JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

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

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[1]. An elevated UACR is more closely associated with increased CVD risk than with the estimated glomerular filtration rate (eGFR) in patients with diabetes[2]. In addition, elevated fasting blood glucose (FBG) level, hyperlipidemia and obesity are not only associated with CVD, but also with chronic kidney disease[3–6]. 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[7–10]. Furthermore, both diabetes and albuminuria are risk factors for CVD, and the morbidity of microalbuminuria remarkably increased in people with diabetes[11,12].

Insulin resistance (IR) plays roles in the pathophysiology of dyslipidemia, type 2 diabetes mellitus and microalbuminuria[9]. 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[13,14]. 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[15]. 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)[3], 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[3]. 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[16]. 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 flow chart 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/m^2). 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 (PBG), 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 ($mL/min/1.73\ m^2$) was calculated according to the following formula: $186 \times (\text{serum creatinine} \times 0.011)^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ if female) $\times 1.233$, 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[17].

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

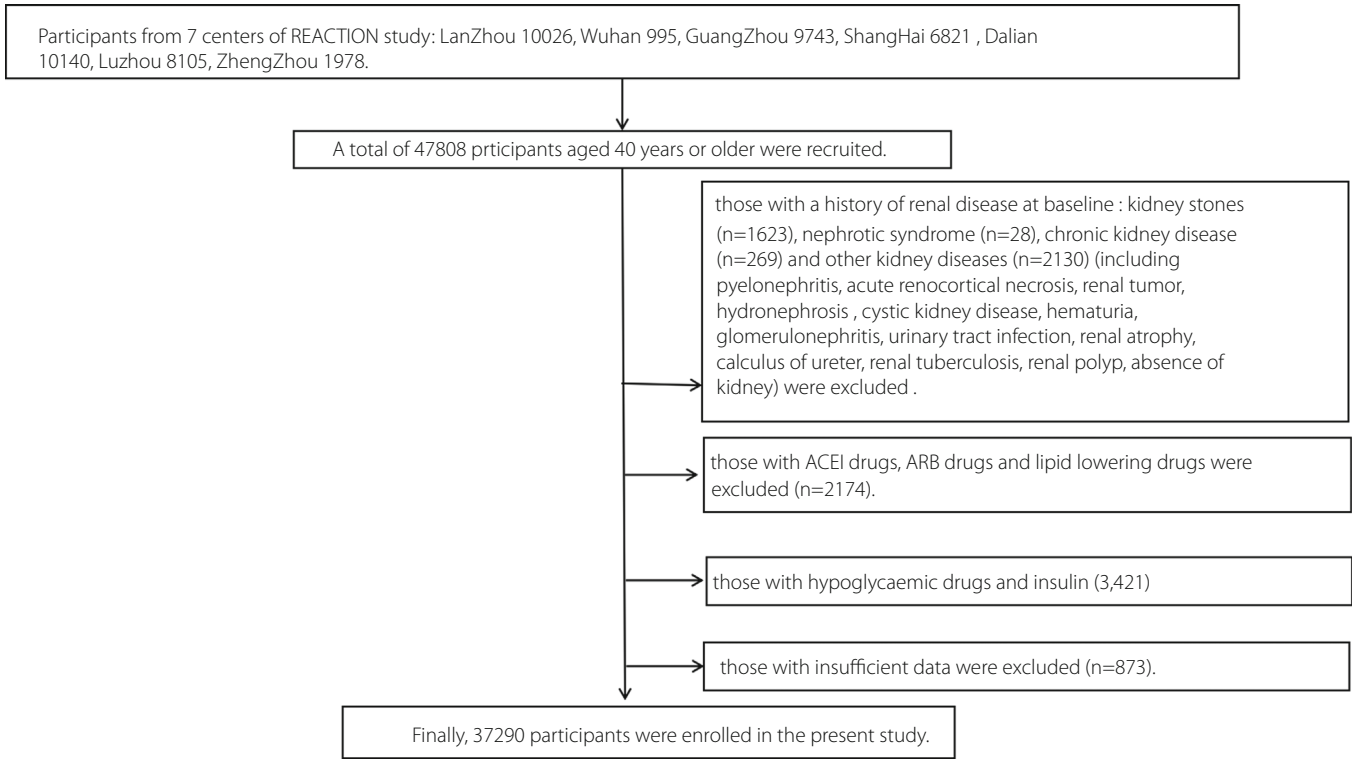

Figure 1 | The flow chart describing the enrollment of the participants in this study. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

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 × FBG{mg/dL} + TG0{mg/dL}] × BMI) / (Ln[HDL-C{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 m^2), 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				*P* value
	Q1 (*n* = 9,322)	Q2 (*n* = 9,323)	Q3 (*n* = 9,323)	Q4 (*n* = 9,322)	
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 (27.3)	6,987 (26.5)	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 (b.p.m.)	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, glycosylated 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.

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.

Association between METS-IR and UACR according to different levels of age, BG, BP and eGFR

Stratified analyses were carried out for the subgroups of age, BG level, BP and eGFR to further investigate whether the

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		Model 2		Model 3		Model 4		Model 5	
	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
METS-IR										
Q1 (17.75–31.63)	Reference		Reference		Reference		Reference		Reference	
Q2 (31.64–36.03)	1.180 (1.075–1.296)	0.001	1.168 (1.061–1.286)	0.002	1.152 (1.047–1.267)	0.004	1.106 (1.005–1.217)	0.039	1.084 (0.978–1.023)	0.124
Q3 (36.04–41.03)	1.310 (1.195–1.435)	<0.001	1.284 (1.167–1.412)	<0.001	1.175 (1.085–1.271)	<0.001	1.107 (1.022–1.199)	0.013	1.028 (0.940–1.124)	0.548
Q4 (41.04–137.55)	1.787 (1.637–1.951)	<0.001	1.857 (1.693–2.037)	<0.001	1.524 (1.423–1.632)	<0.001	1.399 (1.304–1.500)	<0.001	1.260 (1.152–1.378)	<0.001
TG (mmol/L)										
<1.7	Reference		Reference		Reference		Reference		Reference	
≥1.7,<2.3	1.443 (1.331–1.564)	<0.001	1.254 (1.153–1.364)	<0.001	1.239 (1.138–1.348)	<0.001	1.183 (1.086–1.289)	<0.001	1.033 (0.944–1.131)	0.476
≥2.3	1.702 (1.574–1.840)	<0.001	1.385 (1.276–1.503)	<0.001	1.523 (1.402–1.624)	<0.001	1.303 (1.198–1.417)	<0.001	1.158 (1.058–1.268)	0.001
FBG (mmol/L)										
<5.6	Reference		Reference		Reference		Reference		Reference	
≥5.6,<7.0	1.235 (1.156–1.321)	<0.001	1.140 (1.079–1.182)	<0.001	1.035 (1.023–1.038)	<0.001	1.135 (0.968–1.332)	0.067	1.142 (1.032–1.265)	0.01
≥7.0	1.602 (1.506–1.705)	<0.001	1.225 (1.153–1.301)	<0.001	1.196 (1.113–1.285)	<0.001	1.148 (1.068–1.233)	<0.001	1.051 (0.959–1.152)	0.287
BMI (kg/m^2)										
<18.5	Reference		Reference		Reference		Reference		Reference	
≥18.5,<24	0.986 (0.812–1.197)	0.887	1.229 (0.993–1.522)	0.059	1.042 (0.853–1.272)	0.687	0.989 (0.808–1.211)	0.916	0.828 (0.664–1.032)	0.094
≥24,<28	1.108 (0.912–1.345)	0.303	1.220 (0.998–1.491)	0.052	1.174 (1.047–1.316)	0.006	1.083 (0.965–1.215)	0.174	0.908 (0.796–1.035)	0.15
≥28	1.447 (1.182–1.771)	<0.001	1.421 (1.259–1.502)	<0.001	1.513 (1.389–1.568)	<0.001	1.280 (1.427–1.591)	<0.001	0.912 (0.701–1.187)	0.493
HDL (mmol/L)										
≥1	Reference		Reference		Reference		Reference		Reference	
<1	1.291 (1.192–1.397)	<0.001	1.249 (1.146–1.360)	<0.001	1.237 (1.134–1.349)	<0.001	1.178 (1.079–1.286)	<0.001	1.133 (1.020–1.259)	0.02

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	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Men										
Q1 (18.98–32.95)	Reference		Reference		Reference		Reference		Reference	
Q2 (32.96–37.78)	1.129 (0.910–1.400)	0.270	1.165 (0.935–1.452)	0.175	1.131 (0.930–1.376)	0.218	1.045 (0.858–1.273)	0.661	0.991 (0.735–1.129)	0.395
Q3 (37.79–42.71)	1.348 (1.155–1.573)	<0.001	1.389 (1.131–1.707)	<0.001	1.365 (1.166–1.598)	<0.001	1.258 (1.073–1.476)	0.005	1.058 (0.882–1.269)	0.544
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	1.591 (1.387–1.824)	<0.001	1.321 (1.104–1.579)	0.002
TG (mmol/L)										
<1.7	Reference		Reference		Reference		Reference		Reference	
≥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	1.473 (1.256–1.728)	<0.001	0.929 (0.768–1.124)	0.451
≥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	1.100 (1.002–1.113)	0.009	1.166 (0.952–1.426)	0.137
FBG (mmol/L)										
<5.6	Reference		Reference		Reference		Reference		Reference	
≥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	1.051 (0.877–1.259)	0.589	1.060(0.909–1.237)	0.459
≥7.0	1.696 (1.529–1.882)	<0.001	1.187 (1.065–1.324)	0.002	1.353 (1.170–1.563)	<0.001	1.296 (1.120–1.499)	<0.001	1.229(0.960–1.573)	0.101
BMI (kg/m^2)										
<18.5	Reference		Reference		Reference		Reference		Reference	
≥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	0.953 (0.640–1.421)	0.815	0.679 (0.433–1.065)	0.092
≥24,<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	1.196 (0.954–1.499)	0.120	0.637 (0.393–1.032)	0.067
≥28	1.502 (1.009–2.235)	0.045	1.675 (1.448–1.976)	<0.001	1.649 (1.285–1.955)	0.002	1.534 (1.242–1.895)	<0.001	0.747 (0.435–1.282)	0.289
HDL (mmol/L)										
≥1	Reference		Reference		Reference		Reference		Reference	
<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	1.280 (1.103–1.485)	<0.001	1.243 (1.040–1.485)	0.017
Women										
Q1 (17.75–31.18)	Reference		Reference		Reference		Reference		Reference	
Q2 (31.19–35.37)	1.205 (1.086–1.337)	0.001	1.181 (1.061–1.315)	0.002	1.163 (1.041–1.299)	0.007	1.123 (1.005–1.255)	0.041	1.041 (0.989–1.245)	0.077
Q3 (35.38–40.27)	1.356 (1.222–1.504)	<0.001	1.266 (1.136–1.411)	0.001	1.152 (1.052–1.262)	0.002	1.103 (1.006–1.209)	0.037	1.064 (0.960–1.180)	0.234
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	1.340 (1.233–1.456)	<0.001	1.201 (1.083–1.330)	<0.001
TG (mmol/L)										
<1.7	Reference		Reference		Reference		Reference		Reference	
≥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	1.214 (1.101–1.340)	<0.001	0.996 (1.106–1.228)	0.060
≥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	1.245 (1.128–1.375)	<0.001	1.152 (1.023–1.297)	0.020
FBG (mmol/L)										
<5.6	Reference		Reference		Reference		Reference		Reference	
≥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	1.114 (0.964–1.288)	0.142	0.981 (0.898–1.072)	0.671
≥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	1.108 (1.019–1.205)	0.016	1.001 (0.999–1.003)	0.246

Table 3. (*Continued*)

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	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
BMI (kg/m²)										
<18.5	Reference		Reference		Reference		Reference		Reference	
≥18.5,<24	0.995 (0.795–1.246)	0.965	1.036 (0.821–1.307)	0.767	1.030 (0.814–1.303)	0.806	0.993 (0.785–1.257)	0.954	0.854 (0.662–1.102)	0.224
≥24,<28	1.098 (0.876–1.377)	0.417	1.147 (1.006–1.309)	0.041	1.121 (0.981–1.281)	0.094	1.049 (0.917–1.199)	0.489	0.781 (0.595–1.024)	0.074
≥28	1.427 (1.128–1.806)	0.003	1.373 (1.290–1.481)	<0.001	1.353 (1.246–1.533)	<0.001	1.397 (1.230–1.586)	<0.001	0.934 (0.690–1.265)	0.659
HDL (mmol/L)										
≥1	Reference		Reference		Reference		Reference		Reference	
<1	1.390 (1.258–1.537)	<0.001	1.345 (1.080–1.474)	<0.001	1.200 (1.077–1.337)	0.001	1.143 (1.024–1.275)	0.017	1.068 (0.935–1.220)	0.334

Model 1: Unadjusted Model 2: Adjusted for center and age Model 3: Further education status, smoking habits, drinking habits and cardiovascular disease status Model 4: Further diabetes history, hypertension history, 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.

relationships between METS-IR and UACR were still significant (Tables 4 and 5). Furthermore, to better discuss the sex hormone–related associations between METS-IR and UACR, we divided women into two groups, namely, the postmenopausal women group and premenopausal women group (Table S1). Significant interactions were found in the BP and age subgroups (all participants: age [*P* for interaction = 0.136] and BP [*P* for interaction = 0.016]; men: age [*P* for interaction = 0.593] and BP [*P* for interaction = 0.336]; women: age [*P* for interaction = 0.028] and BP [*P* for interaction = 0.035]; postmenopausal women: age [*P* for interaction = 0.028] and BP [*P* for interaction = 0.024]). Significant associations between the fourth METS-IR quartile and UACR years were found among all participants and women aged <65 years. The relationship between the third METS-IR quartile and UACR was also significant in women (55–64 years subgroup). However, among men, a significant association was only observed in men aged 55–64 years (OR 1.494, 95% CI 1.114–2.004, $P = 0.007$). Furthermore, we also analyzed the association between UACR and METS-IR in the BG subgroup. A significant association was found in all participants and men with critical BG levels and diabetes, whereas a significant association was only observed in women with diabetes (Tables 4 and 5). In addition, similar results were found according to BP, the risk of elevated UACR occurrence in the Q4 METS-IR group was increased in the prehypertension and hypertension groups among all participants and men. Among women, this risk was only increased in the hypertension group. We also explored the subgroup associations in postmenopausal and premenopausal women (Additional file 1), and the findings for postmenopausal women were similar to those for men.

To better explore the relationship between UACR and METS-IR according to the kidney function level, we divided the participants into three groups on the basis of eGFR (<60, 60–90 and ≥90 mL/min/1.73 m^2). When eGFR ≥90 mL/min/1.73 m^2, 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, $P < 0.001$).

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/

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	
All participants								0.136
Age (years)†								
<55 (*n* = 14,788)	1	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,<64 (*n* = 14,026)	1	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	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)‡								0.869
FBG <5.6 and PBG <7.8 (*n* = 15,996)	1	1.029 (0.886–1.196)	0.706	0.974 (0.836–1.135)	0.736	1.082 (0.946–1.239)	0.250	
5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1 (*n* = 15,837)	1	1.128 (0.953–1.336)	0.160	0.955 (0.832–1.095)	0.509	1.330 (1.121–1.578)*	0.001	
FBG ≥7.0 or PBG ≥11.1 (*n* = 5,457)	1	1.066 (0.780–1.457)	0.688	1.084 (0.871–1.349)	0.469	1.381 (1.025–1.698)*	0.038	
BP (mmHg)§								0.016
SBP <120 and DBP <80 (*n* = 11,520)	1	1.146 (0.955–1.376)	0.143	1.049 (0.865–1.272)	0.629	1.094 (0.939–1.275)	0.247	
120 ≤ SBP < 140 and/or 80 ≤ DBP < 90 (*n* = 14,145)	1	0.981 (0.820–1.175)	0.838	1.255 (0.686–1.565)	0.404	1.356 (1.165–1.579)*	<0.001	
SBP ≥140 or DBP ≥90 (*n* = 11,625)	1	1.069 (0.929–1.231)	0.351	1.127 (0.903–1.396)	0.302	1.282 (1.124–1.463)*	<0.001	
eGFR (mL/min/1.73 m^2)¶								0.120
eGFR ≥90 (*n* = 34,691)	1	1.088 (0.976–1.212)	0.128	1.037 (0.943–1.141)	0.449	1.289 (1.172–1.417)*	<0.001	
60 ≤ eGFR < 90 (*n* = 2,408)	1	1.189 (0.806–1.755)	0.384	0.959 (0.709–1.298)	0.788	1.042 (0.773–1.406)	0.785	
eGFR <60 (*n* = 191)	1	1.010 (0.989–1.032)	0.359	1.011 (0.960–1.065)	0.676	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							*P*-values for interaction
	Q1	Q2		Q3		Q4		
	Reference	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	
Men								
Age (years)†								0.593
<55 (*n* = 3,477)	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	
≥55,<64 (*n* = 4,361)	1	0.933 (0.631–1.381)	0.730	0.898 (0.652–1.236)	0.508	1.494 (1.114–2.004)*	0.007	
≥65 (*n* = 3,071)	1	1.053 (0.719–1.543)	0.791	1.111 (0.820–1.505)	0.496	1.113 (0.820–1.511)	0.494	
Blood glucose (mmol/L)‡								
FBG <5.6 and PBG <7.8 (*n* = 3,995)	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
5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1 (*n* = 4,797)	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	
FBG ≥7.0 or PBG ≥11.1 (*n* = 2,117)	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)§								0.336
SBP <120 and DBP <80 (*n* = 2,612)	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	
120 ≤ SBP < 140 and/or 80 ≤ DBP < 90 (*n* = 4,256)	1	1.500 (0.915–2.460)	0.108	1.069 (0.663–1.724)	0.784	1.635 (1.020–2.622)*	0.041	
SBP ≥140 or DBP ≥90 (*n* = 4,041)	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	
eGFR (mL/min/1.73 m^2)¶								0.116
eGFR ≥90 (*n* = 10,057)	1	0.991 (0.772–1.273)	0.943	0.939 (0.766–1.151)	0.544	1.316 (1.089–1.589)*	0.004	
60 ≤ eGFR < 90 (*n* = 792)	1	1.496 (0.588–3.804)	0.398	1.282 (0.690–2.384)	0.432	1.128 (0.620–2.051)	0.693	
eGFR <60 (*n* = 60)	1	1.001 (0.788–1.379)	0.688	0.941 (0.849–1.044)	0.254	1.005 (0.998–1.012)	0.168	
Women								
Age (years)								0.198
<55 (*n* = 11,814)	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	
≥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)‡								0.872
FBG <5.6 and PBG <7.8 (*n* = 12,837)	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	
5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1 (*n* = 9,368)	1	1.162 (0.962–1.403)	0.119	1.003 (0.858–1.171)	0.975	1.118 (0.853–1.465)	0.420	
FBG ≥7.0 or PBG ≥11.1 (*n* = 4,176)	1	1.162 (0.962–1.403)	0.119	1.003 (0.858–1.171)	0.975	1.630 (1.398–1.845)*	0.004	
BP (mmHg)								0.035
SBP <120 and DBP <80 (*n* = 8,908)	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	
120 ≤ SBP < 140 and/or 80 ≤ DBP < 90 (*n* = 9,889)	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	
SBP ≥140 or DBP ≥90 (*n* = 7,584)	1	1.055 (0.894–1.246)	0.524	1.182 (0.073–1.284)	0.220	1.242 (1.060–1.456)*	0.007	

Table 5. (*Continued*)

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		
eGFR (mL/min/1.73 m)²¶									
eGFR ≥90 (*n* = 24,634)	1	1.115 (0.989–1.258)	0.076	1.073 (0.963–1.026)	0.199	1.268 (1.135–1.417)*	<0.001	0.225	
60 ≤ eGFR < 90 (*n* = 1,616)	1	1.236 (0.799–1.914)	0.341	0.889 (0.620–1.275)	0.524	1.152 (0.806–1.646)	0.437		
eGFR <60 (*n* = 131)	1	1.051 (0.952–1.162)	0.325	1.294 (0.916–1.294)	0.143	1.258 (0.395–2.167)	0.468		

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. *Meaned *P*-value < 0.05. †Age subgroup: adjusted for 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, 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, centers, ALT, AST, GGT, LDL-C, TC, HbA1c, eGFR, WC, smoking habits, drinking habits and CVD status, diabetes history. ¶eGFR subgroup: adjusted for age, 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.

min/1.73 m^2. 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 m^2. Thus, early monitoring and treatment are essential for increased UACR, and alleviation of IR perhaps conduce 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[3,4], 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[18]. The role of BMI is debatable, as different studies have presented conflicting results[19,20]. 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 subhealth 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 subhealth 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[21]. 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)[22]. Similar findings of another study showed that the influence of lipid variability on unfavorable outcomes was greater in younger adults[23].

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[2]. It has a negative association with the risk of CVD, and is independent of sex and age[24]. Likewise, mortality risk ratios for coronary artery disease among men were halved between the age of 55–64 years and 65–74 years[25]. 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[26]. 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 group, 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[27] or that being male could be considered a risk for the disease[28]. 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[29]. 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[30]. Further evidence could come out in support of the role of endogenous estrogen in the metabolic homeostasis and the decrease of visceral lipid accumulation[31].

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[32]. 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[33]. Given that METS-IR has a particularly strong association with visceral adiposity compared with insulin-based indexes[3], it could be a predictor for ectopic lipid accumulation and visceral fat, which were confirmed risk factors for hypertension and CVD[34,35]. Furthermore, recent studies have proposed that visceral adiposity might be pivotally involved in UACR excretion, and albuminuria might be a manifestation of VAT[36,37].

It is presumptive that adiponectin's role in renal dysfunction might be an underlying factor of the association between albuminuria and VAT[38]. Elevated VAT and increased albuminuria have both been reported to have inverse associations with adiponectin[39,40]. 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[41]. 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[42–45]. 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.

REFERENCES

1. Amadi CE, Mbakwem AC, Kushimo OA, *et al*. Prevalence of positive chronic kidney Disease screening in professional male long haul drivers at risk of cardiovascular Disease in Lagos, Nigeria: a cross-section study. *BMC Public Health* 2019; 19: 1032.
2. Wada T, Haneda M, Furuichi K, *et al*. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. *Clin Exp Nephrol* 2014; 18: 613–620.
3. Bello-Chavolla OY, Almeda-Valdes P, Gomez-Velasco D, *et al*. METS-IR, a novel score to evaluate insulin sensitivity, is predictive of visceral adiposity and incident type 2 diabetes. *Eur J Endocrinol* 2018; 178: 533–544.
4. Eeg-Olofsson K, Gudbjörnsdottir S, Eliasson B, *et al*. The triglycerides-to-HDL-cholesterol ratio and cardiovascular disease risk in obese patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *Diabetes Res Clin Pract* 2014; 106: 136–144.
5. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005; 16: 2134–2140.
6. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes Endocrinol* 2014; 2: 634–647.
7. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive summary of the third report of the national cholesterol education program (ncep) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001; 285: 2486–2497.
8. Rana JS, Liu JY, Moffet HH, *et al*. Metabolic dyslipidemia and risk of coronary heart disease in 28,318 adults with diabetes mellitus and low-density lipoprotein cholesterol < 100 mg/dl. *Am J Cardiol* 2015; 116: 1700–1704.
9. Muntner P, Coresh J, Smith JC, *et al*. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int* 2000; 58: 293–301.
10. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014; 384: 626–635.
11. Mann JF, Yi QL, Gerstein HC, *et al*. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease. *Kidney Int Suppl* 2004; 92: S59–62.
12. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *Lancet* 2012; 380: 601.
13. Mykkänen L, Zaccaro DJ, Wagenknecht LE, *et al*. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: the insulin resistance atherosclerosis study. *Diabetes* 1998; 47: 793–800.
14. Bonora E, Formentini G, Calcaterra F, *et al*. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care* 2002; 25: 1135–1141.
15. Rader DJ. Effect of insulinresistance, dyslipidemia, andintra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Am J Med* 2007; 120: S12–18.
16. Borai A, Livingstone C, Ferns GA. The biochemical assessment of insulin resistance. *Ann Clin Biochem* 2007; 44: 324–342.
17. Ning G. Risk evaluation of cAncers in Chinese diabeTic individuals: a lONgitudinal (REACTION) study. *J Diabetes* 2012; 4: 172–173.
18. Ma Y-C, Zuo LI, Chen J-H, *et al*. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2937–2944.
19. Borg R, Kuenen JC, Carstensen B, *et al*. HbA1(c) and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. *Diabetologia* 2011; 54: 69–72.
20. Dittmann K, Hannemann A, Wallaschofski H, *et al*. U-shaped association between central body fat and the urinary

albumin-to-creatinine ratio and microalbuminuria. *BMC Nephrol* 2013; 17: 87.
21. Lin C-H, Chou C-Y, Lin C-C, *et al*. Waist-to-height ratio is the best index of obesity in association with chronic kidney disease. *Nutrition* 2007; 23: 788–793.
22. Nam GE, Han K, Kim DH, *et al*. Relationship between dyslipidemia and albuminuria in prediabetic adults: The Korea National Health and Nutrition Examination Survey 2011–2012. *Endocrine* 2015; 48: 557–565.
23. Silverwood RJ, Pierce M, Thomas C, *et al*. Association between younger age when first overweight and increased risk for CKD. *J Am Soc Nephrol* 2013; 24: 813–821.
24. Wan EYF, Yu EYT, Chin WY, *et al*. Greater variability in lipid measurements associated with cardiovascular disease and mortality: 10-year diabetes cohort study. *Diabetes Obes Metab* 2020; 22: 1777–1788.
25. Dale AC, Vatten LJ, Nilsen TI, *et al*. Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. *BMJ* 2008; 337: a236.
26. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999; 281: 1291–1297.
27. King DE, Carek P, Mainous AG, *et al*. Inflammatory markers and exercise: differences related to exercise type. *Med Sci Sports Exerc* 2003; 35: 575–581.
28. Holl RW, Grabert M, Thon A, *et al*. Urinary excretion of albumin in adolescents with type 1 diabetes: persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control. *Diabetes Care* 1999; 22: 1555–1560.
29. Jones CA, Krolewski AS, Rogus J, *et al*. Epidemic of end-stage renal disease in people with diabetes in the United States population: do we know the cause? *Kidney Int* 2005; 67: 1684–1691.
30. Maric C. Sex, diabetes and the kidney. *Am J Physiol Renal Physiol* 2009; 296: F680–688.
31. Cho D-H, Joo HJ, Kim M-N, *et al*. Association between epicardial adipose tissue, high-sensitivity C-reactive protein and myocardial dysfunction in middle-aged men with suspected metabolic syndrome. *Cardiovasc Diabetol* 2018; 17: 95.
32. Barros RP, Gustafsson JA. Estrogen receptors and the metabolic network. *Cell Metab* 2011; 14: 289–299.
33. Sandberg K. Mechanisms underlying sex differences in progressive renal disease. *Gend Med* 2008; 5: 10–23.
34. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 2014; 371: 1131–1141.
35. Mozaffarian D, Benjamin EJ, Go AS, *et al*. Heart diseaseand stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015; 131: e29–e322.
36. Abraham TM, Pedley A, Massaro JM, *et al*. Association between visceral and subcutaneous adipose depots and incident cardiovascular disease risk factors. *Circulation* 2015; 132: 1639–1647.
37. Hanai KO, Babazono T, Nyumura I, *et al*. Involvement of visceral fat in the pathogenesis of albuminuria in patients with type 2 diabetes with early stage of nephropathy. *Clin Exp* 2010; 14: 132–136.
38. Cnop M, Havel PJ, Utzschneider KM, *et al*. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 2003; 46: 459–469.
39. Hanley AJG, Bowden D, Wagenknecht LE, *et al*. Associations of adiponectin with body fat distribution and insulin sensitivity in nondiabetic Hispanics and African-Americans. *J Clin Endocrinol Metab* 2007; 92: 2665–2671.
40. Tsioufis C, Dimitriadis K, Chatzis D, *et al*. Relation of microalbuminuria to adiponectin and augmented C-reactive protein levels in men with essential hypertension. *Am J Cardiol* 2005; 96: 946–951.
41. Sharma K, RamachandraRao S, Qiu G, *et al*. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest* 2008; 118: 1645–1656.
42. Yudkin JS, Eringa E, Stehouwer CDA. "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 2005; 365: 1817–1820.
43. Mallamaci F, Tripepi G. Obesity and CKD progression: hard facts on fat CKD patients. *Nephrol Dial Transplant* 2013; 28: 105–108.
44. Stenvinkel P, Ketteler M, Johnson RJ, *et al*. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia–the good, the bad, and the ugly. *Kidney Int* 2005; 67: 1216–1233.
45. Foster MC, Hwang S-J, Massaro JM, *et al*. Association of subcutaneous and visceral adiposity with albuminuria: the framingham heart study. *Obesity* 2011; 19: 1284–1289.

SUPPORTING INFORMATION

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

Table S1