Albuminuria: Prevalence, associated risk factors and relationship with cardiovascular disease

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ABSTRACT

Aims/Introduction: To investigate the prevalence and associated risk factors of micro-albuminuria, and to explore the relationship between albuminuria and cardiovascular disease (CVD).

Materials and Methods: A nationally representative sample of 38,203 Chinese participants was categorized by different levels of urinary albumin-to-creatinine ratio (ACR; 0–10 mg/g, 10–20 mg/g, 20–30 mg/g, 30–300 mg/g). The prevalence of albuminuria was compared by using a single urinary ACR cut-off point and by sex-specific ACR cut-off points. Factors associated with the presence of albuminuria, and the relationship between albuminuria and CVD were analyzed by logistic regression.

Results: Prevalence of albuminuria as measured by a single ACR cut-point was significantly lower for men compared with women (13.9% vs 19.1% in the normal glucose tolerance group; 20.8% vs 26.8% in the impaired glucose tolerance group, $P < 0.01$). The prevalence of albuminuria, as measured by sex-specific ACR cut-points, was higher for men than women (31.4% vs 29.6% in the normal glucose tolerance group; 42.2% vs 39.3% in the impaired glucose tolerance group, $P < 0.01$). The independent risk factors for the presence of albuminuria were aging, female sex, hypertension, hyperglycemia, obesity, dyslipidemia, insulin resistance and metabolic syndrome. The subdivided normal ACR group did not show a linear or statistically significant relationship with CVD after adjusting for conventional CVD risk factors ($P > 0.05$).

Conclusions: The prevalence of albuminuria was high in the general Chinese population. Aging, female sex, hypertension, hyperglycemia, dyslipidemia, insulin resistance, obesity and metabolic syndrome were all independent risk factors for albuminuria. The causal relationship between ACR and CVD might require further follow-up investigation.

INTRODUCTION

Chronic kidney disease (CKD) is highly prevalent worldwide, and is now recognized as a global public health problem with adverse outcomes of kidney failure, cardiovascular diseases and premature death[1,2]. In the USA and Australia, 11–16% of the general population has CKD[3,4]. Studies from Europe have shown a similar high prevalence of CKD in the general population[5]. CKD is also highly prevalent in developing countries[6,7]. Based on a nationwide survey in China[8], the prevalence of

CKD was 10.8%, but awareness of CKD among the survey participants was just 12.5%. Given the high prevalence and the low awareness of CKD, identifying and treating the risk factors for early CKD might be the best approach to prevent or delay adverse outcomes.

Microalbuminuria is an early marker of CKD and vascular dysfunction, and is associated with end-stage renal disease, and cardiovascular mortality and morbidity in both the high-risk and general population[9-11]. The reference method to measure urinary albumin excretion is 24-h urine collection. This is impractical for a large-scale population-based survey. A commonly used substitute is the urinary albumin-to-creatinine ratio (ACR; ACR ≥30 mg/g indicating microalbuminuria; first morning specimen preferred), which is recommended by the National Kidney Foundation[12]. However, this definition of microalbuminuria does not take into account sex differences in creatinine excretion, which have been advocated by Warram et al.[13] Furthermore, several studies have shown the continuous relationship between ACR values and increased cardiovascular risk[14-17]. Thus, the definition of ACR above 30 mg/g as albuminuria might be arbitrary.

The present study, based on a nationally representative sample of Chinese participants, first compared the differences in metabolic disorders within the microalbuminuria (ACR 30–300 mg/g) group and the further subdivided normalbuminuria group. Then we examined the risk factors related to the presence of albuminuria, and the relationship between albuminuria levels and cardiovascular disease (CVD). We also analyzed how the use of a single ACR cut-point vs sex-specific ACR cut-points, measured in a first-morning urine sample, affects the estimated prevalence of microalbuminuria.

MATERIALS AND METHODS

The data we used in the current study were from the China National Diabetes and Metabolic Disorders Study, which was a cross-sectional survey of Chinese adults from June 2007 to May 2008. The study population and design have been described in detail previously[18]. We used a multistage sampling design in this survey. First, a total of 152 cities and 112 counties were selected from around the country based on geographical distribution, economic development, and urbanization. Then individuals who had been residents for more than 5 years were randomly chosen from each region. Exclusion criteria in the present study were as follows: (i) subjects with incomplete demographic information and missing data (mainly regarding fasting/2-h glucose and urinary ACR); (ii) subjects with a previous diagnosis of diabetes or CKD; (iii) subjects with clinical evidence of urinary tract infection; and (iv) subjects with albuminuria above 300 mg/g. The total number of participants selected in the survey was 38,203.

The study protocol was approved by an institutional review board or an independent ethics committee at each participating institution. Informed written consent was requested from each subject before data collection.

Data Collection

Study participants were interviewed privately, face-to-face by trained interviewers using standard questionnaires. Information on demographics, education, lifestyle risk factors, and medical and drug history was collected. Questions related to the diagnosis and treatment of diabetes, hypertension, dyslipidemia and cardiovascular events were included. Anthropometric measures including weight, height, waist circumference (WC) and blood pressure were obtained according to a standard protocol.

After a minimum 10 h of fasting overnight, all participants without known diabetes underwent a standard oral glucose tolerance test (75 g anhydrous glucose in 250 mL water) at each examination. Fasting plasma glucose (FPG), fasting insulin, 2-h plasma glucose (2hPG) and insulin were measured. Blood samples for glucose measurements were taken in sodium fluoride tubes. Plasma glucose was analyzed using the hexokinase enzymatic method. Insulin was measured by radioimmunoassay using a specific antibody. Homeostasis model assessment (HOMA) was used to evaluate the islet β-cell function. Urinary albumin and creatinine were measured from a fresh morning spot urine sample stored at 4°C for <1 week. Urinary albumin was measured with immunoturbidimetric tests. Urinary creatinine was measured with Jaffe's kinetic method. The urinary ACR was calculated to determine the categories for different levels of albuminuria. Serum total cholesterol (TC), triglycerides (TG), and low- and high-density lipoprotein cholesterol (LDL-C, HDL-C) were determined with enzymatic methods.

All of the laboratory data were measured at the clinical biochemical laboratories in each province. Each study laboratory successfully completed a standardization and certification program.

Diabetes Assessment

The World Health Organization (1999) diagnostic criteria were used to classify participants into different categories of glucose intolerance as follows: normal glucose tolerance (NGT; FPG <6.1 mmol/L, 2hPG <7.8 mmol/L); isolated impaired fasting glucose (I-IFG; FPG ≥6.1 mmol/L, but <7.0 mmol/L, 2hPG <7.8 mmol/L); isolated impaired glucose tolerance (I-IGT; FPG <6.1 mmol/L, 2hPG ≥7.8 mmol/L, but <11.1 mmol/L); IFG/IGT (FPG ≥6.1 mmol/L, but <7.0 mmol/L, 2hPG ≥7.8 mmol/L, but <11.1 mmol/L); and newly diagnosed type 2 diabetes mellitus (FPG ≥7.0 mmol/L, 2hPG ≥11.1 mmol/L, and no history of diabetes). Impaired glucose regulation (IGR) was defined as either IFG or IGT.

Definition of Other Variables

We defined microalbuminuria[12] as a urinary ACR of 30–300 mg/g. We also used sex-specific ACR cut-points, proposed by Rong Xu et al.[13,19], 14 mg/g and 20 mg/g for men and women as the normal upper limit of ACR.

The prevalence of albuminuria was compared by using different diagnosis criteria of metabolic syndrome (MS) in the present study. According to the criteria of the Chinese Diabetes

Society (CDS) in 2007[20], MS could be diagnosed if three or more of the following abnormalities were present: (i) central obesity (WC ≥90 cm for men or ≥85 cm for women); (ii) elevated plasma glucose (FPG ≥6.1 mmol/L or 2hPG ≥7.8 mmol/L) or previously diagnosed diabetes mellitus; (iii) elevated blood pressure (≥130/85 mmHg or current treatment for hypertension) or previously diagnosed hypertension; (iv) elevated TG (TG ≥1.7 mmol/L); and (v) reduced HDL-C (<1.04 mmol/L). The International Diabetes Federation (IDF) criteria of MS[21] used central obesity (WC ≥90 cm for South Asian men or ≥80 cm for South Asian women) as a mandatory criterion, and the presence of at least two of the following four criteria: (i) TG ≥1.7 mmol/L; (ii) HDL-C < 1.0 mmol/L (40 mg/dL) for men or <1.29 mmol/L (50 mg/dL) for women; (iii) blood pressure ≥130/85 mmHg or receiving drug treatment; and (iv) FPG ≥5.6 mmol/L (100 mg/dL).

Hypertension was diagnosed as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, or receiving antihypertensive therapy for diagnosed hypertension[22].

Dyslipidemia was defined as: (i) elevated TC ≥5.18 mmol/L; (i) elevated TG ≥1.70 mmol/L; (iii) reduced HDL-C < 1.04 mmol/L; (iv) elevated LDL-C ≥ 3.37 mmol/L; or (v) drug treatment for lipid abnormality[20].

Although the homeostasis model assessment of insulin resistance (HOMA-IR) has been widely used, its cut-off for insulin resistance (IR) has not been conclusive[23,24]. In the present study, from a group of NGT participants without obesity or hypertension or dyslipidemia, we selected the 75th percentile value 1.79 as the cut-off point to define IR. This point is consistent with the that reported by Esteghamati *et al.*[24]

Statistical Analysis

All participants were categorized by different levels of ACR (0 – 10 mg/g, 10 –20 mg/g, 20 –30 mg/g, 30 –300 mg/g). Multivariate analyses of variance and χ^2-tests were used to examine differences in means and proportions, respectively. For continuous variables that do not follow normal distribution, natural logarithmic transformation was applied before analyzing. Data presented as mean ± standard error for continuous variables with normal distribution, interquartile range for continuous variables with highly skewed distribution, and as percentages for categorical variables. The variables age, sex, glucose tolerance status, hypertension, dyslipidemia, body mass index (BMI; or abdominal obesity), insulin resistance, cardiovascular or cerebrovascular disease (CVD) history, diabetes mellitus family history (DMFH) and MS, explored as categorical variables, were included as potential variables in the backwards stepwise logistic regression model to determine associations with albuminuria. The adjusted odds ratio (OR) of CVD was also calculated for the different groups based on ACR levels. A two-sided *P*-value < 0.05 was considered as statistically significant. Statistical analyses were carried out using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The present study analyzed 38,203 participants, including 15,003 men and 23,200 women, with an average age of 44.5 ± 13.5 years. The total prevalence of albuminuria was 19.5% (16.4% in men, 21.7% in women) according to a single ACR cut-point, and 33.3% (34.8% in men, 32.3% in women) according to sex-specific cut-points. Table 1 shows the clinical characteristics of study participants divided according to the ACR levels (0 –10 mg/g; 10 –20 mg/g; 20 –30 mg/g; 30 – 300 mg/g). Participants with higher ACR levels tended to be older, women, and with increased blood glucose, BMI, WC, SBP, DBP, TC, TG, LDL-C, HOMA-IR, and uric acid. Participants in the higher-ACR level group were also more likely to have abnormal glucose metabolism or diabetes, hypertension, dyslipidemia, obesity, insulin resistance and CVD history.

In the NGT group, the median, fifth and 95th percentile values of ACR were 8.6 mg/g, 1.6 mg/g and 74.0 mg/g for men, and 11.7 mg/g, 2.0 mg/g and 87.8 mg/g for women. In the IGR group, those values of ACR were 11.0 mg/g, 1.9 mg/g and 103.7 mg/g for men, and 14.5 mg/g, 2.5 mg/g and 113.1 mg/g for women (participants with BMI values above the 99th percentile and below the 1st percentile in both groups were excluded from the analyses). In both groups, women had a higher age-adjusted ACR than men (*P* < 0.05). Figures 1 and 2 show the differences in the frequency of albuminuria by using a single ACR cut-point, and by using sex-specific ACR cut-points in the NGT and IGR groups. The sex-specific ACR cut-points were lower for both men and women (14 mg/g for men and 20 mg/g for women). Thus, the use of sex-specific ACR cut-points increased the total prevalence of microalbuminuria. Results showed the prevalence of albuminuria was higher in men than in women.

Factors associated with the presence of albuminuria were explored by multiple logistic regression analysis (Table 2). Age, sex, glucose tolerance status, dyslipidemia, hypertension, BMI (or central obesity), IR, HOMA-β cell function index (HBCI), uric acid, previous CVD and DMFH were entered as independent variables in the model. Results showed that older age (≥70 years, odds ratio [OR] 2.07, 95% confidence interval [CI] 1.65 –2.60; age 60 –70 years, OR 1.48, 95% CI 1.24 –1.77 vs age 20 –30 years), women (OR 1.7, 95% CI 1.55 –1.87 vs men), hypertension (OR 1.89, 95% CI 1.71 –2.10 vs no hypertension), hyperglycemia (IFG/IGT, OR 1.56, 95% CI 1.20 –2.04; newly diagnosed diabetes mellitus, OR 1.56, 95% CI 1.32 –1.84 vs NGT) and BMI (≥28 kg/m², OR 1.43, 95% CI 1.26 –1.62 vs BMI <24 kg/m²) were the greatest significant contributors to risk of albuminuria. Other factors (for example, IGT, dyslipidemia, insulin resistance, central obesity), although statistically significant, explained successively smaller proportions of the deviance and contributed little to the overall predicted risk. MS was also an independent risk factor for developing albuminuria, and the adjusted OR was 1.86 (95% CI 1.67 –2.07, *P* = 0.000)

Table 1 | Characteristics of the total study group

	ACR (mg/g)			
	0–10	10–20	20–30	30–300
n	17,564	9,423	3,765	7,451
Men (%)	45.49	35.02*	33.60*	32.86*†
Age (years)	43.3 (0.10)	44.6 (0.14)*	45.5 (0.22)*†	47.2 (0.16)*†‡
FPG (mmol/L)	5.17 (0.01)	5.22 (0.01)*	5.36 (0.02)*†	5.49 (0.01)*†‡
2hPG (mmol/L)	6.36 (0.03)	6.56 (0.03)*	6.95 (0.05)*†	7.21 (0.03)*†‡
FINS (mU/L)§	7.0 (5.0–9.6)	7.0 (5.0–9.7)	7.4 (5.3–10.2)*†	7.8 (5.5–10.7)*‡
2hPINS (mU/L)§	25.2 (14.8–42.8)	27.0 (15.8–45.8)	29.7 (17.2–50.7)*†	30.6 (18.0–53.7)*†
HBCI§	93.8 (63.8–142.1)	91.2 (61.9–140.2)	92.3 (61.8–144.5)*†	92.9 (60.8–140.5)
HOMA-IR§	1.57 (1.11–2.21)	1.58 (1.12–2.27)	1.69 (1.18–2.48)*†	1.79 (1.24–2.63)*†‡
BMI (kg/m^2)	23.87 (0.03)	24.13 (0.04)*	24.39 (0.06)*†	24.87 (0.05)*†‡
WC (cm)	81.61 (0.08)	82.17 (0.11)*	82.72 (0.17)*†	83.91 (0.12)*†‡
TC (mmol/L)	4.68 (0.01)	4.71 (0.01)*	4.79 (0.02)*†	4.80 (0.12)*†
TG (mmol/L)	1.50 (0.01)	1.54 (0.01)*	1.61 (0.02)*†	1.74 (0.01)*†‡
HDL-C (mmol/L)	1.33 (0.00)	1.34 (0.00)	1.34 (0.01)	1.33 (0.00)
LDL-C (mmol/L)	2.76 (0.01)	2.75 (0.01)	2.77 (0.02)	2.79 (0.01)*†
SBP (mmHg)	119.9 (0.13)	122.5 (0.19)*	124.4 (0.30)*†	127.4 (0.21)*†‡
DBP (mmHg)	77.2 (0.08)	78.8 (0.12)*	79.8 (0.19)*†	81.4 (0.13)*†‡
UA (umol/L)	221.3 (1.53)	218.8 (2.28)	232.5 (3.75)*†	236.5 (2.75)*†
HOMA-IR (%)				
>1.79(75th percentile)	39.26	40.16	45.43*†	49.91*†‡
IGR (%)	13.80	15.74*	18.51*†	20.14*†‡
DM (%)	4.60	6.04*	8.84*†	11.37*†‡
Dyslipidemia (%)	53.58	54.41	57.21*†	61.11*†‡
Hypertension (%)	21.11	27.66*	34.1*†	41.84*†‡
Overweight/obesity (%)				
CDS criteria	24.32	27.09*	31.14*†	35.56*†‡
IDF criteria	33.63	38.74*	42.36*†	48.24*†‡
MS (%)				
CDS criteria	15.36	18.26*	23.37*†	30.27*†‡
IDF criteria	21.01	25.61*	30.15*†	38.08*†‡

Data shown are mean (standard error) for normal distribution variables, interquartile notation for non-normal distribution variables, and proportions for categorical variables. *Versus albumin-to-creatinine ratio (ACR) 0–10 mg/g; †versus ACR 10–20 mg/g; ‡versus ACR 20–30 mg/g, $P < 0.05$, adjusted for age and sex. 2hPG, 2-h plasma glucose; 2hPINS, 2-h plasma insulin; BMI, body mass index; CDS, Chinese Diabetes Society; DBP, diastolic blood pressure; DM, diabetes mellitus; FINS, fasting insulin; FPG, fasting plasma glucose; HBCI, homeostasis model assessment of β-cell function index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance index; IDF, International Diabetes Federation; IGR, impaired glucose regulation; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, uric acid; WC, waist circumference. §Natural log transformation was applied before analyzing.

by CDS criteria and 1.59 (95% CI 1.45–1.75, $P = 0.000$) by IDF criteria.

Table 3 shows the prevalence and odds ratio of CVD according to the ACR levels. There was a graded relationship between the ACR level and the CVD prevalence. Compared with the ACR level 0-10 mg/g, the age and sex adjusted OR of CVD was 1.21 (95% CI 1.02–1.43, $P = 0.033$) for the ACR level 10–20 mg/g, 1.21 (95% CI 0.97–1.52, $P = 0.096$) for the ACR level 20–30 mg/g and 1.31 (95% CI 1.11–1.56, $P = 0.002$) for the ACR level ≥30 mg/g. However, the further MS adjusted OR of CVD showed little statistical significance. After adjusting other CVD risk factors (2hPG, LDL-C, DBP, HOMA-IR, WC), the statistical significance did not exist.

DISCUSSION
Microalbuminuria is an early sign of progressive cardiovascular and renal disease. Many epidemiological investigations for albuminuria have been carried out[8,25]. The National Health and Nutrition Examination Survey[25] showed age-standardized prevalence of albuminuria of 11.0% and 14.3% for men and women in the USA, respectively. A recent national survey in China reported that albuminuria prevalence was 9.4% in the general population[8]. The overall prevalence of albuminuria (ACR ≥30 mg/g) in the present study was 19.5%, much higher than that in the previous study. Several factors could contribute to this inconsistency, such as different characteristics of participants, racial/ethnic difference[26], diurnal fluctuation in albumin
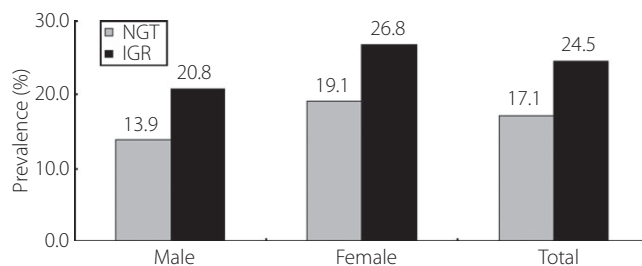
Figure 1 | Distribution of albuminuria in non-diabetes population. A single albumin-to-creatinine ratio cut-point is defined as albumin-to-creatinine ratio ≥30 mg/g. IGR, impaired glucose regulation; NGT, normal glucose tolerance.
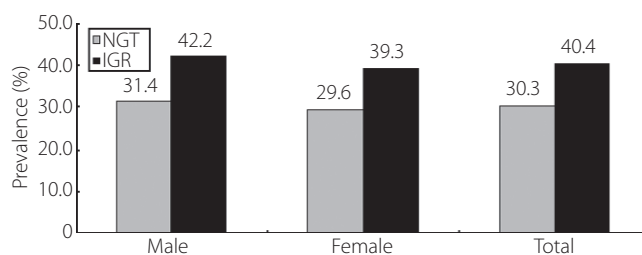

Figure 2 | Distribution of albuminuria in non-diabetes population. The sex-specific albumin-to-creatinine ratio cut-point is defined as albumin-to-creatinine ratio ≥14 mg/g for men and ≥20 mg/g for women. IGR, impaired glucose regulation; NGT, normal glucose tolerance.

Table 2 | Risk factors associated with presence of albuminuria (albumin-to-creatinine ratio 30 –300 mg/g)

	n	Albuminuria (%)	OR (95% CI)	P
Sex				
Men	15,003	16.4	1	0.000
Women	23,200	21.7	1.7 (1.55 –1.87)	
Age (years)				
20 –30	6,041	15.3	1	
30 –40	8,762	16.9	0.96 (0.81 –1.13)	0.583
40 –50	9,549	18.8	0.99 (0.84 –1.15)	0.928
50 –60	8,104	20.7	1.14 (0.97 –1.34)	0.124
60 –70	4,297	26.6	1.48 (1.24 –1.77)	0.000
>70	1,450	33.2	2.07 (1.65 –2.60)	0.000
Glucose status				
NGT	29,543	17.3	1	
IFG	1,254	19.9	1.14 (0.86 –1.50)	0.363
IGT	3,994	24.6	1.19 (1.03 –1.36)	0.016
IFG/IGT	855	31.5	1.56 (1.20 –2.04)	0.001
Newly diagnosed DM	2,557	33.1	1.56 (1.32 –1.84)	0.000
Hypertension				
No	27,489	15.8	1	0.000
Yes	10,714	29.1	1.89 (1.71 –2.10)	

Table 2 (Continued)

	n	Albuminuria (%)	OR (95% CI)	P
Dyslipidemia				
No	16,958	17.1	1	0.000
Yes	21,245	21.4	1.18 (1.08 –1.30)	
Insulin resistance				
No	20,202	17.1	1	0.015
Yes	14,749	23.4	1.13 (1.02 –1.24)	
BMI (kg/m²)				
<24	19,999	16.3	1	
24 –28	12,502	21.0	1.17 (1.06 –1.30)	0.002
≥28	5,611	27.5	1.43 (1.26 –1.62)	0.000
CVD				
No	37,265	19.3	1	0.107
Yes	938	27.3	1.22 (0.96 –1.57)	
Central obesity				
No	27,494	17.4	1	0.001
Yes	10,622	24.9	1.19 (1.07 –1.31)	
MS (CDS)*				
No	30,650	17.0	1	0.000
Yes	7,553	29.9	1.86 (1.67 –2.07)	
MS (IDF)*				
No	28,128	16.4	1	0.000
Yes	10,075	28.2	1.59 (1.45 –1.75)	

Odds ratio and P-value after mutually adjustment for multiple risk factors. *Adjusted for age, sex, cardiovascular disease (CVD) and diabetes mellitus family history. BMI, body mass index; CDS, Chinese Diabetes Society; CI, confidence interval; DM, diabetes mellitus; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OR, odds ratio.

excretion[27], and difference in collection, handling, storage and laboratory conditions[28]. A survey[29] carried out among general practitioners in nine European countries found that repeated tests were requested by 45% –77% of patients if the first test was positive, with considerable variations described in the type of samples tested and reported measurement units. Results from the National Health and Nutrition Examination Survey[25] also highlight differences in national prevalence estimates for albuminuria. In that survey, overall, just 43.5% of adults with increased ACR (>30 mg/g) in a random urine sample also had increased ACR in a repeated morning urine test. The first and second screening results within 3 months of ACR had 69.2 –73.3% concordance according to studies[30,31] in Asia. These studies show that screening and diagnosis of albuminuria should be made more practicable, addressing issues such as type of samples, measurement units and repeat tests. As a single-screening design tends to produce a higher prevalence estimate, it might be reasonable that at least two of the three urinary collections were carried out in a 3 –6 month period because of the variability in albumin excretion[31].

Concerns have been expressed that the commonly cited 30 mg/g as "normal" might not be appropriate for patients of

Table 3 | Prevalence and odds ratio of cardiovascular disease in different albumin-to-creatinine ratio groups

ACR (mg/g)	n	CVD (%)	OR (95%CI)*	P	OR (95% CI)†	P	OR (95% CI)‡	P
0–10	17,564	1.89	1	0.013	1	0.134	1	0.521
10–20	9,423	2.47	1.21 (1.02–1.43)	0.033	1.19 (1.00–1.41)	0.054	1.14 (0.94–1.39)	0.195
20–30	3,765	2.79	1.21 (0.97–1.52)	0.096	1.16 (0.92–1.46)	0.204	1.12 (0.86–1.45)	0.412
30–300	7,451	3.40	1.31 (1.11–1.56)	0.002	1.19 (1.00–1.42)	0.046	1.13 (0.92–1.37)	0.244

*Adjusted for age and sex. †Adjusted for age, gender and metabolic syndrome. ‡Mutually adjusted for multiple risk factors: age, sex, and other cardiovascular disease (CVD) risk factors (2-h plasma glucose, low-density lipoprotein cholesterol, diastolic blood pressure, homeostasis model assessment of insulin resistance, wait circumference). ACR, albumin-to-creatinine ratio; CI, confidence interval; OR, odds ratio.

all ages, sexes and ethnicities[27]. Several studies have showed that the relationship between urinary excretion of albumin and CVD mortality is linear and not categorical, which is already apparent at levels of albuminuria currently considered to be normal[14–17]. An 8-year follow-up study[14] showed that compared with the albumin excretion rate (AER) ≤10 mg/24 h group, the ORs for any cardiovascular end-point were 1.9 (95% CI 0.8–2.5, $P = 0.22$) and 9.8 (95% CI 6.7–12.3, $P = 0.001$) for the AER 10.1–20 mg/24 h group and 20.1–30 mg/24 h group, respectively. Urinary albumin concentration (UAC) increasing from 5 to 10 mg/L or 20 to 40 mg/L was associated with a 1.29-fold higher risk for cardiovascular death, and the 2-year cumulative incidence of cardiovascular death was 0.12% for UAC of 3.8 mg/L and 0.15% for UAC of 9.8 mg/L[16]. Another prospective study[17] also found that participants with urinary ACR (UACR) in the higher quartiles (UACR of 5.4–10.2 mg/g for men and 7.6–12.9 mg/g for women; UACR of 10.2–30 mg/g for men and 12.9–30 mg/g for women) had 41% and 72% greater risks of all CVD incidence, and 118% and 199% greater risks of death as a result of CVD than those in the lowest quartile (UACR of 0–2.7 mg/g for men and 0–4.3 mg/g for women). A high prevalence of CVD for urinary ACR within the normal range was also found in the present study, although the OR for CVD showed little or no statistical significance after adjusting for the conventional CVD risk factors. As the present study was a cross-sectional survey, the causal relationship between albuminuria and CVD could not be made.

The current definition of microalbuminuria as an ACR level between 30 and 300 mg/g in both men and women in a random urine specimen does not take into account sex differences in creatinine excretion. Creatinine is a metabolic byproduct of skeletal muscle creatine and phosphocreatine metabolism, and is thus lower in subjects with lower muscle mass, such as women or the elderly[32]. In the present study, the higher frequency of microalbuminuria among women, defined by an ACR >30 mg/g, is in part as a result of lower urine creatinine concentrations. The reported sex-specific ACR reference value (the 95th percentile) in a healthy Beijing population was 14 mg/g (1.58 mg/mmol) for men and 20 mg/g (2.26 mg/mmol) for women[19]. This value is much lower than that of the 95th percentile in the present study, which was 74 mg/g for men and 87.8 mg/g for women in the NGT group. The

discrepancy might be related to the different inclusion criteria for healthy participants. The present study analyzed the total NGT group (only excluding BMI above the 95th percentile and below the 1st percentile), which did not exclude subjects with hypertension, dyslipidemia, CVD, obesity or underweight condition, as well as those with an estimated glomerular filtration rate >200 mL/min/1.73 m^2 or <60 mL/min/1.73 m^2. As standardizing urinary ACR could underestimate microalbuminuria in subjects with higher muscle mass (men) or overestimate it in subjects with lower muscle mass (women), future research studies that use the ACR to define microalbuminuria should use sex-specific ACR cut-points to help avoid this potential problem. According to the present study, the sex-specific prevalence of albuminuria increased obviously in both the NGT and the IGR groups. Studies have shown that lowering of albuminuria, started at an early phase, was associated with better renal and cardiovascular outcomes with and without diabetes[33–35]. The higher albuminuria prevalence no doubt would increase the burden of healthcare. Thus, results from prospective studies should be used to define the risk of abnormal urinary albumin excretion by sex, and by different levels of ACR. Besides, cut-off levels should also be defined depending on the cost-effectiveness of screening for albuminuria and treatment to lower albuminuria in an attempt to prevent CVD and CKD.

The present study re-affirms previous observations[1,3,4,8,36,37] that aging, female sex, IGT, IR, hypertension, obesity, dyslipidemia, history of CVD and MS are independent risk factors for the presence of albuminuria. Therefore, although cost-effectiveness studies of intervention for albuminuria in the general population are still required[38], it seems sensible to implement early screening strategies for the prevention and treatment of albuminuria in subjects with high-risk factors for albuminuria.

The present study had the strength of being a large, national cohort. However, it had several limitations. First, albuminuria was estimated based on a single urine specimen and, as we aforementioned, the variability in albumin excretion might lead to overestimation of the prevalence of albuminuria. We do not have the ability to confirm the increased ACR results because of financial and energy issues. Additionally, the cross-sectional design of the present study makes it difficult to infer a causal relationship between albuminuria and associated factors or

CVD. A follow-up study is required to determine the factors and outcomes involved in the development of albuminuria. Furthermore, the lack of availability of serum creatinine to further indicate severity of renal dysfunction was also a limitation.

In summary, the prevalence of albuminuria is high in the general Chinese population. Aging, female sex, hypertension, hyperglycemia, dyslipidemia, IR, central obesity and MS are all independent risk factors. In light of the high rate of albuminuria, a screening strategy for the early recognition of CKD should be launched to prevent further progression, and education strategies for awareness of CKD among those high-risk populations should be developed. Before this, efforts are required to standardize urine collection methods and the sex-specific reference system. In addition, further follow-up studies would assist our understanding of the natural history and outcomes of albuminuria in the general population, as well as the determinants for development of albuminuria.

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