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Association of microalbuminuria and high–normal 24-hour urinary albumin excretion with metabolic syndrome and its components in the general Chinese population: cross-sectional study

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ABSTRACT

Objective Microalbuminuria (MAU) has been described as a risk factor for metabolic syndrome (MetS). However, the association between MetS components with MAU and 24-hour urinary albumin excretion (UAE) has not been clearly explained in the general Chinese population. We aimed to analyse the associations between MAU and high–normal 24-hour UAE with MetS and its components.

Design Cross-sectional observational study.

Setting Four selected counties/districts in China's Shandong and Jiangsu Provinces.

Participants A total of 2261 participants aged 18–69 years were included in this study. Participants with missing physical examination data or incomplete urine collection were not included in the analysis.

Results The prevalence of MAU was 9%, and the mean 24-hour UAE was 18 mg/d. The prevalence of MAU was significantly higher for the MetS, high blood pressure (BP), high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C) and hyperglycaemia groups but not for the central obesity group. Both MAU and mean 24-hour UAE were significantly increased in association with a number of MetS components. The adjusted prevalence OR (POR) for MetS with MAU was 2.95 (95% CI 2.15 to 4.04) compared with those without MAU. MAU was significantly associated with three components of MetS: high BP (POR=1.86, 95% CI 1.31 to 2.64), high TG levels (POR=1.80, 95% CI 1.31 to 2.46) and hyperglycaemia (POR=1.84, 95% CI 1.34 to 2.53). No significant association between MAU and central obesity or low HDL-C was found. The presence of MetS gradually increased according to the normal-range 24-hour UAE quartiles: POR=1.00, POR=1.22, POR=1.14 and POR=2.02, respectively. Hyperglycaemia also increased significantly according to the normal-range 24-hour UAE quartiles.

Conclusions MAU and elevated 24-hour UAE within the normal range were closely associated with MetS in the Chinese population, which may provide a basis for the development of early interventions to decrease the effects of MetS.

Strengths and limitations of this study

- We used 24-hour urinary albumin excretion (UAE) to define microalbuminuria (MAU), which is more accurate than most previous studies.
- This is the largest sample size of the general Chinese population to collected 24-hour urine.
- We explored the association between high–normal 24-hour UAE with MetS and its components.
- A causal relationship between MAU and MetS cannot be demonstrated in our cross-sectional study.

INTRODUCTION

Microalbuminuria (MAU), defined by an abnormally high albumin excretion (30–300 mg/d) in a 24-hour urine sample, was significantly associated with chronic kidney disease, cardiovascular disease and progression of end-stage renal disease independent of traditional risk factors.[1–4] Prospective and epidemiological studies have found that MAU is also a powerful predictor of all-cause and cardiovascular mortality in the general population.[5 6]

Metabolic syndrome (MetS) is a widely accepted description of a cluster of metabolic abnormalities characterised by obesity, hypertension, dyslipidaemia and hyperglycaemia.[7] Some studies have evaluated the relationship between MetS and MAU as a marker for early-stage chronic kidney disease.[8–11] Significant associations between MetS and MAU have been demonstrated in Japanese,[9] Korean[10 12] and Chinese populations.[13–16] However, data concerning the relationship between individual MetS components and MAU have been inconsistent, and a causal relationship between MAU and MetS remains unclear despite the predictive value MAU showed in the aforementioned studies. Furthermore,

studies on the association between normal-range 24-hour urinary albumin excretion (UAE) and MetS components have been limited.[15]

Twenty-four-hour UAE level is considered the 'gold standard' for defining MAU.[17 18] However, most of the previous studies of MAU in the Chinese population have used an early morning or random spot urine sample instead of measuring 24-hour UAE. Therefore, in this study, we investigated the prevalence of MAU by analysing 24-hour UAE and analysed the association of MAU and normal-range 24-hour UAE with MetS and its components.

METHODS

Study participants

Data were derived from the supplemental baseline survey of the Shandong Ministry of Health Action on Salt Reduction and Hypertension project, which was a cross-sectional survey conducted at four sites in the Shandong and Jiangsu provinces during 2013 and 2014. We used a stratified, multistage sampling method to select the participants. We selected 80 villages or communities from four sites using proportional probability sampling. A random sample of 120 adults aged 18–69 years was drawn from each village or community. A total of 9600 people were selected, and 8995 of these individuals participated in the survey (response rate of 93.7%). A total of 605 replacements were selected from all individuals in the same village or community after excluding the already selected participants. A total of 9600 individuals participated in the survey and physical examination. A random sample of at least 30 adults was drawn among 120 adults from each village or community. A total of 2480 people were selected, and 2295 participated in the survey (response rate of 92.5%). Of the 185 non-responders, 113 were replaced by adults with similar profiles from the same community or village. Finally, a single 24-hour urine sample was collected from a subsample of 2408 participants. Participants with the following conditions were not required to provide urine samples: (1) patients who had difficulty collecting a urine sample; (2) patients with an acute or chronic urinary infection; (3) women who were pregnant, breastfeeding or actively menstruating; and (4) patients with severe vomiting or diarrhoea. We excluded three subjects with missing data from their physical examination or blood samples and 127 participants with incomplete 24-hour urine collection. For the purpose of the present study on MAU, we also excluded 17 subjects with macroalbuminuria or a 24-hour UAE of >300 mg/d. Therefore, a total of 2261 participants were included in this study.

Written informed consent was obtained from all participants.

Demographic, anthropometrical and biochemical data collection

A face-to-face interview was conducted by local trained health professionals using a standard questionnaire. Relevant variables included age, sex, educational level, smoking status, alcohol intake, regular exercise, and previous diagnosis and treatment of hypertension and diabetes. During the physical examination, height, weight, waist circumference (WC) and blood pressure (BP) were measured by trained researchers using standardised protocols and techniques. Weight and height were measured with participants dressed in light, indoor clothing without shoes using standardised techniques and calibrated equipment. WC was measured at the narrowest point between the lower border of the rib cage and the iliac crest. The body mass index (BMI) was calculated as the weight in kilogram divided by the height in metre squared (kg/m^2). BP was measured three times by an electronic sphygmomanometer (HEM-7071, Omron Corporation, Japan), and the final BP was obtained by averaging the three measurements.

Fasting blood samples collected from each participant were processed and shipped in cold storage to a certified laboratory (ADICON Clinical Laboratory, Jinan, China). Fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol were measured. Plasma glucose was measured using a modified hexokinase enzymatic method. Serum cholesterol and TG levels were analysed enzymatically using commercially available reagents.

24-Hour urine collection and analysis

Eligible participants were instructed not to change their dietary or lifestyle habits. We provided a standard plastic container for each participant to collect a 24-hour urine sample. Trained researchers gave each participant both written and verbal instructions on how to collect a 24-hour urine sample. Health professionals carefully explained to the subjects the purpose of the 24-hour urine collection and asked the subjects to correctly repeat the information. The exact 24-hour urine collection time, including starting and ending times, was recorded by the supervising health professional. The total volume of the collection was measured by a laboratory technician, and urine aliquots were frozen at −20°C for approximately 30 days and were shipped to the ADICON Clinical Laboratory in Jinan. Urinary creatinine was measured by the picric acid method. UAE was measured with an immunonephelometric method using the Olympus AU640 Analyser, for which the coefficient of variation was 3%. Either a 24-hours urinary volume less than 500 mL or a 24-hour urinary creatinine volume that was ±2 SD outside of the sex-specific mean, 0.98–16.17 mmol/L for men and 0.93–13.60 mmol/L for women, was defined as an incomplete urine collection.[19]

Definition of MetS

We adopted the harmonised criteria of MetS, which defines MetS as the presence of ≥3 of the following risk factors[20] : central obesity defined as a WC of ≥90 cm in men and ≥80 cm in women; high BP defined as a systolic blood pressure (SBP) of ≥130 mm Hg, a diastolic blood

pressure (DBP) of ≥85 mm Hg or treatment with an antihypertensive medication; high TG levels defined as a fasting plasma TC level of ≥1.7 mmol/L or drug treatment for increased TC; low HDL-C defined as HDL-C of <1.0 mmol/L in men and <1.3 mmol/L in women or drug treatment for low HDL-C; and hyperglycaemia defined as an FBG level of ≥5.6 mmol/L or drug treatment for increased FBG.

Statistical analysis

Continuous variables are presented as the mean (SD), and categorical variables are presented as percentages. According to their quartiles of 24-hour UAE in a normal range (n=2058), study subjects were divided into four groups: Q1 (0–9.38 mg/d), Q2 (9.39–11.96 mg/d), Q3 (11.97–15.46 mg/d) and Q4 (15.47–29.99 mg/d).

We performed logistic regression analyses to study the association between MAU and 24-hour UAE with MetS and its components while controlling for covariates, including sociodemographic factors (age, sex and education level) and lifestyle factors (regular exercise, alcohol intake and smoking). Participants who did not have MAU or who were in the Q1 group were used as a reference group to estimate the prevalence ORs (PORs) and 95% CIs. Tests of linear trends across increasing quartiles of 24-hour UAE were conducted by treating the medians of the average 24-hour UAE as a continuous variable in the logistic regression models. Statistical analyses were performed with SAS V.9.3. The tests performed were two-sided, and a p value of <0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

RESULTS

Characteristics of subjects

Among the 2261 participants, the prevalence of MAU was 9% (203), and the prevalence was not significantly different between men and women (8.8% vs 9.1%, p=0.08). The mean 24-hour UAE was 18.0 mg/d. The population characteristics are summarised according to MAU and normal-range 24-hour UAE quartiles in table 1.

Table 1 General characteristics of the study participants

	Normal range 24-hour UAE (mg/d)					Microalbuminuria		
	Q1	Q2	Q3	Q4	P value	No	Yes	P value
Number of subjects	515	515	516	512		2058	203	
Age (years)	41.7 (13.5)	42.5 (13.5)	41.8 (13.5)	42.5 (13.3)	0.67	42.1 (13.5)	41.4 (13.5)	0.48
Men (%)	51.8	48.2	50.8	48.4	0.57	49.8	48.8	0.78
Body mass index (kg/cm^2)	24.4 (3.6)	24.6 (3.6)	24.7 (3.9)	25.5 (3.9)	<0.001	24.8 (3.8)	26.0 (4.5)	<0.001
Waist circumference (cm)	82.3 (9.1)	82.4 (9.6)	82.7 (9.9)	84.8 (10.5)	<0.001	83.0 (9.8)	85.8 (12.5)	<0.001
Systolic blood pressure (mm Hg)	129.5 (19.4)	130.7 (18.5)	129.8 (18.7)	133.1 (20.7)	0.0111	130.8 (19.4)	136.1 (23.3)	<0.001
Diastolic blood pressure (mm Hg)	81.8 (11.4)	83.1 (10.8)	82.5 (11.4)	84.9 (12.2)	<0.001	83.1 (11.5)	87.9 (14.4)	<0.001
High-school (%)	24.1	21.9	23.1	25.4	0.61	23.6	26.6	0.34
Smoking (%)	30.1	29.1	29.1	27.3	0.80	28.9	33.0	0.22
Alcohol (%)	23.7	27.6	26.2	27.3	0.47	26.2	27.1	0.78
Regular exercise (%)	17.3	16.7	22.3	22.3	0.03	19.6	30.5	<0.001
Fasting blood glucose (mmol/L)	5.6 (1.1)	5.6 (1.0)	5.7 (1.1)	6.0 (1.7)	<0.001	5.7 (1.3)	6.5 (2.4)	<0.001
Total cholesterol (mmol/L)	4.7 (0.9)	4.8 (0.9)	4.8 (0.9)	4.9 (1.0)	0.0281	4.8 (0.9)	5.1 (1.0)	<0.001
High-density lipoprotein (mmol/L)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)	0.0203	1.3 (0.3)	1.2 (0.3)	0.03
Low-density lipoprotein (mmol/L)	2.4 (0.7)	2.4 (0.6)	2.5 (0.7)	2.5 (0.7)	0.0186	2.4 (0.7)	2.5 (0.7)	0.06
Triglyceride (mmol/L)	1.4 (1.2)	1.4 (1.3)	1.5 (1.4)	1.8 (2.1)	<0.001	1.6 (1.6)	2.3 (2.4)	<0.001
Creatinine (mmol/d)	6.0 (2.2)	7.4 (2.6)	8.0 (3.2)	8.6 (3.1)	<0.001	7.5 (3.0)	8.8 (3.1)	<0.001
24-hour UAE (mg/d)	7.7 (1.2)	10.7 (0.8)	13.5 (1.0)	20.1 (3.7)	<0.001	13.0 (5.0)	68.8 (50.4)	<0.001

UAE, urinary albumin excretion.

Table 2 Association of MAU with MetS and its components

Components	MAU (%) No (n=2058)	Yes (n=203)	P value
Central obesity			
No	91.49	8.51	0.1982
Yes	89.76	10.24	
High blood pressure			
No	93.52	6.48	<0.001
Yes	88.85	11.15	
High triglycerides			
No	93.11	6.89	<0.001
Yes	86.18	13.82	
Low high-density lipoprotein cholesterol			
No	91.81	8.19	0.0249
Yes	88.72	11.28	
Hyperglycaemia			
No	93.94	6.06	<0.0001
Yes	87.78	12.22	
MetS			
No	93.52	6.48	<0.0001
Yes	84.89	15.11	

MAU, microalbuminuria; MetS, metabolic syndrome.

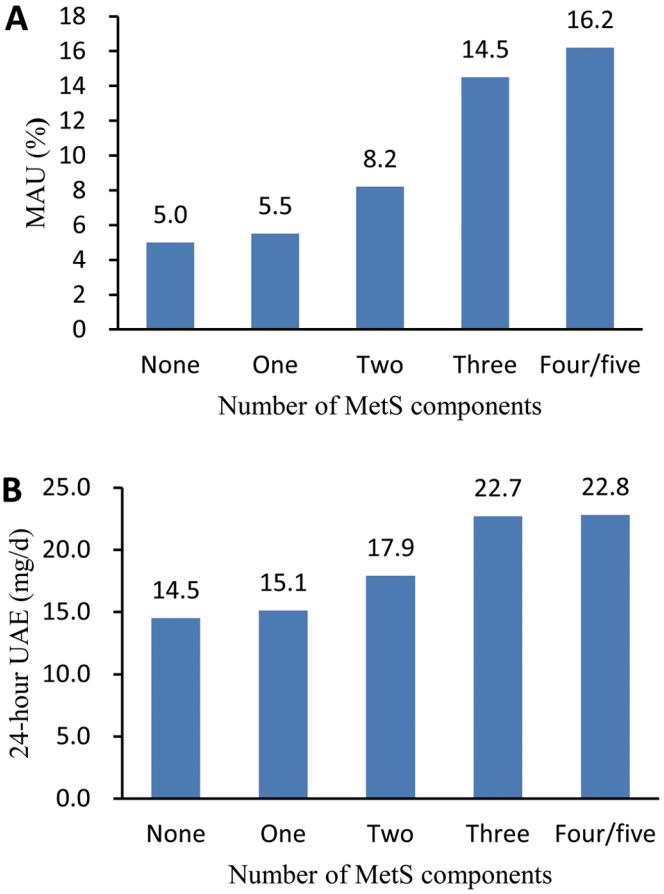

Figure 1 Prevalence of MAU (A) and mean 24-hour UAE (B) according to the number of MetS components. MAU, microalbuminuria; MetS, metabolic syndrome; UAE, urinary albumin excretion.

Compared with those without MAU, participants with MAU were more likely to have higher WC, BMI, SBP, DBP, FBG and TG. Similarly, these variables were also significantly different among increasing quartiles of 24-hour UAE.

MAU and 24-hour UAE by the number of MetS components

The prevalence of MAU in individuals with MetS and its components is shown in table 2. The prevalence of MAU was significantly higher in the MetS, high-BP, high-TG levels and hyperglycaemia groups. The prevalence rates of MAU among subjects with 0 (n=342), one (n=632), two (n=632), three (n=433), and four or five (n=222) components of MetS were 5.0%, 5.5%, 8.2%, 14.5% and 16.2%, respectively. The corresponding mean 24-hour UAE measurements were 14.5, 15.1, 17.9, 22.7 and 22.8 mg/d, respectively. Both the prevalence rate of MAU and the mean 24-hour UAE were significantly elevated according to the number of MetS components with all p values being <0.001 (figure 1).

Association between MAU and MetS components

The associations between MAU and the components of MetS are shown in table 3. Compared with participants without MAU, the age-adjusted and sex-adjusted POR for MetS with MAU was 2.93 (95% CI 2.15 to 4.00), and the multivariate-adjusted POR was 2.95 (95% CI 2.15 to 4.04). For MetS components, in both the age-adjusted and sex-adjusted and multivariate-adjusted models, MAU was strongly associated with high BP, high TG levels and hyperglycaemia. However, no significant association between MAU and central obesity or low HDL-C was found.

Associations between high–normal 24-hour UAE and MetS

Table 4 shows that the odds of MetS gradually increased according to the normal-range 24-hour UAE quartiles. The multivariate-adjusted PORs of MetS were 1.22, 1.14 and 2.02 for 24-hour UAE quartiles 2, 3 and 4, respectively, compared with the lowest quartile (p<0.0001). Furthermore, compared with the lowest 24-hour UAE quartile, the multivariate-adjusted POR of the highest quartile was 1.52 for hyperglycaemia (p<0.01). However, no significant associations between normal-range 24-hour UAE and the other components of MetS were found.

DISCUSSION

Our study showed that the prevalence of MAU was 9.0% in the study population and was much more prevalent in persons with MetS (15.1%) in particular. The prevalence of MAU in our study was moderate compared with that in other studies in China (4.1%–15%).[13 14 21–24] This varied prevalence observed in the Chinese population may be

Table 3 Relationship between MAU and MetS components

	Cases (n)	Without MAU	MAU	
			Model 1*	Model 2†
MetS	655	1.00	2.93 (2.15 to 4.00)	2.95 (2.15 to 4.04)
Central obesity	615	1.00	1.40 (0.92 to 2.13)	1.02 (0.65 to 1.60)
High blood pressure	1211	1.00	2.20 (1.57 to 3.09)	1.86 (1.31 to 2.64)
High triglycerides	680	1.00	2.21 (1.65 to 2.97)	1.80 (1.31 to 2.46)
Low high-density lipoprotein cholesterol	576	1.00	1.71 (1.13 to 2.60)	1.32 (0.85 to 2.04)
Hyperglycaemia	1072	1.00	2.28 (1.68 to 3.11)	1.84 (1.34 to 2.53)

*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, education attainment, regular exercise, alcohol consumption, smoking and for the other components of MetS (except for analyses of MetS).
MAU, microalbuminuria; MetS, metabolic syndrome.

associated with different age distributions, regions and methods of defining MAU.

In the current study, the prevalence of MAU was consistently higher in persons with MetS than in those without MetS. The prevalence of MAU increased significantly with increasing numbers of MetS components after the subjects were divided by the number of MetS components. The same results were obtained in previous studies.[12–15 25 26] This finding indicates that a large number of participants with MAU are easily overlooked in routine health examinations that do not include MAU measurements. This finding also suggests that intervention for MetS should be initiated at the earliest stage of renal injury.

Furthermore, our study showed that MAU was significantly associated with MetS and its components, apart from central obesity and low HDL-C. Many epidemiological studies have suggested an independent association between MAU and MetS. However, findings on the

Table 4 Normal-range 24 hours' urinary albumin excretion quartiles associated with MetS and its components

	Prevalence ORs (95% CI)				
	Q1	Q2	Q3	Q4	P value
MetS					
Model 1*	1.00	1.24 (0.91 to 1.67)	1.15 (0.84 to 1.56)	2.03 (1.51 to 2.72)	<0.0001
Model 2†	1.00	1.22 (0.90 to 1.65)	1.14 (0.84 to 1.55)	2.02 (1.51 to 2.72)	<0.0001
Central obesity					
Model 1*	1.00	1.35 (0.94 to 1.94)	1.07 (0.75 to 1.55)	1.72 (1.19 to 2.48)	0.0154
Model 2†	1.00	1.29 (0.89 to 1.88)	1.07 (0.73 to 1.58)	1.53 (1.04 to 2.25)	0.1221
High blood pressure					
Model 1*	1.00	1.18 (0.90 to 1.54)	0.99 (0.75 to 1.29)	1.43 (1.09 to 1.87)	0.0253
Model 2†	1.00	1.12 (0.85 to 1.48)	0.93 (0.71 to 1.23)	1.24 (0.94 to 1.64)	0.1957
High triglycerides					
Model 1*	1.00	0.96 (0.72 to 1.26)	1.00 (0.76 to 1.32)	1.43 (1.09 to 1.87)	0.0092
Model 2†	1.00	0.84 (0.63 to 1.13)	0.93 (0.69 to 1.24)	1.18 (0.89 to 1.56)	0.1242
Low high-density lipoprotein cholesterol					
Model 1*	1.00	1.37 (0.96 to 1.93)	1.28 (0.90 to 1.81)	1.55 (1.09 to 2.20)	0.0953
Model 2†	1.00	1.34 (0.93 to 1.94)	1.26 (0.87 to 1.83)	1.29 (0.89 to 1.87)	0.4045
Hyperglycaemia					
Model 1*	1.00	1.12 (0.87 to 1.44)	1.37 (1.07 to 1.77)	1.72 (1.33 to 2.21)	0.0001
Model 2†	1.00	1.09 (0.84 to 1.41)	1.34 (1.03 to 1.74)	1.52 (1.17 to 1.98)	0.0055

*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, education attainment, regular exercise, alcohol consumption, smoking and for the other components of MetS (except for the analyses of MetS).
MetS, metabolic syndrome.

associations between various components of MetS and MAU are controversial. BP and fasting glucose were consistently found to be two main risk factors associated with MAU, which was also clearly shown in our study. However, the associations between MAU and abdominal obesity, HDL and TG levels were inconsistent in previous studies.[8 9 16] Thus far, two studies have reported an association between MAU and risk of MetS, with ORs of 5.13 (95% CI 1.96 to 13.45) and 2.71 (95% CI 1.69 to 4.36),[14 15] which is consistent with our finding.

Our study further showed that the prevalence of MetS gradually increased with increasing normal-range 24-hour UAE quartiles, which is consistent with previous studies.[15 26–28] Thus far, only one prospective cohort study reported HRs with 95% CIs for MetS: 1.57 (95% CI 1.14 to 2.18) for the three highest albumin:creatinine ratio quartiles compared with the lowest one.[28] However, the association between the components of MetS and high–normal 24-hour UAE were not exactly the same. Ge *et al* reported that the relationship between 24-hour UAE within the normal range and central obesity, elevated BP and elevated TG levels was significant.[15] Another study also found that the association between low-grade albuminuria and the components of MetS, except for low HDL-C, was significant.[25] In our study, a relationship between high–normal 24-hour UAE and hyperglycaemia in the general Chinese population was found. This association persisted after adjustment for multiple risk factors.

In our study, we found that not only MAU but also elevated 24-hour UAE within the normal range had a significant relationship with an increased risk of MetS in Chinese adults. The magnitude of this association persisted after controlling for traditional risk factors. Our finding has important public health implications for preventing MetS.[15] The prevalence of MetS in China was 24.2%[29] and is becoming a serious public health problem in China. Our findings demonstrated that reducing 24-hour UAE even within the normal range should be an important priority for reducing the effects of MetS. Our study suggested that clinicians should carefully evaluate the risk of MetS in individuals with normal-range UAE. Annual MAU screening in the MetS population should be an essential part of our preventive medicine efforts. Policy makers should support such screening as part of the universal coverage policy programmes.

Our study had strengths. First, we used 24-hour UAE to define MAU in a relatively large sample population, which was more accurate than most previous studies in the general Chinese population. Furthermore, this population-based epidemiological study found an association between high–normal 24-hour UAE and MetS, which is different from most previous studies in China. In addition, our study rigorously used standardised methods and quality control for data collection. However, our study had several limitations. First, due to investigative convenience, we did not use an objective biomarker, such as para-aminobenzoic acid, to assess complete 24-hour urine.[30] We assessed the completeness by measuring urinary volume and creatinine concentration in the present study. Second, we did not evaluate the renal function of the subjects, which may have caused some bias in the results. Third, although multiple covariates were included in the adjustment, some potential confounding factors, such as dietary intake[31] and other medications, could not be ruled out. Finally, because this study had a cross-sectional design, it was difficult to interpret a causal association between MAU and 24-hour UAE with MetS and its components. Therefore, future prospective studies are recommended to confirm our findings.

CONCLUSIONS

Our study confirmed that both MAU and high–normal 24-hour UAE were strong risk factors for MetS in the general Chinese population. The assessment of these risk factors can result in an opportunity for early intervention to decrease the effects of MetS in China.

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Contributors JM, XCh and JW designed the study and supervised the data collection. JX, LY, XCa, XG and YZ participated in field work and data collection. JX and LY analysed the data. JX wrote the manuscript to which all the authors contributed. JM and JW critically revised the manuscript for important intellectual content. All the authors reviewed and approved the final manuscript.

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