

# High-normal urinary albumin-to-creatinine ratio is independently associated with metabolic syndrome in Chinese patients with type 2 diabetes mellitus: A cross-sectional community-based study

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## Keywords

Metabolic syndrome, Type 2 diabetes mellitus, Urinary-to-albumin creatinine ratio

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## ABSTRACT

**Aims/Introduction:** Microalbuminuria is positively related to metabolic syndrome (MetS). Our aim was to investigate whether urinary albumin-to-creatinine ratio (UACR) within the normal range is independently associated with MetS in Chinese community-based patients with type 2 diabetes.

**Materials and Methods:** A total of 514 participants (206 males and 308 females; mean age 66 years) with UACR less than 3.5 mg/mmol were enrolled from two downtown areas of Shanghai. The participants were stratified into quartiles according to UACR levels. The prevalence of MetS was assessed and compared among the four groups by binary logistic regression.

**Results:** Compared with participants with UACRs in the first quartile, the other quartiles had a higher prevalence of MetS (65.9%, 74.4% and 81.3%, respectively,  $P = 0.001$ ) after adjustment for sex and age. After adjusting for potential confounders, participants in the second to the fourth quartile group had a 1.36-, 1.84- and 2.73-fold risk of MetS, respectively, relative to those in the lowest quartile. Furthermore, UACR, whether as quartile groups or as a continuous variable, is an independent predictor of MetS after fully adjusting for other variables.

**Conclusions:** These results suggest that UACR even within the normal range is independently associated with MetS in Chinese community-based patients with type 2 diabetes mellitus.

## INTRODUCTION

Microalbuminuria, usually used to evaluate chronic kidney disease and diabetic nephropathy, has been recognized as a major risk factor for cardiovascular morbidity and mortality in recent decades<sup>1,2</sup>. Recently, several studies have reported that albumin-

uria, even below the microalbuminuria threshold, was independently correlated with cardiovascular events<sup>2,3</sup>, but some scholars argued that the prognostic significance of normoalbuminuria on cardiovascular diseases was lost after adjustment for traditional risk factors<sup>4,5</sup>, which has made the association of normoalbuminuria with cardiovascular diseases become a controversial issue.

Metabolic syndrome (MetS), a disorder of energy utilization and storage, is an independent risk factor of cardiovascular

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diseases<sup>6</sup>. The relationship of microalbuminuria with MetS has been investigated in several studies<sup>7–9</sup>. Recent studies showed that albuminuria within the normal range is positively associated with MetS and several of its related components in hypertensive individuals and diabetic patients<sup>10,11</sup>. However, the data regarding this association in Chinese individuals is extremely limited.

Therefore, in the present study, we investigated the relationship between albuminuria below the microalbuminuria threshold with MetS in a Chinese community-based population of type 2 diabetes mellitus patients to further verify that the association between albuminuria within the normal range and MetS is a common phenomenon in other populations.

## MATERIALS AND METHODS

### Study Participants

We used the data from our previous study, and the study details have been well-described<sup>12</sup>. In brief, 1,039 Chinese patients diagnosed with type 2 diabetes mellitus were recruited from a random sample of 20 residential areas in two downtown areas of Shanghai, China, between February and July 2004. After excluding those who did not have a physical and laboratory examination (21 participants), two of three UACR tests greater than 3.5 mg/mmol (492 participants) and suffered from kidney disease or other diseases contributing to proteinuria (12 participants), 514 individuals (206 males and 308 females), between the ages of 32 and 88 years (mean age  $66 \pm 11$  years), were enrolled into our present analysis. The study was carried out with pre-approval from the institution review board of the HuaShan Hospital, and all the participants provided written informed consent.

### Physical Examination and Laboratory Testing

The physical and laboratory examinations used in the present study have been described previously<sup>13</sup>. The glomerular filtration rate (eGFR) was assessed by the simplified Modification of Diet in Renal Disease formula:  $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$  ( $\times 0.742$  if female)<sup>14</sup>. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: (fasting plasma glucose [mmol/L]  $\times$  fasting serum insulin [mU/L])  $\times 22.5$ <sup>15</sup>. Normoalbuminuria was defined as two of three UACR measurements less than 3.5 mg/mmol within a period of 3 months<sup>16</sup>.

### Definition of MetS

MetS was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian-Americans<sup>17</sup>, by the presence of  $\geq 3$  items of the following components: (i) waist circumferences  $\geq 90$  cm for men or  $\geq 80$  cm for women; (ii) triglycerides  $\geq 1.7$  mmol/L or specific treatment for lipid abnormality; (iii) high-density lipoprotein cholesterol level  $< 1.03$  mmol/L for men or  $< 1.30$  mmol/L for women or special treatment for lipid abnormality; (iv) blood pressure  $\geq 130/85$  mmHg or a history of hypertension; or (v) fasting plasma glucose (FPG)  $\geq 5.6$  mmol/L or previously diagnosed type 2 diabetes mellitus.

### Statistical Analyses

SPSS 15.0 software (SPSS, Chicago, IL, USA) was used for all statistical analyses. Normally distributed variables were given as the mean  $\pm$  standard deviation, and one-way ANOVA with least significant difference was utilized to compare differences among the four groups. Skewed variables were expressed as the median (interquartile range), and the Kruskal–Wallis test was applied to examine differences in the four groups. Categorical variables were represented as absolute numbers (percentages) by the  $\chi^2$ -test. Binary logistic regression analysis was carried out to explore the relationship between UACR and MetS.  $P < 0.05$  (two-sided) was considered to be statistically significant.

## RESULTS

### Participant Characteristics According to UACR Quartiles

The patients were divided into four groups according to the cut-off points of the UACR quartiles. From the lowest quartile to the highest quartile, the range of UACR was  $\leq 1.08$ , 1.08–1.53, 1.53–2.16 and  $> 2.16$  mg/mmol. Table 1 shows the basal clinical and laboratory characteristics for both sexes combined based on UACR quartile groups. Age, body mass index, the history of hypertension, systolic blood pressure and diastolic blood pressure gradually increased with the increment of UACR quartiles (all  $P < 0.05$ ) even after adjustment of age and sex. Significant differences in high-density lipoprotein cholesterol and eGFR were also noticed among UACR quartiles (all  $P < 0.05$ ). Nevertheless, there was no significance among the four groups for other metabolic risk factors after adjusting age and sex.

### Prevalence of MetS Among UACR Quartiles

The prevalence of MetS among the quartiles of UACR is shown in Figure 1. The prevalence of MetS was different, and successively 57.8%, 65.9%, 74.4% and 81.3% across the quartiles of UACR after adjustments for age and sex ( $P$  for trend = 0.001; Figure 1a). Strikingly, participants in the third and the highest quartiles showed a significantly higher incidence of MetS vs those in the lowest quartile ( $P = 0.008$  and  $< 0.001$ , respectively).

The prevalence of MetS was further studied in each quartile group of UACR divided by age or sex. As shown in Figure 1c, the prevalence of MetS had a significant sex-related difference in the fourth UACR quartile, rather than the other three quartiles after adjustment for age. In contrast, no remarkable differences were observed between middle-aged (age  $< 65$  years) and old-aged (age  $\geq 65$  years) patients in each quartile group after adjusting for sex (Figure 1d).

### Association Between UACR and MetS

Table 2 shows the association of UACR according to quartiles and as a continuous variable with MetS. A significant association was shown between the increase of UACR quartiles and MetS after controlling for age, sex, smoking, drinking, duration of diabetes and family history of diabetes ( $P = 0.001$  and

**Table 1** | Clinical characteristics of the participants

Variables	1st Quartile (n = 128)	2nd Quartile (n = 129)	3rd Quartile (n = 129)	4th Quartile (n = 128)	P-value	P-value*
UACR range (mg/mmol)	≤1.08	1.08–1.53	1.53–2.16	>2.16		
AGE (years)	62 ± 11	65 ± 10	67 ± 11	68 ± 9	<0.001	<0.001
Male, n (%)	55 (43.0)	58 (45.0)	44 (34.1)	49 (38.3)	0.282	0.282
Duration of diabetes (years)†	5 (2–9)	6 (3–10)	5 (2–10)	7 (3–11)	0.019	0.260
The history of diabetes, n (%)	59 (46.1)	53 (41.1)	51 (39.5)	52 (40.6)	0.719	0.973
Self-reported CVD, n (%)	26 (20.3)	21 (16.3)	30 (23.3)	25 (19.5)	0.572	0.583
Smoking, n (%)	30 (23.4)	31 (24.0)	31 (24.0)	19 (14.8)	0.203	0.090
Alcohol, n (%)	10 (7.8)	20 (15.5)	17 (13.2)	18 (14.1)	0.270	0.165
BMI (kg/m <sup>2</sup> )	24.09 ± 2.91	24.70 ± 3.09	24.84 ± 3.39	25.06 ± 3.12	0.081	0.014
Waist circumference (cm)†	82 (77–88)	84 (78–90)	86.6 (78.5–93)	84 (78–91.8)	0.026	0.060
Hypertension, n (%)	67 (52.3)	70 (54.3)	72 (55.8)	99 (77.3)	<0.001	<0.001
SBP (mmHg)†	130 (115–142)	140 (120–153)	140 (130–150)	140 (132–160)	<0.001	<0.001
DBP (mmHg)†	80 (70–90)	80 (75–90)	80 (70–90)	84 (80–90)	<0.001	<0.001
FPG (mmol/L)	8.16 ± 2.90	8.51 ± 3.24	8.77 ± 3.30	8.35 ± 2.61	0.443	0.397
2 h PPG (mmol/L)	13.82 ± 5.73	13.96 ± 5.40	14.17 ± 5.37	14.52 ± 5.07	0.752	0.163
HbA1c (%)	6.9 ± 1.6	7.1 ± 1.7	7.1 ± 1.6	6.9 ± 1.2	0.756	0.673
HOMA-IR†	3.20 (2.07–5.96)	4.16 (2.39–7.37)	4.92 (2.58–7.85)	4.08 (2.43–6.80)	0.048	0.488
Scr (μmol/L)	66.51 ± 14.72	67.07 ± 14.61	66.01 ± 16.53	65.09 ± 15.37	0.762	0.376
eGFR (mL/min/1.73 m <sup>2</sup> )	98.95 ± 26.57	102.36 ± 25.36	98.98 ± 26.70	101.70 ± 23.54	0.594	0.026
TC (mmol/L)†	5.04 ± 0.85	5.43 ± 1.03	5.19 ± 0.95	5.10 ± 1.01	0.007	0.676
TG (mmol/L)	1.50 (1.02–2.12)	1.62 (1.21–2.45)	1.49 (1.03–1.95)	1.65 (1.04–2.08)	0.473	0.419
HDL-C (mmol/L)†	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.55)	1.2 (1.0–1.4)	0.449	0.046
LDL-C (mmol/L)	2.87 ± 0.64	3.14 ± 0.76	2.98 ± 0.78	2.90 ± 0.81	0.019	0.652

2 h PPG, 2 h postprandial plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine; Self-reported CVD, self-reported cardiovascular diseases (including stroke and coronary heart disease); TC, total cholesterol; TG, triglyceride; UACR, urine albumin-to-creatinine ratio. Values are presented as mean ± standard deviation, median with interquartile range or percentages. P-value: The P-values were not adjusted for age and sex for the trend. \*P-value: The \*P-values were adjusted by sex and age for the trend †Non-normal distribution of continuous variables.

$P = 0.001$ , respectively; model I and model II). In model III and model IV, the increased UACR quartiles still remained as a significant predictor for MetS even after controlling other clinical indicators ( $P = 0.002$  and  $P = 0.008$ , respectively). Furthermore, compared with the participants in the first UACR quartile, those in the other three quartiles had successively a 1.36-, 1.84- and 2.73-fold risk of MetS after adjustment for various risk factors. Likewise, the UACR value within the normal range was also independently related to MetS from model I to model IV.

When all the patients were grouped according to the number of MetS components, a trend in increasing UACR level accompanying increased numbers of MetS-related components was observed (Figure 1b). The mean values of UACR for those with one to five components were 1.26, 1.49, 1.68, 1.77 and 1.75 mmol/L, respectively, after adjustment for age, sex, alcohol drinking, smoking, duration of diabetes, self-reported cardiovascular diseases and a family history of diabetes.

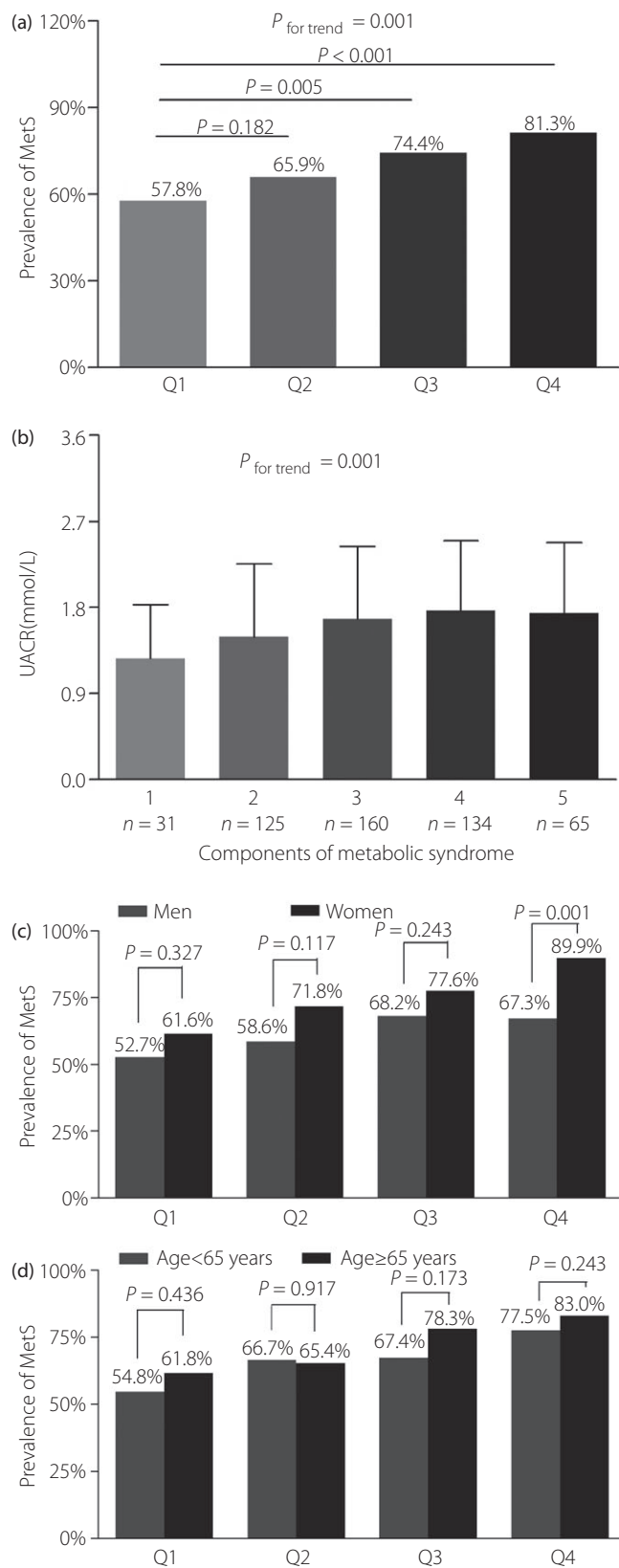
## DISCUSSION

Our current study found that higher normal UACR was remarkably associated with MetS in Chinese community-based

patients with type 2 diabetes mellitus. Furthermore, the normal range of UACR, whether as quartile groups or as a continuous variable, remained a significant predictor of MetS after adjusting for a variety of lifestyle and biochemical risk factors.

A positive relationship of microalbuminuria with the increased incidence of MetS has been well elucidated in hypertensive subjects, type 2 diabetic patients and the general population<sup>7–9</sup>, but it was not until recently that the association of albuminuria within the normal range with MetS was paid much attention. The Randomized Olmesartan and Diabetes Microalbuminuria Prevention study<sup>10</sup> showed that subjects with MetS had remarkably higher albumin excretion rates than subjects without MetS in normoalbuminuric type 2 diabetic patients. Patel *et al.*<sup>18</sup> have also reported that UACR >7 mg/g could be useful as an associated sign of the presence of MetS in women with polycystic ovary syndrome. Furthermore, significantly higher-normal albuminuria levels were observed by Vysoulis *et al.*<sup>11</sup> as the number of MetS components rose in 6,650 patients with essential hypertension.

Early identification and prevention is of great magnitude for MetS because of its contribution to the development and progression of cardiovascular diseases<sup>19,20</sup>. Therefore, we investi-



**Figure 1** | (a) Comparison of the prevalence of metabolic syndrome (MetS) among urinary albumin-to-creatinine ratio (UACR) quartiles. The  $P$ -value for four group comparisons was 0.001. (b) Differential UACR level among participants with MetS-related components.  $P = 0.001$  for trend of elevated UACR level with increasing number of MetS-related components. (c) Comparison of the prevalence of MetS stratified by sex among three groups after adjusting for age. The  $P$ -value for four group comparisons in men and women was 0.336 and 0.005, respectively. (d) Comparison of the prevalence of MetS stratified by age among the four groups after adjusting for sex. The  $P$ -value for the four group comparisons in middle-aged people and old-aged people was 0.131 and 0.014.

gated the association between UACR below the microalbuminuria threshold and MetS in community-based patients with type 2 diabetes.

The 69.8% prevalence of MetS in our Chinese community-based patients with type 2 diabetes mellitus was very close to those reported in South Indian (73.3%) and Nepalese (71%) type 2 diabetic patients<sup>21,22</sup>. In agreement with the present results, Vyssoulis *et al.*<sup>11</sup> and Oh *et al.*<sup>23</sup> also showed that elevated urine albumin excretion within the normal range can reflect an increasing prevalence of MetS in patients with essential hypertension and in the healthy Korean men, respectively. In the present study, women showed a higher prevalence of MetS than men in each UACR quartile, and a significant difference between men and women was shown in the highest UACR quartile. This can be explained by the fact that men did exercise more frequently than women, were prone to a greater intensity level of sports, and being physically active was associated with a lower odds ratio of MetS relative to physically inactive subjects<sup>24,25</sup>. In addition, higher body mass index, and systolic and diastolic blood pressure might be larger contributors to the significant difference in the fourth UACR quartile rather than the other quartiles<sup>26</sup>. Different peak incidence in different samples, such as the fourth to fifth decade for a highly endogamous population<sup>27</sup> and the seventh decade for Omani adults<sup>28</sup>, accounted for no sex-adjusted statistical significance between middle-aged and old-aged patients in each UACR quartile, although the prevalence of MetS generally increased with age<sup>29</sup>.

Consistent with the data from the Shanghai JiaDing study<sup>30</sup>, we found that the odds ratio of MetS increased steadily across UACR quartiles in patients with type 2 diabetes mellitus. In addition, we found that as a continuous variable, elevated UACR value even below the microalbuminuria threshold was significantly associated with MetS. To our knowledge, this is the first time that the relationship between UACR in the normal range and MetS has been comprehensively investigated based on UACR analyzed by quartiles and as a continuous variable.

The present study had clinical significance, as we found that higher UACR even below the microalbuminuria threshold was

**Table 2** | Association of urinary albumin-to-creatinine ratio according to quartile groups and as a continuous variable with metabolic syndrome by binary logistic regression

	Quartile groups for UACR, OR (95%CI)				<i>P</i> for trend	UACR as a continuous variable		<i>P</i> -value
	Q1	Q2	Q3	Q4		OR	95% CI	
Model I	1	1.44 (0.86–2.40)	2.03 (1.19–3.47)	3.14 (1.77–5.57)	0.001	1.717	1.303–2.262	<0.001
Model II	1	1.52 (0.91–2.56)	2.06 (1.20–3.54)	3.34 (1.87–5.97)	<0.001	1.728	1.309–2.282	<0.001
Model III	1	1.48 (0.88–2.50)	2.00 (1.15–3.45)	2.99 (1.67–5.36)	0.002	1.650	1.246–2.186	<0.001
Model IV	1	1.36 (0.80–2.32)	1.84 (1.05–3.21)	2.73 (1.50–4.94)	0.007	1.164	1.083–1.250	0.008

CI, confidence interval; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio. Analyzed using binary logistic regression analysis. Model I, adjusted for age and sex. Model II, adjusted for age, sex, smoking, alcohol, duration of diabetes and family history of diabetes. Model III, adjusted for age, sex, smoking, alcohol, duration of diabetes, family history of diabetes, estimated glomerular filtration rate, glycated hemoglobin and homeostatic model assessment of insulin resistance. Model IV, adjusted for age, sex, smoking, alcohol, duration of diabetes, family history of diabetes, estimated glomerular filtration rate, glycated hemoglobin, homeostatic model assessment of insulin resistance, body mass index and low-density lipoprotein cholesterol.

remarkably related to MetS, which suggested that UACR might be an important risk factor of MetS, although the relationship of microalbuminuria and MetS has been investigated in several studies<sup>7–9</sup>. The common underlying mechanisms including renin–angiotensin system activation, resultant oxidant stress, and inflammation between albuminuria and MetS could strongly explain why albuminuria, even within the normal range, remains a strongly independent indicator for MetS<sup>31,32</sup>. Indeed, the present study also showed that subjects in the higher UACR quartile group had higher levels of systolic blood pressure and diastolic blood pressure, closely associated with renin–angiotensin system activation, compared with subjects in the lower UACR quartile group.

Our findings provide further evidence to support the assumption that UACR, even in the normal range, could predict the occurrence of MetS. However, as a cross-sectional study, there were several limitations we recognized in the present study. First, the number of participants in our study was relatively small. Hence, prospective studies are required in a larger sample to further clarify the relationship between low-grade albuminuria and MetS. Second, we did not investigate medications of the participants, and therefore, we could not eliminate the possible effect of medications for the present findings. Third, the samples we studied in our article were diabetic patients, thus the prevalence of MetS among this sample was indeed higher than that among the general population. In addition, the definition of MetS in diabetic patients was also a little artificial. However, according to the definition of MetS, not all patients with diabetes suffered from MetS, whereas some other patients presented isolated diabetes<sup>17</sup>. Finally, the higher UACR quartile had a higher percentage of more MetS components, but we tackled with this bias by adjusting relative clinical indicators, such as age, sex, smoking, alcohol, duration of diabetes, family history of diabetes, eGFR, glycated hemoglobin, HOMA-IR, body mass index and low-density lipoprotein. In addition, the fact that higher prevalence could be related to more

components in the fourth quartile had also truly reflected the relationship of UACR and MetS. Our data (Table 2) also showed that higher UACR was associated with the prevalence of MetS, which suggested that UACR not only exhibited the prevalence of MetS, but also the severity of MetS, if the number of MetS components was used to estimate the severity of MetS.

In conclusion, we found that low-grade albuminuria has a strongly positive correlation with MetS even after controlling for a variety of lifestyle and biochemical risk factors in Chinese community-based patients with type 2 diabetes mellitus. The present results suggested that a UACR in the normal range is a novel marker for MetS. In clinical practice, diabetic patients can make lifestyle modifications and early medical interventions against MetS through early screening the UACR.

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