                            |
| ≥22, <28               | 1.152 (0.786–1.687)              | 0.469                            | 1.345 (1.080–1.674)              | 0.008                            | 1.360 (0.914–2.023)              | 0.129                            |
| ≥28                    | 1.502 (1.009–2.325)              | 0.045                            | 1.675 (1.448–1.976)              | <0.001                           | 1.649 (1.285–1.955)              | 0.002                            |
| **HDL (mmol/L)**       |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥1                     |                                  |                                  |                                  |                                  |                                  |                                  |
| <1                     | 1.391 (1.211–1.598)              | <0.001                           | 1.249 (1.146–1.360)              | <0.001                           | 1.340 (1.157–1.553)              | <0.001                           |
| **Women**              |                                  |                                  |                                  |                                  |                                  |                                  |
| Q1 (17.75–31.18)       |                                  |                                  |                                  |                                  |                                  |                                  |
| Q2 (11.19–35.37)       | 1.205 (1.086–1.337)              | 0.001                            | 1.181 (1.061–1.315)              | 0.002                            | 1.163 (1.041–1.299)              | 0.007                            |
| Q3 (5.38–40.27)        | 1.356 (1.222–1.504)              | <0.001                           | 1.266 (1.136–1.411)              | 0.001                            | 1.152 (1.052–1.262)              | 0.002                            |
| Q4 (40.28–137.55)      | 1.877 (1.697–2.077)              | <0.001                           | 1.797 (1.614–2.000)              | <0.001                           | 1.410 (1.302–1.526)              | <0.001                           |
| **TG (mmol/L)**        |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥1.7                   |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥1.7, <2.3             | 1.540 (1.405–1.689)              | <0.001                           | 1.278 (1.160–1.407)              | <0.001                           | 1.262 (1.144–1.391)              | <0.001                           |
| ≥2.3                   | 1.817 (1.657–1.992)              | <0.001                           | 1.325 (1.203–1.459)              | <0.001                           | 1.466 (1.329–1.617)              | <0.001                           |
| **FBG (mmol/L)**       |                                  |                                  |                                  |                                  |                                  |                                  |
| <5.6                   |                                  |                                  |                                  |                                  |                                  |                                  |
| ≥5.6, <7.0             | 1.234 (1.143–1.333)              | <0.001                           | 1.142 (1.107–1.212)              | <0.001                           | 1.036 (1.031–1.041)              | <0.001                           |
| ≥7.0                   | 1.640 (1.515–1.774)              | <0.001                           | 1.220 (1.134–1.312)              | <0.001                           | 1.153 (1.061–1.252)              | 0.001                            |
Table 3. (Continued)

| METS-IR  | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|----------|---------|---------|---------|---------|---------|
| BM (kg/m²) | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| < 18.5 | Reference | 0.895 (0.796–1.014) | < 0.001 | 1.027 (0.853–1.236) | 0.622 | 1.040 (0.851–1.267) | 0.741 | 0.981 (0.820–1.168) | 0.767 |
| 18.5–22.9 | 1.094 (0.845–1.406) | 0.549 | 1.316 (1.083–1.596) | 0.002 | 1.283 (1.049–1.558) | 0.008 | 1.047 (0.861–1.269) | 0.659 |
| 23.0–26.9 | 1.062 (0.892–1.260) | 0.509 | 1.199 (0.975–1.475) | 0.078 | 1.173 (0.940–1.457) | 0.152 | 1.035 (0.843–1.271) | 0.720 |
| ≥ 27.0 | 1.357 (1.170–1.575) | 0.001 | 1.537 (1.282–1.836) | < 0.001 | 1.434 (1.162–1.758) | < 0.001 | 1.106 (0.895–1.356) | 0.341 |

**DISCUSSION**

To the best of our knowledge, the present study is the first to explore the association between the METS-IR and UACR among a nationwide community-based population of Chinese adults. The main findings of our study were as follows: (i) UACR was significantly associated with the METS-IR index after controlling for confounding factors, and the association was more significant for the METS-IR index than for its components (FBG, TG, BMI and HDL-C); and (ii) differences among the subgroups were observed on the basis of sex. Among men, the association between METS-IR and UACR was significant in those aged 55–64 years with prediabetes or diabetes, prehypertension or hypertension and eGFR ≥90 mL/min/1.73 m². When eGFR ≥90 mL/min/1.73 m², the positive relationships between the fourth METS-IR quartile and UACR were significant regardless of sex (all participants: OR 1.289, 95% CI 1.172–1.417, P < 0.001; men: OR 1.316, 95% CI 1.089–1.589, P = 0.004; women: OR 1.268, 95% CI 1.135–1.417, P < 0.001).
Table 4 | Association of the Metabolic Score for Insulin Resistance index with urinary albumin-to-creatinine ratio for different levels of age, blood glucose, blood pressure and estimated glomerular filtration rate in total participants

| Variable | METS-IR | P-values for interaction |
|----------|---------|-------------------------|
|          | Q1      | Q2      | Q3      | Q4      | Reference OR (95% CI) | P-value OR (95% CI) | P-value OR (95% CI) | P-value OR (95% CI) | P-value |
|          | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| All participants | 0.136 |
| Age (years)† | 1.099 (0.924–1.307) | 0.288 | 0.943 (0.801–1.110) | 0.483 | 1.313 (1.114–1.547)* | 0.001 |
| <55 (n = 14,788) | 0.991 (0.829–1.185) | 0.920 | 1.118 (0.962–1.300) | 0.146 | 1.208 (1.027–1.574)* | <0.001 |
| ≥65 (n = 7,387) | 1.206 (0.989–1.470) | 0.064 | 0.988 (0.838–1.164) | 0.885 | 1.034 (0.879–1.217) | 0.685 |
| Blood glucose (mmol/L)‡ | 1.029 (0.886–1.196) | 0.706 | 0.974 (0.836–1.135) | 0.736 | 1.082 (0.946–1.239) | 0.250 |
| FBG <5.6 and PBG <7.8 (n = 15,996) | 0.993 (0.829–1.185) | 0.920 | 1.118 (0.962–1.300) | 0.146 | 1.208 (1.027–1.574)* | <0.001 |
| 5.6 ≤ FBG <7.0 or 7.8 ≤ PBG <11.1 (n = 15,837) | 1.128 (0.953–1.336) | 0.160 | 0.935 (0.832–1.069) | 0.509 | 1.330 (1.121–1.578)* | 0.001 |
| FBG ≥7.0 or PBG ≥11.1 (n = 5,457) | 1.066 (0.780–1.457) | 0.688 | 1.084 (0.871–1.349) | 0.469 | 1.381 (1.025–1.698)* | 0.038 |
| Blood pressure (BP)§ | 1.146 (0.955–1.376) | 0.143 | 1.049 (0.865–1.272) | 0.629 | 1.094 (0.939–1.275) | 0.247 |
| SBP <120 and DBP <80 (n = 11,520) | 0.981 (0.820–1.175) | 0.838 | 1.255 (0.968–1.655) | 0.404 | 1.356 (1.165–1.579)* | <0.001 |
| 120 ≤ SBP <140 and/or 80 ≤ DBP <90 (n = 14,145) | 1.069 (0.892–1.321) | 0.351 | 1.127 (0.909–1.396) | 0.302 | 1.282 (1.124–1.463)* | <0.001 |
| eGFR (mL/min/1.73 m²)¶ | 1.088 (0.976–1.212) | 0.128 | 1.037 (0.943–1.141) | 0.449 | 1.289 (1.172–1.417)* | <0.001 |
| eGFR ≥90 (n = 34,691) | 1.189 (0.986–1.575) | 0.384 | 0.959 (0.709–1.298) | 0.788 | 1.042 (0.773–1.406) | 0.785 |
| eGFR <60 (n = 191) | 1.010 (0.992–1.323) | 0.215 | 1.011 (0.960–1.065) | 0.767 | 1.052 (0.983–1.125) | 0.144 |

CI, confidence interval; FBG, fasting blood glucose; METS-IR, Metabolic Score for Insulin Resistance; OR, odds ratio; PBG, 2-h postload blood glucose; UACR, urinary albumin-to-creatinine ratio.

* Meaned P-value < 0.05.
† Age subgroup: adjusted for sex, centers, alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), glycosylated hemoglobin (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated glomerular filtration rate (eGFR), waist circumference (WC), smoking habits, drinking habits, cardiovascular disease (CVD) status, hypertension history, diabetes history and use of hypertension drugs.
‡ Blood glucose (BG) subgroup: adjusted for age, sex, centers, ALT, AST, GGT, LDL-C, TC, SBP, DBP, eGFR, WC, smoking habits, drinking habits, CVD status, hypertension history and use of hypertension drugs.
§ Blood pressure (BP) subgroup: adjusted for age, sex, centers, ALT, AST, GGT, LDL-C, TC, HbA1c, eGFR, WC, smoking habits, drinking habits, CVD status and diabetes history.
¶ eGFR subgroup: adjusted for age, sex, centers, ALT, AST, GGT, LDL-C, TC, HbA1c, SBP, DBP, WC, smoking habits, drinking habits, CVD status, hypertension history, diabetes history and use of hypertension drugs.
Table 5 | Association of the Metabolic Score for Insulin Resistance index with urinary albumin-to-creatinine ratio for different levels of age, blood glucose, blood pressure, and estimated glomerular filtration rate by sex

| Variable                        | METS-IR | Reference | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | P-values for interaction |
|---------------------------------|---------|-----------|-------------|---------|-------------|---------|-------------|---------|--------------------------|
| **Men**                         |         |           |             |         |             |         |             |         |                          |
| Age (years)†                    |         | 1         | 0.862 (0.504–1.475) | 0.589   | 0.862 (0.571–1.300) | 0.478   | 1.078 (0.748–1.555) | 0.686   | 0.593                    |
| <55 (n = 3,477)                 |         | 1         | 0.933 (0.631–1.381) | 0.730   | 0.933 (0.652–1.236) | 0.508   | 1.494 (1.114–2.004)* | 0.007   |                         |
| ≥55, <64 (n = 4,361)            |         | 1         | 1.053 (0.719–1.543) | 0.791   | 1.053 (0.820–1.505) | 0.496   | 1.113 (0.820–1.511) | 0.494   |                         |
| Blood glucose (mmol/L)‡         |         | 1         | 0.846 (0.582–1.231) | 0.382   | 0.738 (0.521–1.045) | 0.087   | 1.020 (0.709–1.469) | 0.914   | 0.564                    |
| FBG <5.6 and PBG <7.8 (n = 3,995) |         | 1         | 1.040 (0.711–1.523) | 0.839   | 0.816 (0.606–1.098) | 0.179   | 1.231 (1.011–1.498)* | 0.001   |                         |
| 5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1 (n = 4,797) |         | 1         | 1.040 (0.579–1.868) | 0.896   | 1.380 (0.933–2.041) | 0.107   | 1.511 (1.070–2.134)* | 0.019   |                         |
| BP (mmHg)§                      |         | 1         | 0.617 (0.410–1.128) | 0.206   | 0.845 (0.602–1.186) | 0.330   | 1.190 (0.865–1.639) | 0.285   | 0.336                    |
| SBB <120 or DBP <80 (n = 2,612) |         | 1         | 1.500 (0.915–2.460) | 0.108   | 1.069 (0.663–1.724) | 0.794   | 1.635 (1.020–2.623)* | 0.041   |                         |
| eGFR (mL/min/1.73 m²)           |         | 1         | 1.451 (0.984–2.140) | 0.060   | 1.114 (0.848–1.464) | 0.439   | 1.368 (1.070–1.750)* | 0.012   | 0.116                    |
| **Women**                       |         |           |             |         |             |         |             |         |                          |
| Age (years)†                    |         | 1         | 1.159 (0.964–1.394) | 0.117   | 0.977 (0.816–1.169) | 0.799   | 1.378 (1.144–1.662)* | 0.001   | 0.198                    |
| ≥55, <64 (n = 10,048)           |         | 1         | 0.998 (0.816–1.220) | 0.981   | 1.203 (1.014–1.429)* | 0.034   | 1.319 (1.105–1.574)* | 0.002   |                         |
| ≥65 (n = 4,519)                 |         | 1         | 1.250 (0.989–1.579) | 0.061   | 0.921 (0.756–1.122) | 0.414   | 0.991 (0.816–1.203) | 0.927   |                         |
| Blood glucose (mmol/L)‡         |         | 1         | 1.083 (0.746–1.572) | 0.674   | 0.973 (0.745–1.270) | 0.838   | 1.127 (0.884–1.436) | 0.334   | 0.872                    |
| FBG <5.6 and PBG <7.8 (n = 12,837) |         | 1         | 1.162 (0.962–1.403) | 0.119   | 1.005 (0.858–1.171) | 0.975   | 1.118 (0.853–1.465) | 0.420   |                         |
| 5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1 (n = 9,368) |         | 1         | 1.162 (0.962–1.403) | 0.119   | 1.005 (0.858–1.171) | 0.975   | 1.630 (1.398–1.845)* | 0.004   |                         |
| BP (mmHg)§                      |         | 1         | 1.102 (0.905–1.342) | 0.335   | 1.058 (0.856–1.308) | 0.603   | 1.170 (0.907–1.509) | 0.227   | 0.035                    |
| SBB <120 or DBP <80 (n = 8,908) |         | 1         | 1.096 (0.897–1.340) | 0.370   | 1.170 (0.985–1.390) | 0.073   | 1.279 (0.999–1.638) | 0.051   |                         |
| 120 ≤ SBB < 140 and/or 80 ≤ DBP < 90 (n = 9,889) |         | 1         | 1.055 (0.894–1.246) | 0.524   | 1.182 (0.973–1.284) | 0.220   | 1.242 (1.060–1.456)* | 0.007   |                         |
Table 5. Continued

| Variable | METS-IR values for interaction | P-value for interaction | Q1 | Q2 | Q3 | Q4 | Reference OR (95% CI) | P-value OR (95% CI) | P-value |
|----------|-------------------------------|-------------------------|-----|----|-----|----|----------------------|----------------------|---------|
| eGFR (mL/min/1.73 m²) | eGFR ≥ 90 (n = 24,634) | 1 | 1 | 1 | 1 | 1 | 1.115 (0.989–1.258) | 0.076 | 0.225 |
| eGFR < 90 (n = 1,616) | 1 | 1 | 1 | 1 | 1 | 1.236 (0.799–1.914) | 0.341 |
| eGFR < 60 (n = 749) | 1 | 1 | 1 | 1 | 1 | 1.051 (0.952–1.162) | 0.325 |

CI, confidence interval; FBG, fasting blood glucose; METS-IR, metabolic score for insulin resistance; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio; PBG, 2-h postload blood glucose.

‡ Meaning value < 0.05.

¶ Age subgroup: adjusted for centers, ALT, AST, GGT, LDL-C, TC, HbA1c, eGFR, WC, smoking habits, drinking habits, CVD status, diabetes history and use of hypertension drugs.

§ Blood glucose (BG) subgroup: adjusted for age, centers, ALT, AST, GGT, LDL-C, TC, SBP, DBP, smoking habits, drinking habits, CVD status, diabetes history and use of hypertension drugs.

¶ Blood pressure (BP) subgroup: adjusted for age, centers, ALT, AST, GGT, LDL-C, TC, SBP, DBP, smoking habits, drinking habits, CVD status, diabetes history and use of hypertension drugs.

Among women, the association between METS-IR and UACR was significant among those aged <65 years with diabetes, hypertension and eGFR ≥ 90 mL/min/1.73 m². Thus, early monitoring and treatment are essential for increased UACR, and alleviation of IR perhaps conduces to the early prevention and intervention of negative consequences, particularly in populations with higher blood glucose and BP abnormalities.

Although previous studies found that the components of METS-IR (BMI, TG, FBG and HDL-C) could be treated as predictors of CVD and hypertension, the present study showed that BMI, FBG and TG in men, and HDL-C in women were not significantly associated with UACR. However, METS-IR remained strongly associated with UACR among all participants. Furthermore, the assessment of these METS-IR components has potential limitations. An increased FBG level is a less competent indicator of cardiovascular outcomes. The role of BMI is debatable, as different studies have presented conflicting results. In the subgroup analyses by BG level, the OR in the group of 5.6 < FBG < 7.0 mmol/L was higher than the group of FBG ≥ 7.0 mmol/L in model 5; perhaps it might be that when the population is in a critical sub-health state, life habits will be worse than the population with diabetes, and they will not pay attention to the reasonable arrangement of diet structure and moderate exercise, meanwhile, the diabetes patients had better compliance with medical orders. In this physical state, the BG in the sub-health level will make the relationship with UACR more significant. Furthermore, lower HDL-C and higher TG levels were significantly associated with a risk of elevated UACR among the conventional parameters of dyslipidaemia. The present study showed that METS-IR might be regarded as a better vigilant value for albuminuria detection than BMI or TG, FBG and HDL-C levels.

Few studies have investigated sex-or age-stratified associations between UACR and METS-IR. In the present study, we found age- and sex-based differences. In this population-based study of middle-aged and older participants, the results showed that an elevated UACR was significantly associated with an increased METS-IR index among men (aged 55–64 years) and women (aged <65 years). A previous study found that BMI, which is a component of METS-IR, is significantly associated with chronic kidney disease, and this association becomes weaker with increasing age (particularly among women). Similar findings of another study showed that the influence of lipid variability on unfavorable outcomes was greater in younger adults. The present findings support the fact that younger adults show greater sensitivity to increasing the variability of cholesterol than older adults. UACR has been reported to be predictive of CVD. It has a negative association with the risk of CVD, and is independent of sex and age. Likewise, mortality risk ratios for coronary artery disease among men were halved between the age of 55–64 years and 65–74 years. The findings of our study were not fully consistent with those of the abovementioned studies. In the present study, there were some
elderly people in retirement to a certain extent; we speculated that such people have possibly more time to exercise to reduce inflammation, which could lead to renal dysfunction. Therefore, early detection and intervention are vital for people with risk factors.

In the subgroup analyses, it was noticeable that the different associations were significant in men with diabetes and prediabetes, prehypertension, and hypertension, and in women with hypertension and diabetes. However, we found that the interaction between BP and METS-IR was only significant among women, particularly premenopausal women. Therefore, the present findings showed that the independent association of METS-IR with UACR were more significant in men and postmenopausal women. Furthermore, the proportion of men was higher in the highest METS-IR quartile, and the OR for elevated UACR was higher in men than in women. Our findings disagree with those of some previous studies that showed that being female seems to intensify the progression of diabetic renal disease or that being male could be considered a risk for the disease. The possible reasons for the conflicting findings are unclear. However, data from a review study confirmed that the risk of incidence of non-diabetic renal disease was higher among men than among age-matched women without diabetes. It suggested that a possible mechanism for the deficiency of the distinct sex discrepancy in the status of diabetes might be due to the imbalance of sex hormone levels with diabetes. This finding was consistent with that of the current study. A sex-stratified study had similar conclusions and showed that the components of METS-IR in men were more impaired than that in women, and that the values of TG or TG-to-HDL ratios were higher in men. Further evidence could come out in support of the role of endogenous estrogen in the metabolic homeostasis and the decrease of visceral lipid accumulation.

The present results might be due to the latent lipid distribution differential based on sex and the different levels of steroid hormone. An animal study showed that estrogen therapy might have a beneficial impact on proteinuria. Therefore, further analysis among postmenopausal and premenopausal women is essential. Similar results to those in men were found in the population of postmenopausal women. Simultaneously, the results of premenopausal women were distinct from those of men, which provided evidence for the hypothetical mechanism, and indicated the higher accumulation of risk factors with gradual elevation of UACR in postmenopausal women and men. The present study provided new insights to support that age and sex should be an essential consideration when referring to albuminuria.

The underlying pathophysiological mechanism linking UACR to METS-IR and its constituents is not fully established. The possible reason might be attributed to visceral obesity. The relationship between IR and visceral adipose tissue (VAT) has long been recognized. Given that METS-IR has a particularly strong association with visceral adiposity compared with insulin-based indexes, it could be a predictor for ectopic lipid accumulation and visceral fat, which were confirmed risk factors for hypertension and CVD. Furthermore, recent studies have proposed that visceral adiposity might be pivotal involved in UACR excretion, and albuminuria might be a manifestation of VAT.

It is presumptive that adiponectin’s role in renal dysfunction might be an underlying factor of the association between albuminuria and VAT. Elevated VAT and increased albuminuria have both been reported to have inverse associations with adiponectin. Adiponectin has a positive correlation with age, and the concentration levels of adiponectin are different based on sex. Intra-abdominal fat was less in women than in men.

These findings are concordant with the present findings. An adiponectin-deficient animal-based model showed that glomerular damage was promoted by lower levels of adiponectin. Furthermore, the adipocytokines of VAT, such as interleukin-6 and tumor necrosis factor-α, could exacerbate renal vascular damage through inflammation and lead to the development of albuminuria owing to increased eGFR. The findings of these studies are consistent with the present findings. Taken together, the aforementioned findings confirm that the relationship between UACR with METS-IR could be explained by the increased VAT associated with both adiponectin and IR.

The major strength of the present study was that the study benefited from a relatively large multicenter investigation of the Chinese population. However, a few limitations should be considered. First, no inference of causality can be drawn owing to the cross-sectional design; a follow-up analysis should be carried out to determine whether METS-IR is a predictor of elevated UACR. Second, the measurement of UACR was based on a single morning spot urine specimen. Despite its recommendation as a reliable method in large epidemiological studies, misestimations of urinary albumin egestion owing to intra-individual variance cannot be eliminated. Finally, despite regulating a series of confounding factors, some remnants or unmeasured confounders could not be excluded.

METS-IR was significantly associated with an elevated UACR among Chinese adults and was superior to its components. Furthermore, men or postmenopausal women with diabetes and hypertension, particularly those aged <65 years, required specific supervision when screening for the METS-IR index. In practice, clinicians should detect the potential risk factors in a timely manner to alleviate the prevalence of kidney dysfunction and CVD based on the novel perceptions of METS-IR, which might be regarded as a convenient tool to identify the patients. The present study also provided proof to support that age and sex should be an essential consideration when referring to albuminuria.

ACKNOWLEDGMENTS
We thank the participants in this study. The study is supported by the Chinese Society of Endocrinology, the Key Laboratory...
for Endocrine and Metabolic Diseases of Ministry of Health (1994DP131044), the National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09303006-001), the National High Technology Research and Development Program of China (863 Program, 2011AA020107), National Science Foundation of China (81300717), the Beijing Municipal Science and Technology Commission (No. D141107005314004); National Science and Technology Major Project 288 (2011ZX09307-001-08), and the REACTION Study.

DISCLOSURE
The authors declare no conflict of interest.

Approval of the research protocol: The study protocol was approved by the Committee on Human Research at Rui-Jin Hospital affiliated with the School of Medicine, Shanghai Jiao Tong University.

Informed consent: Ethics approval and written informed consent were obtained from all participants before data collection.

Approval date of registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

DATA AVAILABILITY STATEMENT
The datasets used to support this study are not freely available to protect the privacy of participants.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1