



BMJ Open Gender-specific and age-specific associations of the homoeostasis model assessment for IR (HOMA-IR) with albuminuria and renal function impairment: a retrospective cross-sectional study in Southeast China

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ABSTRACT

Objectives The study aimed to investigate the association of insulin resistance (IR), which was estimated by the homoeostasis model assessment for IR (HOMA-IR), with albuminuria and renal function impairment in a general Chinese population.

Design A retrospective cross-sectional study.

Setting and participants A total of 13 742 adults (age: ≥18 years) who underwent a health check-up at a hospital in Southeast China during 2013–2014 were enrolled. 216 subjects were excluded due to lack of enough fasting time, be pregnant, have chronic diseases influencing metabolic functions or have glomerulonephritis, renal cancer, kidney transplant. Eventually, 7552 men and 5974 women were included for the present analysis.

Primary outcome measures The association of HOMA-IR with albuminuria and renal function impairment were analysed. The HOMA-IR cut-off value for detecting albuminuria and renal function impairment were determined.

Results An increase in the HOMA-IR quartile was significantly associated with the prevalence of albuminuria and renal function impairment in all men and women aged >45 years. The multivariable logistic regression analyses revealed a significant association of the HOMA-IR with albuminuria and renal function impairment in subjects aged >45 years of the fourth quartiles compared with those of the first quartile after adjusting for potential confounders (albuminuria: men OR, 2.39; 95% CI 1.51 to 3.79, $p<0.001$; women OR, 2.40; 95% CI 1.44 to 4.01; $p=0.001$; renal function impairment: men OR, 2.30; 95% CI 1.50 to 3.51; $p<0.001$; women OR, 2.20; 95% CI 1.35 to 3.58; $p=0.002$). The optimal cut-off value of HOMA-IR for detecting albuminuria and renal function impairment was 2.69 in men aged ≤45 years, 1.60 in men aged >45 years and 1.86 in women aged >45 years.

Conclusions Our study revealed that HOMA-IR was significantly associated with albuminuria and renal function impairment in individuals aged >45 years.

Strengths and limitations of this study

- The study had large, population-based sample, which ensures the credibility of the results.
- This is the first study determining the homoeostasis model assessment of insulin resistance cut-off value by gender and age for detecting albuminuria and renal function impairment in the Chinese population.
- Because of the cross-sectional study design, the causal relationship between IR and renal function impairment could not be evaluated and determined.
- The patients were recruited from a health check-up programme, which might have led to selection bias.
- The blood samples from our participants were obtained only one time instead of three times according to our standard protocol, the method might influence the accuracy due to the pulsatility of insulin.

INTRODUCTION

Chronic kidney disease (CKD) is characterised by increased urinary albumin excretion and a reduced glomerular filtration rate (GFR). CKD is an important health issue worldwide and is associated with increased all-cause and cardiovascular mortality.¹ The worldwide all-age prevalence of CKD and all-age mortality rate from CKD has increased since 1990.²

Insulin resistance (IR) is a primary characteristic contributing to the pathophysiology of type 2 diabetes mellitus and is associated with harmful health outcomes such as cardiovascular disease, obesity, hypertension and dyslipidaemia.³ IR is defined as the reduced sensitivity of target organs to the biological effects of insulin, causing metabolic and haemodynamic alterations. Factors contributing to IR are obesity, race, sex, physical

activity and genetic factors. In addition, IR is associated with altered haemodynamic of cascading reactions in the kidney and has been observed in early non-diabetic CKD.⁴ On the other hand, it is hypothesised that the impairment of kidney functions leads to complex disturbances in glucose metabolism and consequently IR.⁵ Studies have repeatedly reported associations between IR and CKD of different stages.^{6–8}

The early stages of kidney disease are significantly more common (10–1000 times) in the population than renal failure.⁹ Early detection can facilitate appropriate diagnosis and treatment of patients with renal impairment. The GFR and albuminuria are the principal measurements to define and stage CKD and acute kidney disease.⁹ However, not every patient can have a comprehensive health examination including blood and urine test to detect the renal damage, especially in the primary medical clinic with fewer medical resources. In this situation, an easily evaluated surrogate which is associated to renal impairment and albuminuria will be helpful. The homoeostasis model assessment of IR (HOMA-IR) estimates IR from the serum insulin levels and fasting plasma glucose¹⁰ and has been validated to be a robust surrogate tool to evaluate IR in epidemiological researches or clinical settings.^{11–13} Many studies have indicated an association of IR with albuminuria and renal impairment.^{13–17} Although the HOMA-IR is widely used in studies, the cut-off value defining IR varies greatly by race. Furthermore, the age-specific and gender-specific differences in the HOMA-IR level were reported in previous study,¹⁸ suggesting the potential effects of age and gender on the accuracy of the HOMA-IR to identify patients with kidney dysfunction.

Considering the variability in the HOMA-IR level in different populations and the differences in the cut-offs by races, clinical measurements, characteristics and metabolic conditions of the population studied,¹² the present population-based study aimed to assess the HOMA-IR level in the Chinese population and to determine the gender-specific and age-specific differences in the association of the HOMA-IR quartiles with albuminuria and renal function impairment. In addition, we evaluated the cut-off value of HOMA-IR for detecting the presence of albuminuria and renal function impairment.

METHODS

Subjects and data collection

This cross-sectional study enrolled Chinese adults (age: ≥ 18 years) who underwent a health check-up at the Health Examination Centre of Xiamen Chang Gung Hospital, China, during 2013–2014. Well-trained nurses collected the data during the health examination using a standardised questionnaire, comprising questions on medical history, medication use and physiological conditions such as pregnancy and fasting time. Thereafter, nurses collected the venous blood samples of all participants and performed a detailed physical examination, which

included the measurements of body height, body weight, waist circumference (WC) and blood pressure (BP). We included all patients, except those who met any of the exclusion criteria listed below: (1) had fasted for less than 12 hours before blood sampling; (2) were pregnant; (3) had chronic diseases that may influence metabolic functions such as thyroid disease, cirrhosis, chronic hepatitis, adrenal gland disease and hypothalamus disorders; (4) had glomerulonephritis, renal cancer, kidney transplant; (5) incomplete data.

Laboratory measurements

Body weight and height were measured according to the standard protocol. WC was measured at the mid-point between the iliac crest and lowest rib. Body mass index (BMI) was defined as the body weight divided by the square of body height (kg/m^2). BP was measured three times using an automated sphygmomanometer after patients had rested for 15 min in the seated position. We averaged up to three measurements for systolic BP (SBP) and diastolic BP (DBP). The mean arterial pressure (MAP) was calculated using the following equation: $(2/3) \times \text{DBP} + (1/3) \times \text{SBP}$.¹⁹

Freshly urine samples were collected to measure the urinary albumin and creatinine levels by a biochemical test (UniCel Dx C 800 MA&CREA, Reagent) for calculating the spot urine albumin–creatinine ratios (ACRs). Clinical biochemistry tests included the measurement of fasting plasma glucose level using a modified hexokinase enzymatic assay (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, New Jersey, USA). The serum creatinine (SCr), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and urine creatinine levels were measured using a biochemical autoanalyzer (DxC 800, Beckman Coulter UniCel DxCSYNCHRON, Ireland). The fasting serum insulin level was measured by radioimmunoassay (RIA) using a double antibody batch method (Pharmacia Insulin RIA kit; Pharmacia Diagnostics, Uppsala, Sweden).

The SCr level ($1 \text{ mg}/\text{dL} = 88.4 \mu\text{mol}/\text{L}$) was used to calculate the estimated GFR (eGFR) using the modified Modification of Diet in Renal Disease equation for Chinese patients with CKD²⁰: $\text{eGFR} (\text{mL}/\text{min per } 1.73\text{m}^2) = 175 \times \text{SCr}^{-1.234} \times \text{age}^{-0.179} \times 0.79$ (if women). Renal function impairment was defined according to the definition of Kidney Disease Outcomes Quality Initiative as an eGFR of $< 60 \text{ mL}/\text{min}/1.73\text{m}^2$ or the presence of albuminuria ($\text{ACR}: \geq 30 \text{ mg}/\text{g Cr}$).²¹ To evaluate IR, the HOMA-IR level was calculated using the following equation: $(\text{fasting serum insulin } [\text{mIU}/\text{L}] \times \text{fasting plasma glucose } [\text{mmol}/\text{L}]) / 22.5$.¹⁰

Statistical analyses

Statistical analyses were conducted using SPSS V.21.0 (SPSS). Continuous variables are presented as medians and quartiles 1 and 3. Categorical variables are presented as number and percentage. Mann-Whitney U test and Kruskal-Wallis test were performed to compare continuous variables. χ^2 test

was performed to compare categorical variables. Participants were stratified into four groups according to quartiles of HOMA-IR values. Then the participants were classified by gender to examine the differences among the groups.

To identify the association of HOMA-IR with albuminuria and renal function impairment, multivariable logistic regression analyses were performed using two models (model 1: age, waist-to-height ratio (WHtR), and MAP; model 2: variables in model 1 plus TG and HDL-C) with clinical variables that were potentially associated with IR as the independent variables and ORs and 95% CI were calculated for the HOMA-IR quartiles. To analyse the effect of age on the accuracy of HOMA-IR for detecting the presence of albuminuria and renal function impairment, receiver operating characteristic (ROC) analysis was performed by age groups for men and women separately. The area under the ROC curve (AUC) was used to determine the discriminatory ability of HOMA-IR for detecting albuminuria and renal function impairment. The cut-off value for each AUC associated with the HOMA-IR value for detecting albuminuria and renal function impairment was established based on the Youden's index. All statistical analyses were two-sided. P value <0.05 was regarded statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 13 742 individuals were considered for enrolment. However, 216 of 13 742 individuals were excluded based on exclusion criteria. A total of 13 526 individuals (7552 (55.8%) men and 5974 (44.2%) women) were included in the analysis. The anthropometric and clinical characteristics of the study population are summarised in [table 1](#). The median ages of men and women in the study population were 45 and 46 years, respectively. Except for the albuminuria and renal function impairment, significant gender differences were found for the anthropometric and clinical characteristics (all $p < 0.05$). The BMI, WC, WHtR, BP, TG level, TG/HDL-C ratio, insulin level and HOMA-IR level were significantly higher and the HDL-C level and eGFR were significantly lower in men than in women.

The characteristics of the patients according to the HOMA-IR quartiles and age are presented in [tables 2 and 3](#). All variables, except age (in those aged ≤ 45 years), and eGFR (in those aged > 45 years), significantly differed among the quartile groups of men. In men, higher HOMA-IR quartile was significantly associated with higher prevalence of albuminuria and renal function impairment (all $p < 0.05$). Similar results were obtained for women. However, higher HOMA-IR quartile was significantly associated with higher prevalence of albuminuria and renal function impairment ($p < 0.05$) only in women aged > 45 years, but not in women aged ≤ 45 years.

Table 1 General clinical and metabolic characteristics of the study subjects (total n=13526)

Variables	Males	Females	P value
	(n=7552)	(n=5974)	
Age (years old)	45 (39, 53)	46 (39, 55)	0.004
BMI (kg/m ²)	24.46 (22.38, 26.53)	22.68 (20.66, 25.06)	<0.001
Waist circumference (cm)	87 (82.0, 93.0)	78 (72, 85)	<0.001
Waist-to-height ratio	0.52 (0.48, 0.55)	0.50 (0.46, 0.54)	<0.001
SBP (mm Hg)	120 (110, 132)	112 (101, 127)	<0.001
DBP (mm Hg)	75 (69, 83)	68 (61, 76)	<0.001
MAP (mm Hg)	90.33 (82.67, 99.33)	82.67 (74.67, 92.42)	<0.001
Fasting glucose (mmol/L)	5.22 (4.92, 5.64)	5.13 (4.84, 5.48)	<0.001
Total cholesterol (mmol/L)	5.21 (4.62, 5.85)	5.02 (4.42, 5.67)	<0.001
Triglycerides (mmol/L)	1.37 (0.93, 2.08)	0.88 (0.61, 1.32)	<0.001
HDL cholesterol (mmol/L)	1.14 (0.99, 1.33)	1.39 (1.18, 1.61)	<0.001
TG/HDL-C	1.21 (0.74, 1.98)	0.62 (0.40, 1.04)	<0.001
Insulin (mIU/L)	5.90 (4.20, 8.40)	5.70 (4.20, 7.90)	<0.001
HOMA-IR	1.42 (0.96, 2.08)	1.31 (0.93, 1.88)	<0.001
eGFR (mL/min/1.73m ²)	98.42 (87.34, 110.79)	118.18 (103.99, 137.72)	<0.001
Albuminuria, n (%)	392 (5.19%)	331 (5.54%)	0.37
Renal function impairment, n (%)	435 (5.76%)	342 (5.72%)	0.93

Values are expressed as medians and quartiles 1, quartiles 3.

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; SBP, systolic blood pressure; TG, triglycerides.



Table 2 Subjects' characteristics according to HOMA-IR quartiles for males by age (total N=7552)

Variables	Age ≤45 years old				Age >45 years old				P interaction for age in quartiles
	HOMA-IR		HOMA-IR		HOMA-IR		HOMA-IR		
	<0.96 (n=845)	0.96-1.42 (n=1023)	1.42-2.08 (n=1030)	>2.08 (n=1020)	<0.96 (n=1049)	0.96-1.42 (n=880)	1.42-2.08 (n=859)	>2.08 (n=846)	
Age (years old)	39 (35, 42)	40 (36, 43)	40 (36, 42)	40 (36, 42)	55 (50, 61)	54 (49, 59)	52 (48, 59)	52 (49, 59)	<0.001
BMI (kg/m ²)	21.86 (19.93, 23.85)	23.59 (21.97, 25.54)	25.28 (23.71, 26.97)	26.98 (25.25, 29.11)	22.25 (20.40, 23.91)	23.78 (22.22, 25.40)	25.11 (23.54, 26.80)	26.48 (24.84, 28.17)	<0.001
Waist circumference (cm)	80 (74, 84)	84 (80, 89)	89 (84, 93)	93 (89, 98)	82 (76, 86)	86 (82, 91)	90 (85, 94)	94 (89, 99)	<0.001
Waist-to-height ratio	0.47 (0.44, 0.50)	0.50 (0.47, 0.52)	0.52 (0.49, 0.55)	0.55 (0.52, 0.58)	0.49 (0.46, 0.52)	0.52 (0.48, 0.54)	0.53 (0.51, 0.56)	0.55 (0.53, 0.58)	<0.001
SBP (mm Hg)	113 (105, 123)	117 (108, 127)	120 (111, 131)	126 (116, 136)	117 (107, 131)	120 (109, 133)	123 (112, 136)	129.00 (116, 140)	<0.001
DBP (mm Hg)	71 (64, 77)	73 (67, 80)	76 (70, 83)	80 (73, 87)	72 (66, 81)	75 (69, 82)	77 (71, 85)	80.00 (73, 88)	<0.001
MAP (mm Hg)	84.67 (77.67, 92.00)	88 (81.33, 95.33)	91 (83.92, 98.75)	95 (87.33, 103.33)	88 (80, 96)	90 (82, 99)	93 (85, 102)	96.33 (87.33, 105.67)	<0.001
Fasting glucose (mmol/L)	4.84 (4.61, 5.09)	5.08 (4.82, 5.34)	5.21 (4.95, 5.52)	5.51 (5.16, 6.07)	5.05 (4.80, 5.31)	5.23 (4.95, 5.55)	5.40 (5.10, 5.87)	5.95 (5.39, 7.31)	<0.001
Total cholesterol (mmol/L)	4.90 (4.43, 5.52)	5.08 (4.52, 5.69)	5.21 (4.68, 5.85)	5.36 (4.84, 5.99)	5.13 (4.57, 5.68)	5.29 (4.69, 5.89)	5.29 (4.63, 5.96)	5.40 (4.67, 6.10)	<0.001
Triglycerides (mmol/L)	0.95 (0.69, 1.32)	1.25 (0.88, 1.85)	1.61 (1.09, 2.27)	1.96 (1.35, 2.94)	0.96 (0.69, 1.36)	1.29 (0.91, 1.90)	1.54 (1.11, 2.18)	1.81 (1.25, 2.68)	<0.001
HDL cholesterol (mmol/L)	1.28 [1.10, 1.50]	1.16 (1.01, 1.36)	1.11 (0.98, 1.26)	1.06 (0.94, 1.19)	1.27 (1.08, 1.49)	1.16 (1.01, 1.34)	1.09 (0.95, 1.27)	1.07 (0.94, 1.21)	<0.001
TG/HDL-C	0.74 (0.50, 1.12)	1.08 (0.71, 1.69)	1.42 (0.94, 2.21)	1.83 (1.19, 2.90)	0.75 (0.50, 1.18)	1.12 (0.72, 1.74)	1.46 (0.93, 2.20)	1.67 (1.13, 2.68)	<0.001
Insulin (mIU/L)	3.40 (2.80, 3.90)	5.20 (4.70, 5.70)	7.40 (6.70, 8.20)	10.90 (9.40, 13.40)	3.10 (2.50, 3.70)	5.00 (4.50, 5.60)	6.90 (6.20, 7.80)	10.40 (8.88, 12.70)	<0.001
HOMA-IR	0.75 (0.60, 0.86)	1.19 (1.08, 1.30)	1.73 (1.57, 1.89)	2.71 (2.33, 3.54)	0.72 (0.56, 0.85)	1.17 (1.06, 1.30)	1.70 (1.55, 1.88)	2.86 (2.41, 3.57)	<0.001
eGFR (mL/min/1.73m ²)	99.76 (89.71, 112.48)	100.71 (90.90, 112.65)	100.59 (90.45, 113.40)	102.41 (91.35, 115.02)	96.23 (84.46, 107.45)	94.57 (83.11, 107.42)	95.25 (83.48, 107.25)	95.55 (83.85, 108.97)	0.42
Albuminuria, n (%)	17 (2.01%)	24 (2.35%)	33 (3.20%)	77 (7.55%)	38 (3.62%)	39 (4.43%)	64 (7.45%)	100 (11.82%)	<0.001
Renal function impairment, n (%)	18 (2.13%)	26 (2.54%)	33 (3.20%)	78 (7.65%)	48 (4.58%)	51 (5.80%)	69 (8.03%)	112 (13.24%)	<0.001

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; SBP, systolic blood pressure; TG, triglycerides.

Table 3 Subjects' characteristics according to HOMA-IR quartiles for females by age (total N=5974)

Variables	Age ≤45 years old				Age >45 years old				P interaction for age in quartiles	
	HOMA-IR		HOMA-IR		HOMA-IR		HOMA-IR			
	<0.93 (n=799)	0.93-1.31 (n=802)	1.31-1.88 (n=711)	>1.88 (n=557)	<0.93 (n=718)	0.93-1.31 (n=681)	1.31-1.88 (n=778)	>1.88 (n=928)		
Age (years old)	38 (33, 42)	38 (33.75, 42)	39 (34, 42)	39 (35, 42)	53 (49, 59)	55 (50, 60)	54 (50, 59)	56 (50, 61)	<0.001	0.38
BMI (kg/m ²)	20.16 (18.80, 21.62)	21.11 (19.58, 22.66)	22.18 (20.31, 24.06)	23.83 (21.97, 25.96)	21.81 (20.23, 23.66)	23.09 (21.41, 24.87)	24.1 (22.36, 25.94)	25.94 (23.86, 27.88)	<0.001	0.31
Waist circumference (cm)	71 (67, 75)	73 (69, 78)	76 (71, 81)	80 (75, 85)	76 (71, 82)	80 (75, 86)	83 (78, 88)	87 (82, 93)	<0.001	0.18
Waist-to-height ratio	0.44 (0.42, 0.47)	0.46 (0.43, 0.49)	0.48 (0.44, 0.51)	0.50 (0.47, 0.54)	0.49 (0.45, 0.52)	0.51 (0.48, 0.55)	0.53 (0.50, 0.56)	0.56 (0.52, 0.59)	<0.001	0.12
SBP (mm Hg)	102 (95, 109)	104 (96, 111)	105 (99, 113)	110 (101, 122)	113 (103, 127)	121 (107, 137)	123 (110, 137)	129.00 (116, 144)	<0.001	<0.001
DBP (mm Hg)	63 (57, 69)	64 (59, 70)	64 (59, 71)	68 (61, 75)	67 (61, 75)	71 (64, 78)	72 (66, 81)	75.00 (67, 82)	<0.001	0.10
MAP (mm Hg)	76.00 (70.00, 81.67)	77.00 (71.67, 83.00)	78.00 (73.00, 84.67)	82.33 (75.00, 90.00)	82.33 (75.00, 92.00)	88.33 (78.33, 97.00)	89 (81, 100)	93.33 (84.67, 101.67)	<0.001	0.01
Fasting glucose (mmol/L)	4.79 (4.56, 5.03)	4.96 (4.72, 5.20)	5.09 (4.88, 5.36)	5.3 (5.03, 5.64)	4.97 (4.72, 5.22)	5.15 (4.90, 5.43)	5.32 (5.04, 5.60)	5.71 (5.30, 6.40)	<0.001	<0.001
Total cholesterol (mmol/L)	4.71 (4.19, 5.23)	4.69 (4.22, 5.19)	4.70 (4.17, 5.27)	4.83 (4.32, 5.37)	5.28 (4.64, 5.89)	5.30 (4.72, 5.99)	5.40 (4.75, 6.05)	5.36 (4.76, 6.04)	0.06	0.50
Triglycerides (mmol/L)	0.58 (0.44, 0.81)	0.68 (0.50, 0.90)	0.79 (0.57, 1.08)	1.05 (0.74, 1.45)	0.765 (0.57, 1.11)	0.96 (0.69, 1.32)	1.12 (0.80, 1.63)	1.39 (1.02, 2.01)	<0.001	<0.001
HDL cholesterol (mmol/L)	1.53 (1.35, 1.78)	1.48 (1.29, 1.67)	1.37 (1.18, 1.57)	1.26 (1.10, 1.45)	1.49 (1.30, 1.73)	1.41 (1.21, 1.62)	1.33 (1.15, 1.51)	1.22 (1.09, 1.41)	<0.001	0.11
TG/HDL-C	0.38 (0.26, 0.56)	0.46 (0.32, 0.64)	0.57 (0.40, 0.84)	0.86 (0.53, 1.25)	0.52 (0.36, 0.79)	0.67 (0.45, 1.02)	0.84 (0.56, 1.35)	1.13 (0.77, 1.75)	<0.001	0.002
Insulin (mIU/L)	3.40 (2.80, 3.90)	5.10 (4.70, 5.50)	6.80 (6.20, 7.50)	10.00 (8.90, 11.95)	3.30 (2.70, 3.70)	4.90 (4.50, 5.40)	6.60 (6.00, 7.20)	9.90 (8.50, 12.00)	<0.001	0.02
HOMA-IR	0.72 (0.59, 0.84)	1.12 (1.03, 1.22)	1.55 (1.42, 1.70)	2.32 (2.09, 2.86)	0.74 (0.60, 0.84)	1.13 (1.04, 1.22)	1.56 (1.43, 1.71)	2.57 (2.14, 3.24)	<0.001	<0.001
eGFR (mL/min/1.73m ²)	124.62 (110.53, 141.49)	122.54 (110.76, 143.59)	125.25 (111.39, 146.43)	126.62 (110.41, 147.18)	110.69 (98.71, 128.34)	110.32 (97.94, 128.60)	113.05 (99.74, 131.23)	111.94 (99.04, 130.28)	0.28	0.23
Albuminuria, n (%)	23 (2.88%)	19 (2.37%)	22 (3.09%)	20 (3.59%)	21 (2.92%)	40 (5.87%)	57 (7.33%)	129 (13.90%)	<0.001	0.003
Renal function impairment, n (%)	23 (2.88%)	19 (2.37%)	22 (3.09%)	20 (3.59%)	24 (3.34%)	41 (6.02%)	59 (7.58%)	134 (14.44%)	<0.001	0.003

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; SBP, systolic blood pressure; TG, triglycerides.

Table 4 Association between homoeostasis model assessment of insulin resistance quartiles and albuminuria

Variables	Crude		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Male						
≤45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.17 (0.62 to 2.19)	0.62	0.84 (0.44 to 1.60)	0.60	0.93 (0.48 to 1.80)	0.83
Quartile 3	1.61 (0.89 to 2.92)	0.11	0.75 (0.40 to 1.61)	0.37	0.80 (0.41 to 1.54)	0.50
Quartile 4	3.98 (2.33 to 6.78)	<0.001	1.21 (0.64 to 2.27)	0.56	1.24 (0.65 to 2.39)	0.51
>45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.23 (0.78 to 1.95)	0.37	1.12 (0.70 to 1.80)	0.63	1.10 (0.69 to 1.77)	0.68
Quartile 3	2.14 (1.42 to 3.23)	<0.001	1.83 (1.17 to 2.86)	0.01	1.77 (1.13 to 2.79)	0.01
Quartile 4	3.57 (2.43 to 5.24)	<0.001	2.54 (1.62 to 4.00)	<0.001	2.39 (1.51 to 3.79)	<0.001
Female						
≤45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	0.82 (0.44 to 1.52)	0.52	0.79 (0.42 to 1.48)	0.47	0.78 (0.42 to 1.47)	0.45
Quartile 3	1.08 (0.60 to 1.95)	0.81	0.97 (0.52 to 1.81)	0.93	0.94 (0.50 to 1.78)	0.85
Quartile 4	1.26 (0.68 to 2.31)	0.46	0.95 (0.48 to 1.91)	0.89	0.90 (0.43 to 1.86)	0.77
>45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	2.07 (1.21 to 3.55)	0.01	1.56 (0.90 to 2.70)	0.12	1.54 (0.88 to 2.67)	0.13
Quartile 3	2.62 (1.57 to 4.37)	<0.001	1.70 (1.00 to 2.89)	0.05	1.63 (0.96 to 2.78)	0.07
Quartile 4	5.36 (3.34 to 8.59)	<0.001	2.59 (1.56 to 4.30)	<0.001	2.40 (1.44 to 4.01)	0.001

Model 1: adjusted for age, waist-to-height ratio and mean arterial pressure.

Model 2: adjusted for the variables in model 1 plus triglycerides, high-density lipoprotein cholesterol.

Tables 4 and 5 present the association of HOMA-IR with albuminuria (ACR: ≥ 30 mg/g Cr) and renal function impairment. No significant association was found between HOMA-IR and albuminuria in individuals aged ≤ 45 years in the unadjusted model except men of the fourth quartile. In model 1 and model 2, a significant association was found in men of the third and fourth quartiles and women of the fourth quartiles. Similar association was found between HOMA-IR and renal function impairment for both men and women (table 5). After adjusting for potential confounders, a significant association was found between HOMA-IR and renal function impairment in individuals aged >45 years of the fourth quartiles compared with those of the first quartile (in model 2: men: OR, 2.30; 95% CI 1.50 to 3.51; $p < 0.001$; women: OR, 2.20; 95% CI 1.35 to 3.58; $p = 0.002$).

Table 6 summarises the AUC, sensitivities, and specificities for the HOMA-IR cut-off value for detecting albuminuria and renal function impairment. The HOMA-IR cut-off value, according to the Youden's index, for detecting both albuminuria and renal function impairment was 2.69 in men aged ≤ 45 years (AUC: 0.68 for albuminuria; AUC: 0.67 for renal function impairment; both

$p < 0.001$) and 1.60 in men aged >45 years (AUC: 0.65 for albuminuria; AUC: 0.63 for renal function impairment; both $p < 0.001$). The HOMA-IR was not statistically significantly associated with renal function impairment and albuminuria in women aged ≤ 45 years. The HOMA-IR cut-off value for detecting both albuminuria and renal function impairment in women aged >45 years was 1.86 (AUC: 0.67; $p < 0.001$). The HOMA-IR cut-off values for detecting albuminuria and renal function impairment were lower in men than in women aged >45 years.

DISCUSSION

This cross-sectional study adds to the growing evidence that the HOMA-IR is associated with albuminuria and renal function impairment. Our study has three main findings. First, an increase in the prevalence of albuminuria and renal function impairment was associated with an increase in the HOMA-IR quartile in all men and women age >45 years. Second, higher HOMA-IR quartile was associated with higher prevalence of albuminuria and renal function impairment in individuals age >45 years. Third, the optimal cut-off value of the HOMA-IR for detecting albuminuria and renal function

Table 5 Association between homoeostasis model assessment of insulin resistance quartiles and renal function impairment

Variables	Crude		Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Males						
≤45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.20 (0.65 to 2.20)	0.56	0.88 (0.47 to 1.64)	0.68	0.96 (0.50 to 1.81)	0.89
Quartile 3	1.52 (0.85 to 2.72)	0.16	0.73 (0.39 to 1.36)	0.32	0.77 (0.40 to 1.46)	0.42
Quartile 4	3.80 (2.26 to 6.41)	<0.001	1.22 (0.66 to 2.26)	0.53	1.24 (0.65 to 2.34)	0.51
>45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.28 (0.86 to 1.92)	0.23	1.22 (0.80 to 1.85)	0.36	1.18 (0.77 to 1.80)	0.44
Quartile 3	1.82 (1.25 to 2.66)	0.002	1.66 (1.10 to 2.51)	0.02	1.58 (1.04 to 2.40)	0.03
Quartile 4	3.18 (2.24 to 4.52)	<0.001	2.48 (1.63 to 3.76)	<0.001	2.30 (1.50 to 3.51)	<0.001
Females						
≤45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	0.82 (0.44 to 1.52)	0.52	0.79 (0.42 to 1.48)	0.47	0.78 (0.42 to 1.47)	0.45
Quartile 3	1.08 (0.60 to 1.95)	0.81	0.97 (0.52 to 1.81)	0.93	0.94 (0.50 to 1.78)	0.85
Quartile 4	1.26 (0.68 to 2.31)	0.46	0.95 (0.48 to 1.91)	0.89	0.90 (0.43 to 1.86)	0.77
>45 years old						
Quartile 1	Reference		Reference		Reference	
Quartile 2	1.85 (1.11 to 3.10)	0.02	1.38 (0.82 to 2.35)	0.23	1.36 (0.80 to 2.31)	0.25
Quartile 3	2.37 (1.46 to 3.86)	<0.001	1.55 (0.94 to 2.57)	0.09	1.48 (0.89 to 2.46)	0.13
Quartile 4	4.88 (3.12 to 7.62)	<0.001	2.38 (1.48 to 3.86)	<0.001	2.20 (1.35 to 3.58)	0.002

Model 1: adjusted for age, waist-to-height ratio and mean arterial pressure.

Model 2: adjusted for the variables in model 1 plus triglycerides, high-density lipoprotein cholesterol.

Table 6 The areas under receiver operating characteristic curve (AUC), sensitivity and specificity by the cut-off values for homoeostasis model assessment of insulin resistance in the detection of albuminuria and renal function impairment

Variables	AUC (95% CI)	P value	Cut-off point according to		
			Youden's index	Sensitivity	Specificity
Males					
≤45 years old					
Albuminuria	0.68 (0.63 to 0.72)	<0.001	2.69	0.42	0.88
Renal function impairment	0.67 (0.62 to 0.72)	<0.001	2.69	0.41	0.88
>45 years old					
Albuminuria	0.65 (0.62 to 0.69)	<0.001	1.60	0.61	0.63
Renal function impairment	0.63 (0.60 to 0.67)	<0.001	1.60	0.58	0.63
Females					
≤45 years old					
Albuminuria	0.54 (0.47 to 0.61)	0.19	1.15	0.67	0.44
Renal function impairment	0.54 (0.47 to 0.61)	0.19	1.15	0.67	0.44
>45 years old					
Albuminuria	0.67 (0.64 to 0.71)	<0.001	1.86	0.54	0.71
Renal function impairment	0.67 (0.63 to 0.70)	<0.001	1.86	0.54	0.71

impairment was lower for men aged >45 years than for men aged ≤45 years (1.60 vs 2.69). The optimal cut-off value of the HOMA-IR for detecting albuminuria and renal function impairment was estimated to be 1.86 for women aged >45 years; however, no satisfactory cut-off value could be determined for women aged ≤45 years in this study population.

The prevalence of albuminuria and renal function impairment in our study population was lower than that reported in a recent national survey in China (5.35% vs 9.5% for albuminuria; 5.74% vs 11.6% for renal function impairment).²² The findings might be because that our participants were recruited from a health check-up programme, who were relatively healthy population.

In this study, we found significant differences among the HOMA-IR quartiles groups of all men and women aged >45 years for the prevalence of albuminuria and renal function impairment. Our result is similar to those reported in previous studies, which demonstrated that HOMA-IR is associated with CKD and albuminuria.^{17,23–25} Two studies involving Korean patients reported that an increase in the HOMA-IR tertile or quintile was associated with the development of albuminuria.^{23,24} According to the third National Health and Nutrition Examination Survey (NHANES III) in the United States, the prevalence of CKD was significantly and progressively increased with an increase in the HOMA-IR level in middle-aged individuals without diabetes in the USA.¹⁷

In our study, no significant association was found between the HOMA-IR and the prevalence of albuminuria and renal function impairment in women aged ≤45 years. Previous studies have reported gender-specific association between the HOMA-IR and the ACR.^{16,25} Utsunomiya found that microalbuminuria is associated with the HOMA-IR only in Japanese men with central obesity and not in Japanese women.²⁵ Another study in Caucasian patients with type 2 diabetes indicated that a significant association existed between the ACR and the HOMA-IR in men but not in women.¹⁶ These aforementioned studies suggested that the involvement of sex hormones might be associated with the pathogenesis of albuminuria and IR. The factors that may contribute to the sex difference in renal diseases include direct effects of sex hormones on cellular processes and metabolism, lifestyle factors such as tobacco use, hypertension control and dietary habits, differences in the glomerular and renal haemodynamics between the sexes.²⁶

Previous studies have also reported age-specific and gender-specific differences in HOMA-IR levels in a Spanish population without diabetes.^{18,27} A Spanish study²⁷ investigated the effects of age and gender on the HOMA-IR cut-off value to discriminate the cardiometabolic risk and suggested that the HOMA-IR cut-off value should be estimated separately for different age groups because of the non-linear effect of age on the accuracy of the HOMA-IR, especially in women. The authors concluded that changes in body fat distribution after menopause increase the gender-specific differences in women aged >50 years.¹⁸

The potential mechanisms linking IR and clinical outcomes remain incompletely understood; moreover, risk factors associated with IR, such as obesity, sedentary lifestyle

and unhealthy diet,²⁸ are highly prevalent in patients with CKD. The decline in renal function in CKD is associated with the development of IR, and IR is an independent risk factor for mortality in patients with CKD.²⁹ Nevertheless, the exact causal relationships between IR and CKD are poorly defined.^{30,31} IR can occur early in CKD³²; however, the presence of IR may not be apparent in patients with CKD because it can occur in the absence of diabetes and obesity. Previous studies investigated the effects of insulin on cells in the kidney and reported that glomerulosclerosis results from IR in podocytes,³³ systemic inflammation³⁴ and nitric oxide release in vascular endothelial cells.³⁵

The strength of our study is the large, population-based sample, which ensures the credibility of the results. Compared with other studies participants enrolled from patients who visit hospitals or clinics with illness, the characteristics of our participants were closer to the characteristics of general population. This is the first study determining the HOMA-IR cut-off value by gender and age for detecting albuminuria and renal function impairment in the Chinese population. Some limitations should be considered. First, the causal relationship between IR and renal function impairment could not be evaluated and determined because of the cross-sectional study design. Second, the patients were recruited from a health check-up programme, which might lead to selection bias. Third, the blood samples from our participants were obtained only one time instead of three times according to our standard protocol, the method might influence the accuracy due to the pulsatility of insulin. Fourth, because our participants were individuals who underwent a health check-up, information on confounders such as physical activity, dietary factors and socioeconomic status was not collected in the standardised questionnaire because these items were not compulsory to fill in.

CONCLUSIONS

Our results reveal that the prevalence of albuminuria and renal function impairment increase with an increase in the HOMA-IR quartile in all men and women age >45 years. Significant association was found between the HOMA-IR and albuminuria or renal function impairment in individuals aged >45 years. The optimal cut-off value of the HOMA-IR for detecting albuminuria and renal function impairment is 2.69 in men aged ≤45 years, 1.60 in men aged >45 years and 1.86 in women aged >45 years. The gender-specific and age-specific HOMR-IR cut-off values can be used as an effective measurement tool to detect albuminuria and renal function impairment in a general population. Careful evaluation and early intervention for renal function decline should be considered in individuals with a higher HOMA-IR value.

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