Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes: cross sectional study

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Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes

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Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes: cross sectional study

Abstract

Objective To investigate the prevalence of microalbuminuria (MAU) among Chinese individuals without diabetes and the relationship between MAU and metabolic factors, individual socioeconomic status (SES), and regional economic development level.

Design Cross sectional study of prevalence of MAU.

Setting 152 urban street districts and 112 rural villages from northeast, north, east, south central, northwest, and southwest China.

Participants 46,239 subjects were recruited using a multi-stage stratified sampling design from 2007 to 2008. 41,290 subjects without diabetes determined by oral glucose tolerance test were included in the present study. ACR results of 35,430 individuals were available.

Primary and secondary outcome measures Positive detection of MAU was determined using a urine albumin/creatinine ratio (ACR) of 30 to 299 mg.

Results The prevalence of MAU in men was 16.9% and 25.1% in women. In developed, intermediate-developed, and under-developed areas, the prevalence of MAU in men was 13.4%, 16.7% and 22.0%, respectively; in women the prevalence was 20.1%, 26.8%, and 30.0%, respectively. Prevalence of MAU increased as the number of metabolic disorders present increased, and as the number of lower Socio-Economic Status (SES) components increased (female sex, farmer, below university education level, and low income). Prevalence of MAU in developed and intermediate developed areas had adjusted risk ratios of 0.49 (95% C.I.: 0.43 to 0.55) and 0.71 (95% C.I.: 0.61 to 0.82), respectively. Multivariate logistic analyses demonstrated MAU was strongly associated with female sex, low education level, low occupational level, high blood pressure, obesity, older age, and higher blood glucose.

Conclusions Several factors had independent correlations to MAU in China: older age, metabolic abnormalities, lower SES level and living in economically underdeveloped areas, which encourage the development of strategies to lower the risk for MAU in these susceptible populations.

Keywords: microalbuminuria, prevalence, socioeconomic status, regional economic development level.

Introduction

Microalbuminuria (MAU) is defined as a urinary albumin excretion ranging from 30 to 300 mg per 24 h, and is a marker for chronic kidney damage and a risk factor for the progression of chronic kidney diseases, cardiovascular and cerebrovascular diseases, and mortality. [1-3] Prevalence of MAU has been shown to vary within and between populations. For example, an analysis of data from the Third National Health and Nutrition Examination Survey, found the prevalence of MAU in the general U.S. population was 6.1% for men and 9.7% for women. [4] Prevalence of MAU has been estimated at 6% in Australians [5], 20% in native Canadians [6], and 36.9% in Singaporeans ≥ 40 years. [7] Prevalence estimates from the same areas of Shanghai, China have varied widely between 5% and 19.4%. [8,9] Factors that may have caused dissimilar prevalence estimates include varying definitions of MAU and different study methodologies. The excretion rate of urine albumin is unstable and may be affected by physiological factors such as sports participation and body position. [10,11] High-performance liquid chromatography to determine urinary albumin concentrations revealed higher values compared to nephelometry, especially in the lower concentration range, which resulted in a higher prevalence of MAU. [12] The urinary microalbuminuria/creatinine ratio (ACR) method has been recommended due to a lack of reliable 24-h urine collection methods.

Risk factors for MAU and kidney diseases include components of the metabolic syndrome [13-16] and lower socioeconomic status. Higher odds for MAU have been found in Singaporeans with lower educational obtainment (OR = 1.76, 95% CI: 1.23 to 2.52), lower income in retirement (OR = 1.64, 95% CI: 1.16 to 2.31), smaller housing type (OR = 1.44, 95% CI: 1.01 to 2.06), and coexistence of multiple low socio-economic status (SES) factors (OR = 2.37, 95% CI: 1.56 to 3.60). [7] Whereas affluence has been shown to be protective against chronic kidney disease (CKD) among blacks in the U.S. [17], higher occupational grade has been shown

to be protective among whites in Europe. [18]

There are many international epidemiologic studies on MAU, especially in diabetic populations, but there are few studies in non-diabetic Chinese populations. As the Chinese economy has developed over the last 30 years, the prevalence of metabolic diseases has increased with varying estimates in different parts of China. The aim of the present study was to explore prevalence of MAU in China people without diabetes and to examine the relationship between MAU and metabolic factors, individual socioeconomic statuses (SES), and regional economic development levels.

Methods

Subjects and Experimental Design

A multi-stage stratified sampling design was used to select participants that were greater than 20 years in age throughout 14 Chinese provinces. A detailed description of the study population and methodology has been published previously. [19] A total of 46,239 subjects were recruited that included 41,290 subjects without diabetes as determined by inquiry of disease history and oral glucose tolerance test (OGTT). Among the enrolled subjects, 41,290 were used in the final statistical analyses, including 35,430 individuals with results of ACR. Geographic areas were divided into three categories based upon the per capita GDP of China by provinces in 2006: (1) developed area (Chinese yuan (CNY) 23,663 to 65,473), (2) intermediate developed area (CNY 13,123 to 19,363) and (3) underdeveloped area (CNY 6,742 to 12,843). The highest educational level attained by the subjects was dichotomized between under university level education and university level education or above. Income level was defined as annual family income in CNY and divided into three categories: (1) low (CNY < 5,000), (2) middle (CNY 5,000 to < 30,000) and (3) high (CNY ≥ 30,000).

Prior to conducting the assessments, interviewers received training on the questionnaire

and how to explain each item to increase the reliability. [20] Waist circumference, weight and height were measured using standard methods. [19] Blood pressure (BP) was measured two separate times at five min apart while participants were in the sitting position using an upright standard sphygmomanometer. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the China Japan Friendship Hospital. Informed consent from the subjects was obtained after explaining the nature and possible consequences of the study procedures.

Blood was drawn from the antecubital vein in the morning after fasting for 10 to 14 h following three days of normal activity and diet. Blood samples were tested for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and plasma glucose levels. Oral glucose tolerance tests (OGTT 75-g) were then performed 0.5 h later followed by another blood draw 2 h later. In addition, spot morning urine specimens were collected to measure ACR. All assessments were performed using a standard protocol that conformed to the international standards for definitions and measurements. Plasma glucose was determined using the hexokinase method. Urine albumin concentration and serum level of immune reactivity insulin were measured using radioimmunoassay (North Biotechnology Institute, Beijing, China; inter-and inter-assays coefficient of variation <5%). The picric acid method was used to measure the level of urine creatinine. ACR ratio was calculated as the urine micro protein (mg/L) divided by urinary creatinine (g/L), with urine creatinine levels less than 0.5 mg/g defined as missing values.

Microalbuminuria and Covariates

Patients with diabetes, as diagnosed according to the 1999 WHO criteria [20], were excluded from the analyses. MAU was defined as a urinary ACR in the range of 30 to 299 mg/g. Central obesity was defined as a waist circumference greater than 90 cm in men and greater

than 80 cm in women. Overweight was defined as a body mass index (BMI) greater than 25 kg/m^2 and less than 30 kg/m^2, and obesity was defined as a BMI greater than 30 kg/m^2. Hypertension was defined as the subject having a history of high blood pressure or blood pressure greater than 140/90 mmHg. Dyslipidemia was defined as triglyceride at a level greater than or equal to 1.7 mmol/L, or high density lipoprotein cholesterol at a level less than 0.9 mmol/L for men and 1.0 mmol/L for women. Impaired fasting glucose (IFG) was defined as a fasting blood glucose level between 6.1 and 7.0 mmol/L, and two-hour post-load plasma glucose level less than 7.8 mmol/L. Impaired glucose tolerance (IGT) was defined as two-hour post-load plasma glucose level between 7.8 and 11.1 mmol/L, and a fasting plasma glucose level < 6.1 mmol/L . Impaired glucose regulation was defined as the presence of both IFG and IGT. Matsuda ISI was calculated by the formula (Matsuda ISI =10000/(sqrt(Ins0×FPG×18×(Ins0+Ins30+Ins120)/3×(FPG+Glu30+PG2h)×18/3)). [21] The value for the 25th percentile in NGT was determined as the cut-off value. Individuals with NGT values below the cut-off were defined as insulin resistant while all others were considered insulin sensitive.

Statistical Analyses

SUDAAN software version 1.0 (Research Triangle Institute) was used to conduct weighted analyses to account for the complex stratified study design to adjust according to Chinese population data in 2006. [22] Student's t-tests were used to examine differences between continuous variables and chi-square tests for categorical variables. Logistic regression analyses were used to examine the prevalence of MAU by sex, age, education level, occupational level, incomes, metabolic status, and economic level. All *P*-values were 2-sided using < 0.05 as the level for significance.

Results

Among the 41,290 subjects (mean age = 43.9 yr, range 20 to 100 yr) included in this study, 35,470 subjects had ACR data. There were 125 (0.35%, comprised of males 0.31% and females 0.39%) individuals with macroalbuminuria, defined as ACR ≥300 mg/g. Among the qualified MAU subjects (300>ACR ≥30 mg/g), there were 16.9% in men and 25.1% in women. Prevalence of MAU was higher in progressively increasing age categories for females. The highest prevalence rate of MAU in males was among those in their 60's (Figure 1A).

MAU was more prevalent in individuals who were insulin resistant, hypertensive, had impaired glucose regulation, and had higher BMI (Figure 1B). MAU prevalence also varied by socioeconomic status; residence in underdeveloped areas, lower educational obtainment, lower income, and occupation as a farmer were associated with elevated prevalence of MAU (Figure 1C).

Metabolic abnormalities that were examined included IGR, hypertension, high TG, low HDL-C, central obesity and IR. The subjects were placed into six groups according to the number of metabolic problems. As expected, the number of metabolic abnormalities increased the prevalence of MAU (Figure 2A). Individuals from developed areas had significantly lower prevalence of MAU compared to intermediate-developed and under-developed groups that had a similar number of metabolic problems.

The SES components that were examined included female sex, farmer, education level under university, and annual family income less than CNY 30,000. The subjects were placed into five groups according to the number of SES components present, and by the degree of development in the area in which they live (Figure 2B). Prevalence of MAU increased as the number of SES components increased within different categories of development.

Sample characteristics according to ARC value quartiles are shown in Table 1. Males had

higher average metabolic values within each ARC quartile than females. Higher values for ARC were associated with higher prevalence of hypertension and higher values for other metabolic parameters.

The average MAU for males and females in intermediate-developed and developed areas were significantly lower than in under-developed areas (Table 2). There were no age differences between the three economic development areas; BMI, blood pressure, blood glucose, insulin and IR were all higher in developed areas than in under-developed areas.

Family income and rural residence were not significantly associated with microalbuminuria (Table 3), and therefore were not included in the multivariate models. There was no significant relationship between insulin resistance and MAU after adjusting for the two-hour post-challenge plasma glucose concentration and other variables. However, older age, female sex, higher BMI, high blood pressure, low regional development level, and increased blood glucose were significantly associated with ACR in adjusted analyses.

Discussion

Statement of principal findings

To our knowledge, this is the largest population based study of MAU in Chinese individuals without diabetes. The prevalence of MAU was 16.9% in males and 25.1% in females, respectively. Results from the multivariate analyses suggest that high blood pressure, obesity, increasing age, and increased blood glucose were independent risk factors for MAU. Results from the univariate analyses demonstrated that MAU was more prevalent in subjects with insulin resistance than those who were insulin sensitive. However, after adjusting for blood glucose level in multivariate analyses, insulin resistance was not significantly associated with MAU. The prevalence of MAU increased as the number of metabolic abnormalities increased in both developed areas and in under-developed areas; over 50% of

subjects with five metabolic abnormalities in under-developed areas had MAU. Some SES parameters were associated with MAU. For example, the prevalence of MAU was higher in individuals with under a university education and in those who were farmers. Annual family income and urban vs. rural residence were not significantly associated with MAU. Level of regional economic development was significantly associated with MAU with the intermediate-developed and developed areas having 29% and 50% lower prevalence than under-developed areas, respectively. This association appeared to be independent of metabolic abnormalities and SES.

Strengths and limitations of the study

Strengths of this study included the large population based sample from diverse economic levels, with analyses accounting for the complex sampling design to provide a representative sample of 14 Chinese provinces; the use of RIA methods to test for urine albumin to increase sensitivity. Limitations of our study included the cross sectional design that limited the ability to make cause-effect inferences and the one-time collection of urine specimens that did not allow an evaluation for the persistence of MAU.

Comparison with other studies

Both men and women in our study had significantly higher prevalence of MAU compared to individuals in developed countries. [4,5] Prevalence of MAU in the general U.S. population was 6.1% in men and 9.7% in women [4], and 6% in Australians. [5] Prevalence of MAU in the Chinese participants of this study was lower than the prevalence found in Singaporeans aged 40 to 80 years, which may be explained by the fact that study used lower cut-off values to define MAU (ACR≥17 mg/g for men and ≥25 mg/g for women). [7] However, a similar result (19.4%) was observed in Shanghai, China. [8] This study was consistent with studies in

Singapore where higher odds of MAU were found in individuals with lower educational obtainment, lower income in retirement, smaller housing type, and coexistence of multiple low SES factors. [7] In this study, females had a higher prevalence of ACR than males, which is consistent with the results from a U.S. sample from the NHANES study. [4] Higher levels of ACR in healthy women than in healthy men that have been observed in many studies could result in the overestimation of MAU in females, if the same criteria for MAU are used for both males and females.

Meaning of the study

MAU has been recognized as an early sign of renal damage, and a significant predictor of end-stage renal disease, cardiovascular mortality, and morbidity in patients with diabetes. [13-15] In patients with type 1 diabetes, MAU is considered an indicator of the third stage of diabetic nephropathy. [13] A recent study demonstrated methods that decrease MAU may reduce the risk for end-stage renal disease. [3] Endothelial dysfunction and micro-inflammation of vasculature have been proposed as pathogenic mechanisms of MAU, which also links MAU to vascular atherosclerosis. Monitoring MAU levels may help identify endothelial dysfunction and vascular micro-inflammation in subjects with obesity, high blood pressure, dyslipidemia, and blood glucose. [1] For this reason, the World Health Organization (WHO) has included MAU in their criteria for the metabolic syndrome (MS). [14] MAU was strongly associated with older age, obesity, metabolic abnormalities, lower SES, and residence in lower economic development areas. Limited access to health care services for low SES subjects could help explain some of the association between SES and MAU. Many studies have shown an association between MAU and CRP level, a marker for microinflammation [23], which has been shown to be higher in low healthcare utilization and low SES populations. Additional research could help clarify the relationship between SES and MAU. Higher

prevalence of MAU in under-developed areas could be due in part to inadequate availability of health care services and to unfavorable environmental factors. Development of strategies to lower the risk for MAU in these susceptible populations should be emphasized.

Conclusions

In conclusion, MAU was strongly associated with older age, obesity, metabolic abnormalities, lower SES, and residence in lower economic development areas. It is suggested that future research studies explore the extent to which MAU could mediate the association between low SES and metabolic, cardiovascular, and cerebrovascular diseases.

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All of the authors designed the study, revised and approved the paper, and decided to publish the paper. JX, XX, JL, JW, WJ, LJ, ZS, JL, HT, QJ, DZ, JG, GC, LC, XG, Z Zhao, QL, Z Zhou, ZY and WY contributed to the acquisition of data. JX, XX and ZY were responsible for the analysis and interpretation of data. JX, XX and WY drafted the manuscript. WY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JX and XX contributed equally to the study.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

The research ethics board of China-Japan Friendship Hospital approved this study.

Data sharing: No further data are available.

Article summary

Article focus:

To investigate the prevalence of MAU among Chinese without diabetes. To study the relationship between MAU and metabolic factors, individual SES, and regional economic development level.

Key message:

In Chinese individuals without diabetes, the prevalence of MAU was 16.9% in males and 25.1% in females, respectively, which was significantly higher than individuals in developed countries. MAU was strongly associated with older age, obesity, metabolic abnormalities, lower SES, and residence in lower economic development areas, which encouraged the development of strategies to lower the risk for MAU in these susceptible populations.

Strengths and limitations of the study:

It was the first study on prevalence of MAU in Chinese which based on a large population-based sample from diverse economic levels, with analyses accounting for the complex sampling design to provide a representative sample of 14 Chinese provinces. Moreover, using of RIA methods in urine albumin measurement increased the sensitivity. However, the limitation is that it is a cross-sectional study, which could not demonstrate cause-effect relationship.

References

1. Bigazzi R, Bianchi S, Baldari D, et al. Microalbuminuriapredicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 1998;16(9):1325-1333.

2. Stehouwer CD, Gall MA, Twisk JW, et al. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes* 2002;51(4):1157–1165.

3. Wachtell K, Olsen MH, Dahlöf B, et al. Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE Study. *J Hypertens* 2002;20(3):405-412.

4. Jones CA, Francis ME, Eberhardt MS, et al. Microalbuminuriain the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2002;39(3):445-459.

5. Atkins RC, Polkinghorne KR, Briganti EM, et al. Prevalence of albuminuria in Australia. *Aus Diab Kidney Int* 2004;66(S92):S22–S24.

6. Zacharias JM, Young TK, Riediger ND, et al. Prevalence, risk factors and awareness of albuminuria on a Canadian First Nation: A community-based screening study. *BMC Public Health* 2012;12: 290.

7. Sabanayagam C, Shankar A , Saw SM, et al. Socioeconomic status and microalbuminuria in an Asian population. *Nephrol Dial Transplant* 2009;24(1):123–129.

8. Jia W, Gao X, Pang C, et al. Prevalence and risk factors of albuminuria and chronic kidney disease in Chinese population with type 2 diabetes and impaired glucose regulation: Shanghai diabetic complications study (SHDCS). *Nephrol Dial Transplant* 2009;24(12):3724-3731.

9. Li M, Xu M, Bi Y, et al. Association between higher serum fetuin-A concentrations and abnormal albuminuria in middle-aged and elderly chinese with normal glucose tolerance.

Diabetes Care 2010;33(11):2462-2464.

10. Brandt JR, Jacobs A, Raissy HH, et al. Orthostatic proteinuria and the spectrum of diurnal variability of urinary protein excretion inhealthy children. *Pediatr Nephrol* 2010;25(6):1131–1137.

11. Jefferson IG, Greene SA, Smith MA, et al. Urine albumin to creatinine ratio-response to exercise in diabetes. *Arch Dis Child* 1985;60(4):305–310.

12. Brinkman JW, Bakker SJ, Gansevoot RT, et al. Which method for quantifying urinary albumin excretion gives what outcome? A comparison of immunonephelometry with HPLC. *Kidney Int* 2004;66(S92):S69–S75.

13. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;310(6):356-360.

14. Gobal F, DeshmukhA, Shah S, et al. Triad of Metabolic Syndrome, chronic kidney disease, and coronary heart disease with a focus on microalbuminuria - death by overeating. *J Am Coll Cardiol* 2011;57(23):2303–2308.

15. Kannel WB, Stampfer MJ, Castelli WP, et al. The prognostic significance of proteinuria: The Framingham Study. *Am Heart J* 1984;108(5):1347-1352.

16. Chew GT, Gan SK, Watts GF. Revisiting the metabolic syndrome. *Med J Aust* 2006;185(8):445-449.

17. Martins D, Tareen N, Zadshir A, et al. The association of poverty with the prevalence of albuminuria: data from the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2006;47(6):965–971.

18. Al-Qaoud TM, Nitsch D, Wells J, et al. Socioeconomic status and reduced kidney function in the Whitehall II Study: role of obesity and metabolic syndrome. *Am J Kidney Dis* 2011;58(3):389-397.

19. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N*

Engl J Med 2010;362(12):1090-1101.

20. Luepker RV EA, McKeigue P, Reddy KS. *Cardiovascular survey methods. 3rd ed.* Geneva: World Health Organization; 2004.

21. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006;29(5):1130-1139.

22. National Bureau of Statistics of China. China statistical yearbook — 2006. http://www.stats.gov.cn/tjsj/ndsj/2006/indexeh.htm. Accessed February 26, 2010.

23. Pravenec M, Kajiya T, Zídek V, et al. Effects of human C-reactive protein on pathogenesis of features of the metabolic syndrome. *Hypertension* 2011;57(4):731-737.

Figure legends

Figure 1. Prevalence of MAU in various categories in Chinese without diabetes

A. age and sex specific prevalence of MAU; B. prevalence of MAU in different obesity, blood pressure and ISI groups; C. prevalence of MAU in different education level, income level, profession, and SES level groups. **P*<0.001 men vs. women in all age subgroups; †*P*<0.01 in different sex, ISI, BMI, blood pressure and glucose tolerance groups; ‡*P*<0.01 in different sex, economic developed areas, education level, incomes and profession groups.

Figure 2. Prevalence of MAU in individuals with different metabolic status and SES level

A. prevalence of MAU in individuals with different numbers of components of metabolic status. †*P*-trend<0.001 for comparing different risk factor numbers; **P*<0.05 vs. developing area; $^{\#}P$<0.05 vs. intermediate developing area.

B. prevalence of MAU in individuals with different numbers of low SES level. †*P*-trend<0.001 for comparing different SES numbers; **P*<0.05 vs. developing area $^{\#}P$<0.05 vs. intermediate developing area.

Tables

Table 1. Characteristics of participants presented by ACR quartiles in Chinese men and women

ACR (mg/g)	Men				Women			
	Q1 (0.5 to 6.8)	**Q2 (6.9 to 12.5)**	**Q3 (12.6 to 26.3)**	**Q4 (≥26.4)**	**Q1 (0.5 to 6.8)**	**Q2 (6.9 to 12.5)**	**Q3 (12.6 to 26.3)**	**Q4 (≥26.4)**
N=35,470	4,265	3,682	2,960	2,820	4,589	5,264	5,839	6,051
Age (year)	41.1(40.4,41.9)	42.8(41.9,43.7)*	45.2(44.2,46.2)*	48.3(47.3,49.3)*	41.6(40.8,42.4)	41.2(40.5,42.0)	43.2(42.4,44.0)*	47.6(46.4,48.9)*
Overweight	26.8(23.2,23.5)	27.9(23.4,23.8)	29.0(24.3,24.6)*	33.1(30.2,36.1)*	19.9(17.7,22.4)#	23.6(21.6,25.7)*#	21.7(20.0,23.5)#	27.3(25.1,29.7)*#
Obese	4.3(3.1,6.0)	5.5(4.4,6.8)*	4.5(3.6,5.7)	8.9(7.3,10.9)*	4.2(3.3,5.3)	3.3(2.7,4.1)*	3.9(3.2,4.8)	6.3(5.2,7.5)*#
Central obesity	24.2(22.0,26.6)	24.8(22.7,27.1)	24.7(22.3,27.3)	31.9(29.1,34.9)*	34.6(32.0,37.4)#	34.8(32.6,37.1)#	36.7(34.5,38.9)*#	45.9(42.8,48.9)*#
HTG	31.3(31.0,33.8)	29.7(28.8,34.0)	32.1(29.3,35.0)	38.0(35.0,41.1)*	21.1(18.9,23.4)#	18.9(17.1,20.8)#	20.6(18.9,22.5)#	27.0(24.4,29.8)*#
Hypertension	15.8(14.2,17.6)	24.0(21.8,26.3)*	29.9(27.2,32.7)*	43.0(39.9,46.3)*	13.3(11.4,15.5)	12.5(11.2,13.9)#	19.5(17.8,21.4)*#	36.1(33.0,39.4)*#
IGR	15.8(13.7,18.1)	17.2(15.2,19.4)	18.7(16.4,21.2)*	25.0(22.3,27.8)*	13.4(11.7,15.2)	13.8(13.9,16.9)#	15.4(13.9,16.9)*#	23.3(20.4,26.4)*
IR	24.0(21.8,26.4)	24.7(22.4,27.2)	22.8(20.4,25.4)	30.1(27.2,33.1)*	22.5(20.4,24.8)	23.4(21.5,25.5)	24.0(22.0,26.1)	28.0(25.6,30.5)*

*P<0.05 vs. ACR 0.5 to 6.8 mg/g; #P<0.05 vs. men at same ACR quartiles.

Table 2. Clinical characteristics for men and women presented by level of economic development

	Men			Women		
	Under-developed	**Intermediate-Developed**	**Developed**	**Under-developed**	**Intermediate-developed**	**Developed**
N=41,290	4,340	3,376	8,482	6,404	5,179	13,509
Age(year)	43.7(43.4,44.0)	43.8(43.0,44.5)	44.2(43.3,45.2)	43.7(43.1,44.2)	43.7(42.6,44.9)	43.7(43.2,44.3)
Body mass index (kg/m^2)	23.3(23.2,23.5)	23.6(23.4,23.8)	24.5(24.3,24.6)*#	22.9(22.8,23.1)	23.1(23.0,23.2)	23.5(23.4,23.6)*#
Waist circumference (cm)	82.1(81.6,82.6)	80.5(79.9,81.1)*	85.2(84.9,85.6)*#	77.2(76.8,77.6)	76.2(75.5,76.9)*	78.2(77.9,78.5)*#
Systolic blood pressure (mmHg)	119.1(118.2,120.0)	121.6(120.5,122.7)*	125.8(125.2,126.4)*#	115.4(114.5,116.3)	118.5(117.3,119.7)*	120.6(120.1,121.1)*#
Fasting plasma glucose (mmol/L)	4.9(4.9,5.0)	4.9(4.9,5.0)	5.1(5.0,5.1)*#	4.9(4.9,4.9)	4.8(4.8,4.9)	5.0(5.0,5.1)*#
Plasma glucose at 30' (mmol/L)	8.1(8.0,8.2)	8.6(8.5,8.7)*	9.0(8.9,9.1)*#	7.5(7.5,7.7)	8.1(8.0,8.2)*	8.4(8.4,8.5)*#
Plasma glucose at 120' (mmol/L)	5.8(5.7,5.8)	6.2(6.1,6.3)*	6.1(6.1,6.2)*	5.9(5.8,6.0)	6.2(6.1,6.3)*	6.2(6.2,6.3)*
ACR (mg/g)	14.1(7.2,27.1)	10.4(6.6,19.7)*	9.8(6.0.18.8)*#	17.1(8.2,37.0)	15.4(9.3,33.6)*	13.3(7.6,25.1)*#
Fasting serum insulin (mU/L)	6.4(4.8,8.7)	6.4(4.4,9.1)	7.3(5.1,10.4)*#	6.6(4.9,8.8)	6.5(4.6,9.1)	7.1(5.1,10.0)*#
Serum insulin at 30' (mU/L)	28.0(16.6,47.4)	30.2(16.7,49.4)	39.1(22.4,67.7)*#	31.5(19.4,50.4)	30.9(20.1,49.3)	39.5(24.7,61.9)*#
Serum insulin at 120' (mU/L)	21.1(11.8,35.1)	19.9(11.6,35.4)	26.6(15.3,47.0)*#	24.3(16.5,42.2)	25.9(11.8,37.3)	30.7(18.8,50.1)*#
Total cholesterol (mmol/L)	4.57(4.52,4.62)	4.62(4.57,4.67)	4.79(4.76,4.83)*#	4.55(4.51,4.59)	4.68(4.62,4.74)*	4.76(4.73,4.79)*#
Triglycerides (mmol/L)	1.23(0.91,1.89)	1.21(0.85,1.83)	1.37(0.93,2.16)*	1.17(0.85,1.66)	1.05(0. 78,1.55)*	1.09(0.78,1.63)*
HDL-cholesterol (mmol/L)	1.25(1.24,1.27)	1.24(1.22,1.26)	1.26(1.25,1.27)	1.33(1.32,1.35)	1.32(1.30,1.33)	1.40(1.38,1.41)*#
HOMA-IR	1.36(1.00,1.88)	1.38(0.94,2.01)	1.64(1.15,2.38)*#	1.40(1.03,1.95)	1.39(0.95,2.00)	1.59(1.15,2.26)*#

Matsuda ISI	9.3(6.5,12.3)	8.8(6.0,12.8)	6.9(4.7,10.0)*#	8.6(6.2,11.8)	8.5(5.8,11.7)	7.1(4.9,9.5)*#

SI conversion factors: To convert insulin to pmol/L, multiple values by 6.945.

* Significant difference compared with developed area, $P<0.01$.

Significant difference compared with intermediate developed area, $P<0.01$.

Table 3. Results from multivariate logistic regression analyses for individuals with ACR≥30 mg/g *

	Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI
Sex (women vs. men)	1.81 (1.62,2.03)	1.66 (1.44,1.92)
Age (per 10ys increment)	1.16 (1.11,1.22)	1.11 (1.06,1.18)
BMI (per 2 kg/m^2 increment)	1.06 (1.03,1.09)	1.05 (1.01,1.08)
Blood pressure (hypertension vs. normotension)	2.38 (2.08,2.72)	2.30 (2.00,2.65)
Insulin sensitivity † (IS. vs. IR)	1.14 (1.01,1.28)	1.07 (0.94,1.21)
2 hour plasma glucose (per 2 mmol/L increase)	NI	1.16 (1.08,1.26)
Education (less than college vs. college)	NI	1.21 (1.02,1.45)
Occupation (workers vs. officials or intellectuals)	NI	1.20 (1.01,1.42)
Occupation (farmers vs. officials or intellectuals)	NI	1.24 (1.01,1.52)
Development ‡ (developed vs. underdeveloped)	0.50 (0.44,0.57)	0.49 (0.43,0.55)
Development ‡ (intermediated- vs. under-developed)	0.73 (0.63,0.84)	0.71 (0.61,0.83)
Residence (rural vs. urban)	1.07 (0.97,1.19)	1.00 (0.89-1.14)

* Odds ratios were calculated using multivariate logistic models. All covariates listed were included in the model simultaneously.

† Insulin resistance was defined as Matsuda ISI <25th percentile in individuals with normal glucose tolerance

‡ Economic development levels were placed into 3 categories (under-developed, intermediate-developed, and developed).

NI: not included in the model 1.

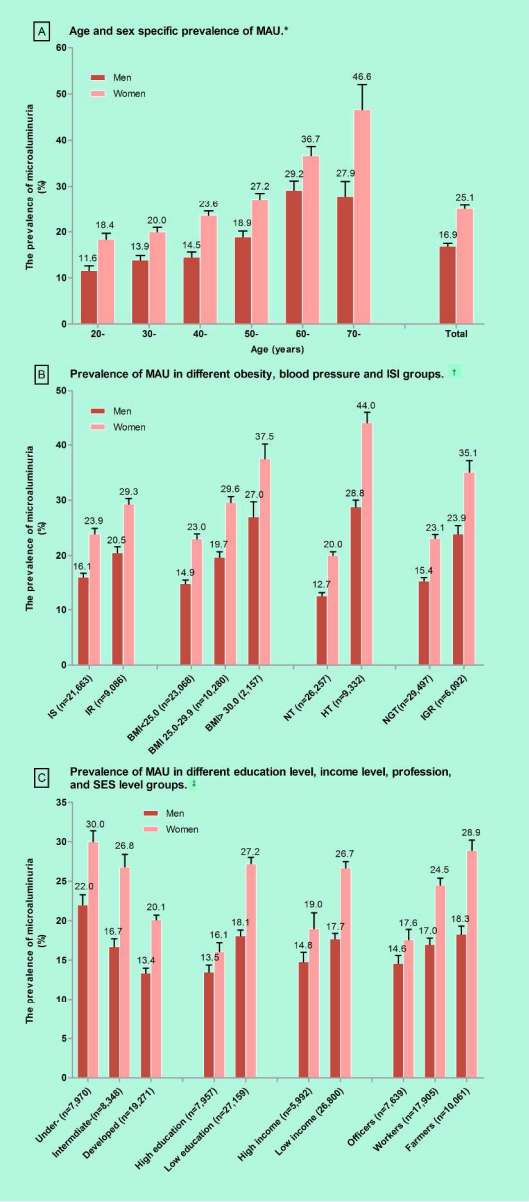

Figure 1. Prevalence of MAU in various categories in Chinese without diabetes
A. age and sex specific prevalence of MAU; B. prevalence of MAU in different obesity, blood pressure and ISI groups; C. prevalence of MAU in different education level, income level, profession, and SES level groups. *P<0.001 men vs. women in all age subgroups; †P<0.01 in different sex, ISI, BMI, blood pressure and glucose tolerance groups; ‡P<0.01 in different sex, economic developed areas, education level, incomes and profession groups.

297x674mm (300 x 300 DPI)

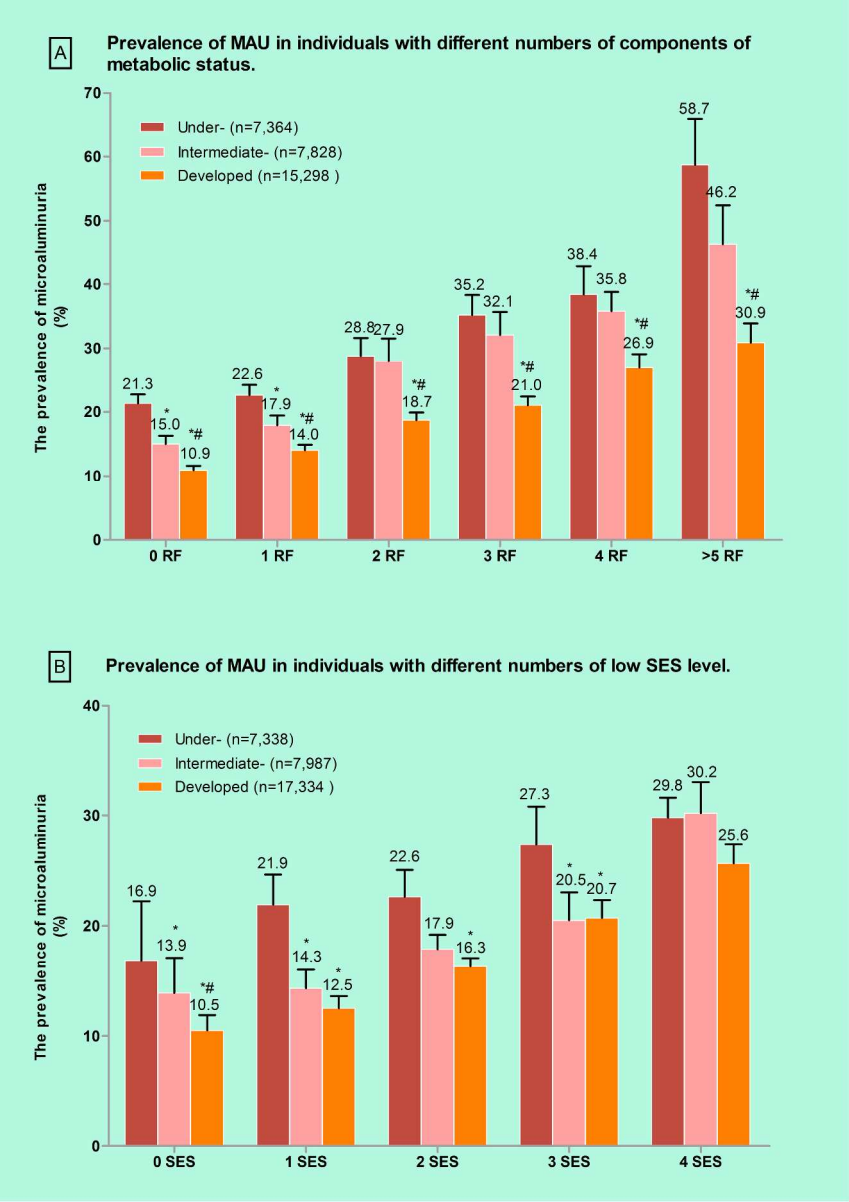

Figure 2. Prevalence of MAU in individuals with different metabolic status and SES level
A. prevalence of MAU in individuals with different numbers of components of metabolic status. †P-trend<0.001 for comparing different risk factor numbers; *P<0.05 vs. developing area; #P<0.05 vs. intermediate developing area.
B. prevalence of MAU in individuals with different numbers of low SES level. †P-trend<0.001 for comparing different SES numbers; *P<0.05 vs. developing area #P<0.05 vs. intermediate developing area.

267x377mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	na

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,2
		(b) Indicate number of participants with missing data for each variable of interest	Table 1,2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Na
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Na
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Na
		Cross-sectional study—Report numbers of outcome events or summary measures	Table 1,2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 1,2
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes: cross sectional study

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	microalbuminuria, prevalence, socioeconomic status, regional economic development level

Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes

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Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes: cross sectional study

Abstract

Objective To investigate the prevalence of microalbuminuria (MAU) among Chinese individuals without diabetes and the relationship between MAU and metabolic factors, individual Socio-Economic Status (SES), and regional economic development level.

Design Cross sectional study of prevalence of MAU.

Setting 152 urban street districts and 112 rural villages from northeast, north, east, south central, northwest, and southwest China.

Participants 46,239 subjects were recruited using a multi-stage stratified sampling design from 2007 to 2008. 41,290 subjects without diabetes determined by oral glucose tolerance test were included in the present study. Urine albumin/creatinine ratio (ACR) results of 35,430 individuals were available.

Primary and secondary outcome measures Positive detection of MAU was determined using a ACR of 22.1 to 299 mg/g in men 30.9 to 299 mg/g in women.

Results The prevalence of MAU in men was 22.4% and 24.5% in women. In developed, intermediate-developed, and under-developed areas, the prevalence of MAU in men was 20.7%, 21.9% and 32.5%, respectively; in women the prevalence was 19.6%, 26.0%, and 29.5%, respectively. Prevalence of MAU increased as the number of metabolic disorders present increased, and as the number of lower SES components increased (farmer, below university education level, and low income). Prevalence of MAU in developed and intermediate developed areas had adjusted risk ratios of 0.52 (95% C.I.: 0.42 to 0.60) and 0.65 (95% C.I.: 0.57 to 0.76), respectively. Multivariate logistic analyses demonstrated MAU was strongly associated with older age, high blood pressure, higher blood glucose low

education level, low occupational level, and residence in under-developed region.

Conclusions Several factors had independent correlations to MAU in China: older age, metabolic abnormalities, lower SES level and living in economically underdeveloped areas, which encourage the development of strategies to lower the risk for MAU in these susceptible populations.

Keywords: microalbuminuria, prevalence, socioeconomic status, regional economic development level.

Introduction

Microalbuminuria (MAU) is defined as a urinary albumin excretion ranging from 30 to 299 mg per 24 h, and is a marker for chronic kidney damage and a risk factor for the progression of chronic kidney diseases, cardiovascular and cerebrovascular diseases, and mortality. [1-3] Prevalence of MAU has been shown to vary within and between populations. For example, an analysis of data from the Third National Health and Nutrition Examination Survey, found the prevalence of MAU in the general U.S. population was 6.1% for men and 9.7% for women. [4] Prevalence of MAU has been estimated at 6% in Australians [5], 6.6% in Netherland[3], 20% in native Canadians [6], and 36.9% in Singaporeans ≥ 40 years. [7] Prevalence estimates from the same areas of Shanghai, China have varied widely between 5% and 19.4%. [8,9] Factors that may have caused dissimilar prevalence estimates include varying definitions of MAU and different study methodologies. The excretion rate of urine albumin is unstable and may be affected by physiological factors such as sports participation and body position. [10,11] High-performance liquid chromatography to determine urinary albumin concentrations revealed higher values compared to nephelometry, especially in the lower concentration range, which resulted in a higher prevalence of MAU. [12] The urinary microalbuminuria/creatinine ratio (ACR) method has been recommended due to a lack of reliable 24-h urine collection methods.

Risk factors for MAU and kidney diseases include components of the metabolic syndrome [13-16] and lower socioeconomic status. Higher odds for MAU have been found in Singaporeans with lower educational obtainment (OR = 1.76, 95% CI: 1.23 to 2.52), lower income in retirement (OR = 1.64, 95% CI: 1.16 to 2.31), smaller housing type (OR = 1.44, 95% CI: 1.01 to 2.06), and coexistence of multiple low socio-economic status (SES) factors (OR = 2.37, 95% CI: 1.56 to 3.60). [7] Whereas affluence has been shown to be protective against chronic kidney disease (CKD) among blacks in the U.S. [17], higher occupational grade has been shown

to be protective among whites in Europe. [18]

There are many international epidemiologic studies on MAU, especially in diabetic populations, but there are few studies in non-diabetic Chinese populations. As the Chinese economy has developed over the last 30 years, the prevalence of metabolic diseases has increased with varying estimates in different parts of China. We reported that the prevalence of diabetes was not only associated with personal metabolic factors, but also with personal socioeconomic factors and regional economic development levels[19]. The aim of the present study was to explore prevalence of MAU in China people without diabetes and to examine the relationship between MAU and metabolic factors (such as obesity, hypertension, hyperglycemia, and hypertriglyceridemia), individual socioeconomic statuses (SES, education, income, occupation), and regional economic development levels.

Methods

Subjects and Experimental Design

A multi-stage stratified sampling design was used to select participants that were greater than 20 years in age throughout 14 Chinese provinces. A detailed description of the study population and methodology has been published previously. [19] A total of 46,239 subjects were recruited that included 41,290 subjects without diabetes as determined by inquiry of disease history and oral glucose tolerance test (OGTT). Among the enrolled subjects, 41,290 were used in the final statistical analyses, including 35,430 individuals with results of ACR. Geographic areas were divided into three categories based upon the per capita GDP of China by provinces in 2006: (1) developed area (Chinese yuan (CNY) 23,663 to 65,473), (2) intermediate developed area (CNY 13,123 to 19,363) and (3) underdeveloped area (CNY 6,742 to 12,843)[20]. The highest educational level attained by the subjects was dichotomized between under university level education and university level education or above. Income

level was defined as annual family income in CNY and divided into three categories: (1) low (CNY < 5,000), (2) middle (CNY 5,000 to < 30,000) and (3) high (CNY ≥ 30,000).

Prior to conducting the assessments, interviewers received training on the questionnaire and how to explain each item to increase the reliability. [19]Waist circumference, weight and height were measured using standard methods. [19] Blood pressure (BP) was measured two separate times at five min apart while participants were in the sitting position using an upright standard sphygmomanometer. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the China Japan Friendship Hospital. Informed consent from the subjects was obtained after explaining the nature and possible consequences of the study procedures.

Blood was drawn from the antecubital vein in the morning after fasting for 10 to 14 h following three days of normal activity and diet. Blood samples were tested for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and plasma glucose levels. Oral glucose tolerance tests (OGTT 75-g) were then performed 0.5 h later followed by another blood draw 2 h later. In addition, spot urine specimens were collected in the morning to measure ACR. All assessments were performed using a standard protocol that conformed to the international standards for definitions and measurements. Plasma glucose was determined using the hexokinase method. Urine albumin concentration and serum level of immune reactivity insulin were measured using radioimmunoassay in the central laboratory (North Biotechnology Institute, Beijing, China; inter-and inter-assays coefficient of variation <5%). The picric acid method was used to measure the level of urine creatinine in the central laboratory. ACR ratio was calculated as the urine micro protein (mg/L) divided by urinary creatinine (g/L), with urine creatinine levels less than 0.5 mg/g defined as missing values.

Microalbuminuria and Covariates

Patients with diabetes, as diagnosed according to the 1999 WHO criteria [21], were excluded from the analyses. MAU was defined as a urinary ACR in the range of 21.1 to 299 mg/g in men and 30.9 to 299 mg/g in women[22]. Central obesity was defined as a waist circumference greater than 90 cm in men and greater than 80 cm in women. Overweight was defined as a body mass index (BMI) greater than 25 kg/m^2 and less than 30 kg/m^2, and obesity was defined as a BMI greater than 30 kg/m^2. Hypertension was defined as the subject having a history of high blood pressure or blood pressure greater than 140/90 mmHg. Dyslipidemia was defined as triglyceride at a level greater than or equal to 1.7 mmol/L, or high density lipoprotein cholesterol at a level less than 0.9 mmol/L for men and 1.0 mmol/L for women. Impaired fasting glucose (IFG) was defined as a fasting blood glucose level between 6.1 and 7.0 mmol/L, and two-hour post-load plasma glucose level less than 7.8 mmol/L. Impaired glucose tolerance (IGT) was defined as two-hour post-load plasma glucose level between 7.8 and 11.1 mmol/L, and a fasting plasma glucose level < 6.1 mmol/L . Impaired glucose regulation (IGR) was defined as the presence of IFG or IGT. Matsuda ISI was calculated by the formula (Matsuda ISI =10000/(sqrt(Ins0×FPG×18×(Ins0+Ins30+Ins120)/3×(FPG+Glu30+PG2h)×18/3)). [23] The value for the 25th percentile in NGT was determined as the cut-off value. Individuals with NGT values below the cut-off were defined as insulin resistant while all others were considered insulin sensitive.

Statistical Analyses

SUDAAN software version 1.0 (Research Triangle Institute) was used to conduct weighted analyses to account for the complex stratified study design to adjust according to Chinese population data in 2006. [20] Student's t-tests were used to examine differences between continuous variables and chi-square tests for categorical variables. Logistic regression analyses were used to examine the prevalence of MAU by sex, age, education level,

occupational level, incomes, metabolic status, and economic level. All *P*-values were 2-sided using < 0.05 as the level for significance.

Results

Among the 41,290 subjects (mean age = 43.9 yr, range 20 to 100 yr) included in this study, 35,470 subjects had ACR data. There were 125 (0.35%, comprised of males 0.31% and females 0.39%) individuals with macroalbuminuria, defined as ACR ≥300 mg/g. Among the qualified MAU subjects (300>ACR ≥22.1 in men and 300>ACR ≥30.9 mg/g in women), there were 24.4% in men（95% CI:23.6-25.4%） and 24.5.% in women（95% CI: 23.2 -25.9%）. Prevalence of MAU was higher in progressively increasing age categories both in men and in women (Figure 1A).

MAU was more prevalent in individuals who were insulin resistant, hypertensive, had impaired glucose regulation, and had higher BMI (Figure 1B). MAU prevalence also varied by socioeconomic status; residence in underdeveloped areas, lower educational obtainment, lower income, and occupation as a farmer were associated with elevated prevalence of MAU (Figure 1C).

Metabolic abnormalities that were examined included IGR, hypertension, high TG, low HDL-C, central obesity and IR. The subjects were placed into six groups according to the number of metabolic problems. As expected, the number of metabolic abnormalities increased the prevalence of MAU (Figure 2A). Individuals from developed areas had significantly lower prevalence of MAU compared to intermediate-developed and under-developed groups that had a similar number of metabolic problems.

The SES components that were examined included occupation as farmer, education level under university, and annual family income less than CNY 30,000. The subjects were placed into four groups according to the number of low SES components present, and by the degree

of development in the area in which they live (Figure 2B). Prevalence of MAU increased as the number of low SES components increased within different categories of development. There was higher prevalence of MAU in men who had 1 or less low SES components. In those with 2-3 low SES components, there was no significant difference between men and women in prevalence of MAU （2C）.

Sample characteristics according to ACR value quartiles are shown in Table 1. Males had higher average metabolic values within each ACR quartile than females. Higher values for ACR were associated with higher prevalence of hypertension and higher values for other metabolic parameters.

The average MAU for males and females in intermediate-developed and developed areas were significantly lower than in under-developed areas (Table 2). There were no age differences between the three economic development areas; BMI, blood pressure, blood glucose, insulin and IR were all higher in developed areas than in under-developed areas.

Three multivariate logistic models were used to examine the relationship between demographic data, metabolic factors, personal SES, rural/urban residence and regional economic development (Table 3). In model 1, old age, increase of PG, and hypertension were independently associated with MAU. In model 2, where SES components were included, low education level and low annual family income category were also associated with MAU. In the model 3, individual residence, where regional economic development levels were added.In the following variables were independently associated with MAU, older age, , higher blood glucose, high blood pressure, low education levels and low regional economic development level.

Discussion

Statement of principal findings

To our knowledge, this is the largest population based study of MAU in Chinese individuals without diabetes. The prevalence of MAU was 24.4% in males and 24.5% in females, respectively. Individuals with higher level of ACR had higher prevalence of hypertension, obese/overweight, and IGR(table 1). In contrast to the higher level of blood pressure, plasma glucose, serum triglycerides, and insulin resistance in economically developed regions, the level of ACR was lower in economically developed regions (table 2). Results from the multivariate analyses suggest that increasing age, high blood pressure , and increased blood glucose were independent risk factors for MAU. Results from the univariate analyses demonstrated that MAU was more prevalent in subjects with insulin resistance than those who were insulin sensitive. However, after adjusting for blood glucose level in multivariate analyses, insulin resistance was not significantly associated with MAU. The prevalence of MAU increased as the number of metabolic abnormalities increased in both developed areas and in under-developed areas; over 50% of subjects with five metabolic abnormalities in under-developed and intermediate-developed areas had MAU. Some low SES parameters were associated with MAU. For example, the prevalence of MAU was higher in individuals with under a university education and in those who had low annual family income. Level of regional economic development was significantly associated with MAU with the intermediate-developed and developed areas having 35% and 48% lower prevalence than under-developed areas, respectively. This association appeared to be independent of metabolic abnormalities and low SES.

Strengths and limitations of the study

Strengths of this study included the large population based sample from diverse economic levels, with analyses accounting for the complex sampling design to provide a representative sample of 14 Chinese provinces; the use of RIA methods to test for urine albumin to increase

sensitivity. Limitations of our study included the cross sectional design that limited the ability to make cause-effect inferences, and the one-time collection of spot urine specimens due to a large variability in albumin excretion rates that did not allow an evaluation for the persistence of MAU.

Comparison with other studies

Both men and women in our study had significantly higher prevalence of MAU compared to individuals in developed countries. [4,5] Prevalence of MAU in the general U.S. population was 6.1% in men and 9.7% in women [4], and 6% in Australians. [5] Prevalence of MAU in the Chinese participants of this study was lower than the prevalence found in Singaporeans aged 40 to 80 years, which may be explained by the fact that study used lower cut-off values to define MAU (ACR≥17 mg/g for men and ≥25 mg/g for women). [7] However, a similar result (19.4%) was observed in Shanghai, China. [8] This study was consistent with studies in Singapore where higher odds of MAU were found in individuals with lower educational obtainment, lower income in retirement, smaller housing type, and coexistence of multiple low SES factors. [7]

Meaning of the study

MAU has been recognized as an early sign of renal damage, and a significant predictor of end-stage renal disease, cardiovascular mortality, and morbidity in patients with diabetes. [13-15] In patients with type 1 diabetes, MAU is considered an indicator of the third stage of diabetic nephropathy. [13] A recent study demonstrated methods that decrease MAU may reduce the risk for end-stage renal disease. [24,25] Endothelial dysfunction and micro-inflammation of vasculature have been proposed as pathogenic mechanisms of MAU, which also links MAU to vascular atherosclerosis. Monitoring MAU levels may help identify endothelial dysfunction and vascular micro-inflammation in subjects with obesity, high blood pressure,

dyslipidemia, and blood glucose. [1] For this reason, the World Health Organization (WHO) has included MAU in their criteria for the metabolic syndrome (MS). [14] MAU was strongly associated with older age, obesity, metabolic abnormalities, lower SES, and residence in lower economic development areas. Limited access to health care services for low SES subjects could help explain some of the association between SES and MAU. Many studies have shown an association between MAU and CRP level, a marker for microinflammation [26], which has been shown to be higher in low healthcare utilization and low SES populations. Periodental diseases have also been shown to be more common in low SES populations and are associated with increased CRP level. We did not have data to explore the association between periodontal diseases and MAU. Additional research could help clarify the relationship between SES and MAU, especially the underlying mechanism. Higher prevalence of MAU in under-developed areas could be due in part to inadequate availability of health care services and to unfavorable environmental factors. Development of strategies to lower the risk for MAU in these susceptible populations should be emphasized. Besides measures to prevent and control metabolic disorders, we propose that reforming the health system, improving access to health facilities, prompting health education, preventing periodontal diseases especially in low SES population and in under-development region, may reduce the prevalence of MAU and reduce the incidence of CVD and mortality in general population.

Conclusions

In conclusion, MAU was strongly associated with older age, metabolic abnormalities, lower SES, and residence in lower economic development areas. It is suggested that future research studies explore the extent to which MAU could mediate the association between low

SES and metabolic, cardiovascular, and cerebrovascular diseases.

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All of the authors designed the study, revised and approved the paper, and decided to publish the paper. JX, XX, JL, JW, WJ, LJ, ZS, JL, HT, QJ, DZ, JG, GC, LC, XG, Z Zhao, QL, Z Zhou, ZY and WY contributed to the acquisition of data. JX, XX and ZY were responsible for the analysis and interpretation of data. JX, XX and WY drafted the manuscript. WY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JX and XX contributed equally to the study.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

The research ethics board of China-Japan Friendship Hospital approved this study.

Article summary

Article focus:

To investigate the prevalence of MAU among Chinese without diabetes. To study the relationship between MAU and metabolic factors, individual SES, and regional economic development level.

Key message:

In Chinese individuals without diabetes, the prevalence of MAU was 24.4% in males and 24.5% in females, respectively, which was significantly higher than individuals in developed countries. MAU was strongly associated with older age, metabolic abnormalities, lower SES, and residence in lower economic development areas, which encouraged the development of strategies to lower the risk for MAU in these susceptible populations.

Strengths and limitations of the study:

It was the first study on prevalence of MAU in Chinese which based on a large population-based sample from diverse economic levels, with analyses accounting for the complex sampling design to provide a representative sample of 14 Chinese provinces. Moreover, using of RIA methods in urine albumin measurement increased the sensitivity. However, the limitation is that it is a cross-sectional study, which could not demonstrate cause-effect relationship.

References

1. Bigazzi R, Bianchi S, Baldari D, et al. Microalbuminuriapredicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 1998;16(9):1325-1333.

2. Stehouwer CD, Gall MA, Twisk JW, et al. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes* 2002;51(4):1157–1165.

3.Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106(14):1777-82.

4. Jones CA, Francis ME, Eberhardt MS, et al. Microalbuminuriain the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2002;39(3):445-459.

5. Atkins RC, Polkinghorne KR, Briganti EM, et al. Prevalence of albuminuria in Australia. *Aus Diab Kidney Int* 2004;66(S92):S22–S24.

6. Zacharias JM, Young TK, Riediger ND, et al. Prevalence, risk factors and awareness of albuminuria on a Canadian First Nation: A community-based screening study. *BMC Public Health* 2012;12: 290.

7. Sabanayagam C, Shankar A , Saw SM, et al. Socioeconomic status and microalbuminuria in an Asian population. *Nephrol Dial Transplant* 2009;24(1):123–129.

8. Jia W, Gao X, Pang C, et al. Prevalence and risk factors of albuminuria and chronic kidney disease in Chinese population with type 2 diabetes and impaired glucose regulation: Shanghai diabetic complications study (SHDCS). *Nephrol Dial Transplant* 2009;24(12):3724-3731.

9. Li M, Xu M, Bi Y, et al. Association between higher serum fetuin-A concentrations and

abnormal albuminuria in middle-aged and elderly chinese with normal glucose tolerance. *Diabetes Care* 2010;33(11):2462-2464.

10. Brandt JR, Jacobs A, Raissy HH, et al. Orthostatic proteinuria and the spectrum of diurnal variability of urinary protein excretion inhealthy children. *Pediatr Nephrol* 2010;25(6):1131–1137.

11. Jefferson IG, Greene SA, Smith MA, et al. Urine albumin to creatinine ratio-response to exercise in diabetes. *Arch Dis Child* 1985;60(4):305–310.

12. Brinkman JW, Bakker SJ, Gansevoot RT, et al. Which method for quantifying urinary albumin excretion gives what outcome? A comparison of immunonephelometry with HPLC. *Kidney Int* 2004;66(S92):S69–S75.

13. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;310(6):356-360.

14. Gobal F, DeshmukhA, Shah S, et al. Triad of Metabolic Syndrome, chronic kidney disease, and coronary heart disease with a focus on microalbuminuria - death by overeating. *J Am Coll Cardiol* 2011;57(23):2303–2308.

15. Kannel WB, Stampfer MJ, Castelli WP, et al. The prognostic significance of proteinuria: The Framingham Study. *Am Heart J* 1984;108(5):1347-1352.

16. Chew GT, Gan SK, Watts GF. Revisiting the metabolic syndrome. *Med J Aust* 2006;185(8):445-449.

17. Martins D, Tareen N, Zadshir A, et al. The association of poverty with the prevalence of albuminuria: data from the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2006;47(6):965–971.

18. Al-Qaoud TM, Nitsch D, Wells J, et al. Socioeconomic status and reduced kidney function in the Whitehall II Study: role of obesity and metabolic syndrome. *Am J Kidney Dis* 2011;58(3):389-397.

19. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362(12):1090-1101.

20. Luepker RV EA, McKeigue P, Reddy KS. *Cardiovascular survey methods. 3rd ed.* Geneva: World Health Organization; 2004.

21. National Bureau of Statistics of China. China statistical yearbook — 2006. http://www.stats.gov.cn/tjsj/ndsj/2006/indexeh.htm. Accessed February 26, 2010.

22. Houlihan CA, Tsalamandris C, Akdeniz A,et al. Albumin to creatinine ratio:a screening test with limitations. Am J Kidney Dis. 2002;39(6):1183-9.

23. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006;29(5):1130-1139.

24.Asselbergs FW, Diercks GF, Hillege HL,et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110(18):2809-16.

25. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348(5):383-93.

26. Pravenec M, Kajiya T, Zídek V, et al. Effects of human C-reactive protein on pathogenesis of features of the metabolic syndrome. *Hypertension* 2011;57(4):731-737.

Figure legends

Figure 1. Prevalence of MAU in various categories in Chinese without diabetes

1A. Age and sex specific prevalence of MAU; 1B. Prevalence of MAU in different obesity, blood pressure and ISI groups; 1C. prevalence of MAU in different education level, income level, profession, and SES level groups. *P trend<0.001 among age groups,†*P* <0.001 men vs. women in corresponding age subgroups; ‡*P*<0.01 in different ISI, BMI, blood pressure, glucose tolerance, economic developed areas, education level, incomes and profession groups;#*P*<0.01 men vs. women in corresponding subgroups.

Figure 2. Prevalence of MAU in individuals with different metabolic status and SES level

2A.Prevalence of MAU in individuals with different numbers of components of metabolic risk factors. †*P*-trend<0.001 for comparing different risk factor numbers; **P*<0.05 vs. under-developed area; $^{\#}P$<0.05 vs. intermediate developing area.

2B. Prevalence of MAU in individuals with different numbers of low SES level. †*P*-trend<0.001 for comparing different low SES numbers; **P*<0.05 vs. under-developed area

2C.Number of low SES level and gender-specific prevalence of MAU. †*P*-trend<0.001 for comparing different low SES numbers;**P*<0.01 men vs. women。

Tables

Table 1. Characteristics of participants presented by ACR quartiles in Chinese men and women

ACR (mg/g)	Men				Women			
	Q1 (0.5 to 6.8)	Q2 (6.9 to 12.5)	Q3 (12.6 to 26.3)	Q4 (≥26.4)	Q1 (0.5 to 6.8)	Q2 (6.9 to 12.5)	Q3 (12.6 to 26.3)	Q4 (≥26.4)
N=35,470	4,265	3,682	2,960	2,820	4,589	5,264	5,839	6,051
Age (year)	41.1(40.4,41.9)	42.8(41.9,43.7)*	45.2(44.2,46.2)*	48.3(47.3,49.3)*	41.6(40.8,42.4)	41.2(40.5,42.0)	43.2(42.4,44.0)*	47.6(46.4,48.9)*
Overweight	26.8(23.2,23.5)	27.9(23.4,23.8)	29.0(24.3,24.6)*	33.1(30.2,36.1)*	19.9(17.7,22.4)#	23.6(21.6,25.7)*#	21.7(20.0,23.5)#	27.3(25.1,29.7)*#
Obese	4.3(3.1,6.0)	5.5(4.4,6.8)*	4.5(3.6,5.7)	8.9(7.3,10.9)*	4.2(3.3,5.3)	3.3(2.7,4.1)*	3.9(3.2,4.8)	6.3(5.2,7.5)*#
Central obesity	24.2(22.0,26.6)	24.8(22.7,27.1)	24.7(22.3,27.3)	31.9(29.1,34.9)*	34.6(32.0,37.4)#	34.8(32.6,37.1)#	36.7(34.5,38.9)*#	45.9(42.8,48.9)*#
HTG	31.3(31.0,33.8)	29.7(28.8,34.0)	32.1(29.3,35.0)	38.0(35.0,41.1)*	21.1(18.9,23.4)#	18.9(17.1,20.8)#	20.6(18.9,22.5)#	27.0(24.4,29.8)*#
Hypertension	15.8(14.2,17.6)	24.0(21.8,26.3)*	29.9(27.2,32.7)*	43.0(39.9,46.3)*	13.3(11.4,15.5)	12.5(11.2,13.9)#	19.5(17.8,21.4)*#	36.1(33.0,39.4)*#
IGR	15.8(13.7,18.1)	17.2(15.2,19.4)	18.7(16.4,21.2)*	25.0(22.3,27.8)*	13.4(11.7,15.2)	13.8(13.9,16.9)#	15.4(13.9,16.9)*#	23.3(20.4,26.4)*
IR	24.0(21.8,26.4)	24.7(22.4,27.2)	22.8(20.4,25.4)	30.1(27.2,33.1)*	22.5(20.4,24.8)	23.4(21.5,25.5)	24.0(22.0,26.1)	28.0(25.6,30.5)*

*P<0.05 vs. ACR 0.5 to 6.8 mg/g; #P<0.05 vs. men at same ACR quartiles.HTG, serum triglyceride≥1.7 mmol/l; IGR, impaired glucose regulation, IR, insulin resistant.

Table 2. Clinical characteristics for men and women presented by level of economic development

	Men			Women		
	Under-developed	Intermediate-Developed	Developed	Under-developed	Intermediate-developed	Developed
N=41,290	4,340	3,376	8,482	6,404	5,179	13,509
Age(year)	43.7(43.4,44.0)	43.8(43.0,44.5)	44.2(43.3,45.2)	43.7(43.1,44.2)	43.7(42.6,44.9)	43.7(43.2,44.3)
Body mass index (kg/m^2)	23.3(23.2,23.5)	23.6(23.4,23.8)	24.5(24.3,24.6)*#	22.9(22.8,23.1)	23.1(23.0,23.2)	23.5(23.4,23.6)*#
Waist circumference (cm)	82.1(81.6,82.6)	80.5(79.9,81.1)*	85.2(84.9,85.6)*#	77.2(76.8,77.6)	76.2(75.5,76.9)*	78.2(77.9,78.5)*#
Systolic BP (mmHg)	119.1(118.2,120.0)	121.6(120.5,122.7)*	125.8(125.2,126.4)*#	115.4(114.5,116.3)	118.5(117.3,119.7)*	120.6(120.1,121.1)*#
Fasting PG (mmol/L)	4.9(4.9,5.0)	4.9(4.9,5.0)	5.1(5.0,5.1)*#	4.9(4.9,4.9)	4.8(4.8,4.9)	5.0(5.0,5.1)*#
PG at 30' (mmol/L)	8.1(8.0,8.2)	8.6(8.5,8.7)*	9.0(8.9,9.1)*#	7.5(7.5,7.7)	8.1(8.0,8.2)*	8.4(8.4,8.5)*#
PGat 120' (mmol/L)	5.8(5.7,5.8)	6.2(6.1,6.3)*	6.1(6.1,6.2)*	5.9(5.8,6.0)	6.2(6.1,6.3)*	6.2(6.2,6.3)*
ACR (mg/g)	14.1(7.2,27.1)	10.4(6.6,19.7)*	9.8(6.0.18.8)*#	17.1(8.2,37.0)	15.4(9.3,33.6)*	13.3(7.6,25.1)*#
Fasting serumIRI (mU/L)	6.4(4.8,8.7)	6.4(4.4,9.1)	7.3(5.1,10.4)*#	6.6(4.9,8.8)	6.5(4.6,9.1)	7.1(5.1,10.0)*#
SerumIRI at 30' (mU/L)	28.0(16.6,47.4)	30.2(16.7,49.4)	39.1(22.4,67.7)*#	31.5(19.4,50.4)	30.9(20.1,49.3)	39.5(24.7,61.9)*#
Serum IRI at 120' (mU/L)	21.1(11.8,35.1)	19.9(11.6,35.4)	26.6(15.3,47.0)*#	24.3(16.5,42.2)	25.9(11.8,37.3)	30.7(18.8,50.1)*#
Total cholesterol (mmol/L)	4.57(4.52,4.62)	4.62(4.57,4.67)	4.79(4.76,4.83)*#	4.55(4.51,4.59)	4.68(4.62,4.74)*	4.76(4.73,4.79)*#
Triglycerides (mmol/L)	1.23(0.91,1.89)	1.21(0.85,1.83)	1.37(0.93,2.16)*	1.17(0.85,1.66)	1.05(0. 78,1.55)*	1.09(0.78,1.63)*
HDL-cholesterol (mmol/L)	1.25(1.24,1.27)	1.24(1.22,1.26)	1.26(1.25,1.27)	1.33(1.32,1.35)	1.32(1.30,1.33)	1.40(1.38,1.41)*#
HOMA-IR	1.36(1.00,1.88)	1.38(0.94,2.01)	1.64(1.15,2.38)*#	1.40(1.03,1.95)	1.39(0.95,2.00)	1.59(1.15,2.26)*#
Matsuda ISI	9.3(6.5,12.3)	8.8(6.0,12.8)	6.9(4.7,10.0)*#	8.6(6.2,11.8)	8.5(5.8,11.7)	7.1(4.9,9.5)*#

SI conversion factors: To convert insulin to pmol/L, multiple values by 6.945.BP, blood pressure; PG, plasma glucose; IRI, immunoreactive insulin.

* Significant difference compared with developed area, $P<0.01$.

Significant difference compared with intermediate developed area, $P<0.01$.

Table 3. Results from multivariate logistic regression analyses for individuals with ACR≥22.1 mg/g in men 30.9 mg/g in women *

	Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI)	Model 3 (OR, 95% CI)
Sex (women vs. men)	1.06 (0.95,1.17)	1.03 (0.90,1.17)	1.02 (0.89,1.17)
Age (per 10ys increment)	1.15 (1.10,1.21)	1.12 (1.07,1.18)	1.12 (1.07,1.18)
BMI (per 2 kg/m^2 increment)	1.02 (0.99,1.05)	1.02 (0.99,1.06)	1.03 (1.00,1.06)
Blood pressure (hypertension vs. normotension)	2.09 (1.84,2.37)	2.10 (1.85,2.40)	2.17 (1.90,2.48)
Insulin sensitivity † (IS. vs. IR)	1.04 (0.93,1.17)	1.09 (0.96,1.23)	1.11 (0.98,1.25)
2 hour plasma glucose (per 2 mmol/L increase)	1.13 (1.05,1.21)	1.10 (1.02,1.19)	1.14 (1.06,1.23)
Education (less than college vs. college)	NI	1.37 (1.18,1.60)	1.34 (1.15,1.55)
Annual family income (<30,000 vs.>=30,000 CNY)	NI	1.26 (1.07,1.49)	1.08 (0.91,1.27)
Occupation (workers vs. officials or intellectuals)	NI	0.79 (0.69,0.90)	0.88 (0.77,1.01)
Occupation (farmers vs. officials or intellectuals)	NI	1.06 (0.93,1.22)	1.03 (0,89,1.20)
Development ‡ (developed vs. under-developed)	NI	NI	0.52 (0.46,0.60)
Development ‡ (intermediate- vs. under-developed)	NI	NI	0.65 (0.57,0.76)
Residence (rural vs. urban)	NI	NI	1.01 (0.90 -1.14)

* Odds ratios were calculated using multivariate logistic models. All covariates listed were included in the model simultaneously. Serum triglycerides, smoking status included the 3 models without significant difference not presented.,

† Insulin resistance was defined as Matsuda ISI <25th percentile in individuals with normal glucose tolerance

‡ Economic development levels were placed into 3 categories (under-developed, intermediate-developed, and developed).

NI: not included in the model.

Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes

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Prevalence and associated factors of microalbuminuria in Chinese individuals without diabetes: cross sectional study

Abstract

Objective To investigate the prevalence of microalbuminuria (MAU) among Chinese individuals without diabetes and the relationship between MAU and metabolic factors, individual Socio-Economic Status (SES)~~socioeconomic status (SES)~~, and regional economic development level.

Design Cross sectional study of prevalence of MAU.

Setting 152 urban street districts and 112 rural villages from northeast, north, east, south central, northwest, and southwest China.

Participants 46,239 subjects were recruited using a multi-stage stratified sampling design from 2007 to 2008. 41,290 subjects without diabetes determined by oral glucose tolerance test were included in the present study. Urine albumin/creatinine ratio (ACR) results of 35,430 individuals were available.

Primary and secondary outcome measures Positive detection of MAU was determined using a ~~urine albumin/creatinine ratio (~~ACR~~)~~ of 22.1 to 299 mg/g in men 30.9 to 299 mg/g in women.

Results The prevalence of MAU in men was 22.4~~16.9~~% and 24.5~~.1~~% in women. In developed, intermediate-developed, and under-developed areas, the prevalence of MAU in men was 20.7~~13.4~~%, 21.9~~16.7~~% and 32.5~~22.0~~%, respectively; in women the prevalence was ~~20.1~~19.6%, 26.0~~8~~%, and 29.5~~30.0~~%, respectively. Prevalence of MAU increased as the number of metabolic disorders present increased, and as the number of lower ~~Socio-Economic Status (~~SES~~)~~ components increased (~~female sex,~~ farmer, below university education level, and low income). Prevalence of MAU in developed and intermediate

developed areas had adjusted risk ratios of 0.5249 (95% C.I.: 0.423 to 0.6055) and 0.6571 (95% C.I.: 0.5761 to 0.7682), respectively. Multivariate logistic analyses demonstrated MAU was strongly associated with female sex, low education level, low occupational level, older age, high blood pressure, obesity, older age, and higher blood glucose low education level, low occupational level, and residence in under-developed region.

Conclusions Several factors had independent correlations to MAU in China: older age, metabolic abnormalities, lower SES level and living in economically underdeveloped areas, which encourage the development of strategies to lower the risk for MAU in these susceptible populations.

Keywords: microalbuminuria, prevalence, socioeconomic status, regional economic development level.

Introduction

Microalbuminuria (MAU) is defined as a urinary albumin excretion ranging from 30 to 299~~300~~ mg per 24 h, and is a marker for chronic kidney damage and a risk factor for the progression of chronic kidney diseases, cardiovascular and cerebrovascular diseases, and mortality. [1-3] Prevalence of MAU has been shown to vary within and between populations. For example, an analysis of data from the Third National Health and Nutrition Examination Survey, found the prevalence of MAU in the general U.S. population was 6.1% for men and 9.7% for women. [4] Prevalence of MAU has been estimated at 6% in Australians [5], 6.6% in Netherland[3], 20% in native Canadians [6], and 36.9% in Singaporeans ≥ 40 years. [7] Prevalence estimates from the same areas of Shanghai, China have varied widely between 5% and 19.4%. [8,9] Factors that may have caused dissimilar prevalence estimates include varying definitions of MAU and different study methodologies. The excretion rate of urine albumin is unstable and may be affected by physiological factors such as sports participation and body position. [10,11] High-performance liquid chromatography to determine urinary albumin concentrations revealed higher values compared to nephelometry, especially in the lower concentration range, which resulted in a higher prevalence of MAU. [12] The urinary microalbuminuria/creatinine ratio (ACR) method has been recommended due to a lack of reliable 24-h urine collection methods.

Risk factors for MAU and kidney diseases include components of the metabolic syndrome [13-16] and lower socioeconomic status. Higher odds for MAU have been found in Singaporeans with lower educational obtainment (OR = 1.76, 95% CI: 1.23 to 2.52), lower income in retirement (OR = 1.64, 95% CI: 1.16 to 2.31), smaller housing type (OR = 1.44, 95% CI: 1.01 to 2.06), and coexistence of multiple low socio-economic status (SES) factors (OR = 2.37, 95% CI: 1.56 to 3.60). [7] Whereas affluence has been shown to be protective against chronic kidney disease (CKD) among blacks in the U.S. [17], higher occupational grade has been shown

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to be protective among whites in Europe. [18]

There are many international epidemiologic studies on MAU, especially in diabetic populations, but there are few studies in non-diabetic Chinese populations. As the Chinese economy has developed over the last 30 years, the prevalence of metabolic diseases has increased with varying estimates in different parts of China. We reported that the prevalence of diabetes was not only associated with personal metabolic factors, but also with personal socioeconomic factors and regional economic development levels[19]. The aim of the present study was to explore prevalence of MAU in China people without diabetes and to examine the relationship between MAU and metabolic factors (such as obesity, hypertension, hyperglycemia, and hypertriglyceridemia), individual socioeconomic statuses (SES, education, income, occupation), and regional economic development levels.

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Methods

Subjects and Experimental Design

A multi-stage stratified sampling design was used to select participants that were greater than 20 years in age throughout 14 Chinese provinces. A detailed description of the study population and methodology has been published previously. [19] A total of 46,239 subjects were recruited that included 41,290 subjects without diabetes as determined by inquiry of disease history and oral glucose tolerance test (OGTT). Among the enrolled subjects, 41,290 were used in the final statistical analyses, including 35,430 individuals with results of ACR. Geographic areas were divided into three categories based upon the per capita GDP of China by provinces in 2006: (1) developed area (Chinese yuan (CNY) 23,663 to 65,473), (2) intermediate developed area (CNY 13,123 to 19,363) and (3) underdeveloped area (CNY 6,742 to 12,843)[20]. The highest educational level attained by the subjects was dichotomized between under university level education and university level education or above. Income

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level was defined as annual family income in CNY and divided into three categories: (1) low (CNY < 5,000), (2) middle (CNY 5,000 to < 30,000) and (3) high (CNY ≥ 30,000).

Prior to conducting the assessments, interviewers received training on the questionnaire and how to explain each item to increase the reliability. [20] [19] Waist circumference, weight and height were measured using standard methods. [19] Blood pressure (BP) was measured two separate times at five min apart while participants were in the sitting position using an upright standard sphygmomanometer. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the China Japan Friendship Hospital. Informed consent from the subjects was obtained after explaining the nature and possible consequences of the study procedures.

Blood was drawn from the antecubital vein in the morning after fasting for 10 to 14 h following three days of normal activity and diet. Blood samples were tested for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and plasma glucose levels. Oral glucose tolerance tests (OGTT 75-g) were then performed 0.5 h later followed by another blood draw 2 h later. In addition, spot ~~morning~~ urine specimens were collected in the morning to measure ACR. All assessments were performed using a standard protocol that conformed to the international standards for definitions and measurements. Plasma glucose was determined using the hexokinase method. Urine albumin concentration and serum level of immune reactivity insulin were measured using radioimmunoassay in the central laboratory (North Biotechnology Institute, Beijing, China; inter-and inter-assays coefficient of variation <5%). The picric acid method was used to measure the level of urine creatinine in the central laboratory. ACR ratio was calculated as the urine micro protein (mg/L) divided by urinary creatinine (g/L), with urine creatinine levels less than 0.5 mg/g defined as missing values.

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Microalbuminuria and Covariates

Patients with diabetes, as diagnosed according to the 1999 WHO criteria [21][10], were excluded from the analyses. MAU was defined as a urinary ACR in the range of 21.1 to 299 mg/g in men and 30.9 to 299 mg/g in women[22]. Central obesity was defined as a waist circumference greater than 90 cm in men and greater than 80 cm in women. Overweight was defined as a body mass index (BMI) greater than 25 kg/m^2 and less than 30 kg/m^2, and obesity was defined as a BMI greater than 30 kg/m^2. Hypertension was defined as the subject having a history of high blood pressure or blood pressure greater than 140/90 mmHg. Dyslipidemia was defined as triglyceride at a level greater than or equal to 1.7 mmol/L, or high density lipoprotein cholesterol at a level less than 0.9 mmol/L for men and 1.0 mmol/L for women. Impaired fasting glucose (IFG) was defined as a fasting blood glucose level between 6.1 and 7.0 mmol/L, and two-hour post-load plasma glucose level less than 7.8 mmol/L. Impaired glucose tolerance (IGT) was defined as two-hour post-load plasma glucose level between 7.8 and 11.1 mmol/L, and a fasting plasma glucose level < 6.1 mmol/L . Impaired glucose regulation (IGR) was defined as the presence of ~~both~~ IFG or ~~and~~ IGT. Matsuda ISI was calculated by the formula (Matsuda ISI =10000/(sqrt(Ins0×FPG×18×(Ins0+Ins30+Ins120)/3×(FPG+Glu30+PG2h)×18/3)). [23][11] The value for the 25th percentile in NGT was determined as the cut-off value. Individuals with NGT values below the cut-off were defined as insulin resistant while all others were considered insulin sensitive.

Statistical Analyses

SUDAAN software version 1.0 (Research Triangle Institute) was used to conduct weighted analyses to account for the complex stratified study design to adjust according to Chinese population data in 2006. [20][12] Student's t-tests were used to examine differences between continuous variables and chi-square tests for categorical variables. Logistic regression

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analyses were used to examine the prevalence of MAU by sex, age, education level, occupational level, incomes, metabolic status, and economic level. All *P*-values were 2-sided using < 0.05 as the level for significance.

Results

Among the 41,290 subjects (mean age = 43.9 yr, range 20 to 100 yr) included in this study, 35,470 subjects had ACR data. There were 125 (0.35%, comprised of males 0.31% and females 0.39%) individuals with macroalbuminuria, defined as ACR ≥300 mg/g. Among the qualified MAU subjects (300>ACR ≥22.1 in men and 300>ACR ≥30.9 mg/g in women), there were ~~16.9~~24.4% in men（95% CI:23.6-25.4%） and 24.5.~~1~~% in women（95% CI: 23.2 -25.9%）. Prevalence of MAU was higher in progressively increasing age categories both in men and in women~~for females. The highest prevalence rate of MAU in males was among those in their 60's~~ (Figure 1A).

MAU was more prevalent in individuals who were insulin resistant, hypertensive, had impaired glucose regulation, and had higher BMI (Figure 1B). MAU prevalence also varied by socioeconomic status; residence in underdeveloped areas, lower educational obtainment, lower income, and occupation as a farmer were associated with elevated prevalence of MAU (Figure 1C).

Metabolic abnormalities that were examined included IGR, hypertension, high TG, low HDL-C, central obesity and IR. The subjects were placed into six groups according to the number of metabolic problems. As expected, the number of metabolic abnormalities increased the prevalence of MAU (Figure 2A). Individuals from developed areas had significantly lower prevalence of MAU compared to intermediate-developed and under-developed groups that had a similar number of metabolic problems.

The SES components that were examined included ~~female sex,~~ occupation as farmer,

education level under university, and annual family income less than CNY 30,000. The subjects were placed into four~~ive~~ groups according to the number of low SES components present, and by the degree of development in the area in which they live (Figure 2B). Prevalence of MAU increased as the number of SES components increased within different categories of development. There were higher prevalence of MAU in men who had 1 or less low SES components. In those with 2-3 low SES components, there was no significant difference between men and women in prevalence of MAU （2C）.

Sample characteristics according to ACR~~C~~ value quartiles are shown in Table 1. Males had higher average metabolic values within each ACR~~C~~ quartile than females. Higher values for ACR~~C~~ were associated with higher prevalence of hypertension and higher values for other metabolic parameters.

The average MAU for males and females in intermediate-developed and developed areas were significantly lower than in under-developed areas (Table 2). There were no age differences between the three economic development areas; BMI, blood pressure, blood glucose, insulin and IR were all higher in developed areas than in under-developed areas.

Three multivariate logistic models were used to examine the relationship between demographic data, metabolic factors, personal SES, rural/urban residence and regional economic development (Table 3). In model 1, old age, increase of PG, and hypertension were independently associated with MAU. In model 2, where SES components were included, low education level and low annual family income category were also associated with MAU. In the model 3, individual residence, where regional economic development levels were added,. ~~Family income and rural residence were not significantly associated with microalbuminuria (Table 3), and therefore were not included in the multivariate models. There was no significant relationship between insulin resistance and MAU after adjusting for the two-hour post-challenge plasma glucose concentration and other variables. However,~~In

the following variables were independently associated with MAU, older age, ~~female sex, higher BMI~~, higher blood glucose, high blood pressure, low education levels and low regional economic development level~~, and increased blood glucose were significantly associated with ACR in adjusted analyses~~.

Discussion

Statement of principal findings

To our knowledge, this is the largest population based study of MAU in Chinese individuals without diabetes. The prevalence of MAU was 24.4~~16.9~~% in males and 24.5~~.1~~% in females, respectively. Individuals with higher level of ACR had higher prevalence of hypertension, obese/overweight, and IGR(table 1). In contrast to the higher level of blood pressure, plasma glucose, serum triglycerides, and insulin resistance in economically developed regions, the level of ACR was lower in economically developed regions(table 2). Results from the multivariate analyses suggest that increasing age, high blood pressure, ~~obesity, increasing age~~, and increased blood glucose were independent risk factors for MAU. Results from the univariate analyses demonstrated that MAU was more prevalent in subjects with insulin resistance than those who were insulin sensitive. However, after adjusting for blood glucose level in multivariate analyses, insulin resistance was not significantly associated with MAU. The prevalence of MAU increased as the number of metabolic abnormalities increased in both developed areas and in under-developed areas; over 50% of subjects with five metabolic abnormalities in under-developed and intermediate-developed areas had MAU. Some low SES parameters were associated with MAU. For example, the prevalence of MAU was higher in individuals with under a university education and in those who had low annual family income~~were farmers. Annual family income and urban vs. rural residence were not significantly associated with MAU.~~

Level of regional economic development was significantly associated with MAU with the intermediate-developed and developed areas having ~~29~~35% and ~~50~~48% lower prevalence than under-developed areas, respectively. This association appeared to be independent of metabolic abnormalities and low SES.

Strengths and limitations of the study

Strengths of this study included the large population based sample from diverse economic levels, with analyses accounting for the complex sampling design to provide a representative sample of 14 Chinese provinces; the use of RIA methods to test for urine albumin to increase sensitivity. Limitations of our study included the cross sectional design that limited the ability to make cause-effect inferences, and the one-time collection of spot urine specimens due to a large variability in albumin excretion rates that did not allow an evaluation for the persistence of MAU.

Comparison with other studies

Both men and women in our study had significantly higher prevalence of MAU compared to individuals in developed countries. [4,5] Prevalence of MAU in the general U.S. population was 6.1% in men and 9.7% in women [4], and 6% in Australians. [5] Prevalence of MAU in the Chinese participants of this study was lower than the prevalence found in Singaporeans aged 40 to 80 years, which may be explained by the fact that study used lower cut-off values to define MAU (ACR≥17 mg/g for men and ≥25 mg/g for women). [7] However, a similar result (19.4%) was observed in Shanghai, China. [8] This study was consistent with studies in Singapore where higher odds of MAU were found in individuals with lower educational obtainment, lower income in retirement, smaller housing type, and coexistence of multiple low SES factors. [7] ~~In this study, females had a higher prevalence of ACR than males, which is~~

~~consistent with the results from a U.S. sample from the NHANES study.[4] Higher levels of ACR in healthy women than in healthy men that have been observed in many studies could result in the overestimation of MAU in females, if the same criteria for MAU are used for both males and females.~~

Meaning of the study

MAU has been recognized as an early sign of renal damage, and a significant predictor of end-stage renal disease, cardiovascular mortality, and morbidity in patients with diabetes. [13-15] In patients with type 1 diabetes, MAU is considered an indicator of the third stage of diabetic nephropathy. [13] A recent study demonstrated methods that decrease MAU may reduce the risk for end-stage renal disease. [~~3~~24,25] Endothelial dysfunction and micro-inflammation of vasculature have been proposed as pathogenic mechanisms of MAU, which also links MAU to vascular atherosclerosis. Monitoring MAU levels may help identify endothelial dysfunction and vascular micro-inflammation in subjects with obesity, high blood pressure, dyslipidemia, and blood glucose. [1] For this reason, the World Health Organization (WHO) has included MAU in their criteria for the metabolic syndrome (MS). [14] MAU was strongly associated with older age, obesity, metabolic abnormalities, lower SES, and residence in lower economic development areas. Limited access to health care services for low SES subjects could help explain some of the association between SES and MAU. Many studies have shown an association between MAU and CRP level, a marker for microinflammation [2~~3~~6], which has been shown to be higher in low healthcare utilization and low SES populations. Periodental diseases have also been shown to be more common in low SES populations and are associated with increased CRP level. We did not have data to explore the association between periodontal diseases and MAU.Additional research could help clarify the relationship between SES and MAU, especially the underlying mechanism. Higher

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prevalence of MAU in under-developed areas could be due in part to inadequate availability of health care services and to unfavorable environmental factors. Development of strategies to lower the risk for MAU in these susceptible populations should be emphasized. Besides measures to prevent and control metabolic disorders, we propose that reforming the health system, improving access to health facilities, prompting health education, preventing periodontal diseases especially in low SES population and in under-development region, may reduce the prevalence of MAU and reduce the incidence of CVD and mortality in general population.

Conclusions

In conclusion, MAU was strongly associated with older age, ~~obesity,~~ metabolic abnormalities, lower SES, and residence in lower economic development areas. It is suggested that future research studies explore the extent to which MAU could mediate the association between low SES and metabolic, cardiovascular, and cerebrovascular diseases.

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All of the authors designed the study, revised and approved the paper, and decided to publish the paper. JX, XX, JL, JW, WJ, LJ, ZS, JL, HT, QJ, DZ, JG, GC, LC, XG, Z Zhao, QL, Z Zhou, ZY and WY contributed to the acquisition of data. JX, XX and ZY were responsible for the analysis and interpretation of data. JX, XX and WY drafted the manuscript. WY had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JX and XX contributed equally to the study.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

The research ethics board of China-Japan Friendship Hospital approved this study.

Article summary

Article focus:

To investigate the prevalence of MAU among Chinese without diabetes. To study the relationship between MAU and metabolic factors, individual SES, and regional economic development level.

Key message:

In Chinese individuals without diabetes, the prevalence of MAU was ~~16.9~~24.4% in males and 24.5~~.1~~% in females, respectively, which was significantly higher than individuals in developed countries. MAU was strongly associated with older age, ~~obesity,~~ metabolic abnormalities, lower SES, and residence in lower economic development areas, which encouraged the development of strategies to lower the risk for MAU in these susceptible populations.

Strengths and limitations of the study:

It was the first study on prevalence of MAU in Chinese which based on a large population-based sample from diverse economic levels, with analyses accounting for the complex sampling design to provide a representative sample of 14 Chinese provinces. Moreover, using of RIA methods in urine albumin measurement increased the sensitivity. However, the limitation is that it is a cross-sectional study, which could not demonstrate cause-effect relationship.

References

1. Bigazzi R, Bianchi S, Baldari D, et al. Microalbuminuriapredicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 1998;16(9):1325-1333.

2. Stehouwer CD, Gall MA, Twisk JW, et al. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes* 2002;51(4):1157–1165.

~~3. Wachtell K, Olsen MH, Dahlöf B, et al. Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE Study. *J Hypertens* 2002;20(3):405-412.~~

3.Hillege HL, Fidler V, Diercks GF, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106(14):1777-82.

4. Jones CA, Francis ME, Eberhardt MS, et al. Microalbuminuriain the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2002;39(3):445-459.

5. Atkins RC, Polkinghorne KR, Briganti EM, et al. Prevalence of albuminuria in Australia. *Aus Diab Kidney Int* 2004;66(S92):S22–S24.

6. Zacharias JM, Young TK, Riediger ND, et al. Prevalence, risk factors and awareness of albuminuria on a Canadian First Nation: A community-based screening study. *BMC Public Health* 2012;12: 290.

7. Sabanayagam C, Shankar A , Saw SM, et al. Socioeconomic status and microalbuminuria in an Asian population. *Nephrol Dial Transplant* 2009;24(1):123–129.

8. Jia W, Gao X, Pang C, et al. Prevalence and risk factors of albuminuria and chronic kidney disease in Chinese population with type 2 diabetes and impaired glucose regulation: Shanghai

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diabetic complications study (SHDCS). *Nephrol Dial Transplant* 2009;24(12):3724-3731.

9. Li M, Xu M, Bi Y, et al. Association between higher serum fetuin-A concentrations and abnormal albuminuria in middle-aged and elderly chinese with normal glucose tolerance. *Diabetes Care* 2010;33(11):2462-2464.

10. Brandt JR, Jacobs A, Raissy HH, et al. Orthostatic proteinuria and the spectrum of diurnal variability of urinary protein excretion inhealthy children. *Pediatr Nephrol* 2010;25(6):1131–1137.

11. Jefferson IG, Greene SA, Smith MA, et al. Urine albumin to creatinine ratio-response to exercise in diabetes. *Arch Dis Child* 1985;60(4):305–310.

12. Brinkman JW, Bakker SJ, Gansevoot RT, et al. Which method for quantifying urinary albumin excretion gives what outcome? A comparison of immunonephelometry with HPLC. *Kidney Int* 2004;66(S92):S69–S75.

13. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;310(6):356-360.

14. Gobal F, DeshmukhA, Shah S, et al. Triad of Metabolic Syndrome, chronic kidney disease, and coronary heart disease with a focus on microalbuminuria - death by overeating. *J Am Coll Cardiol* 2011;57(23):2303–2308.

15. Kannel WB, Stampfer MJ, Castelli WP, et al. The prognostic significance of proteinuria: The Framingham Study. *Am Heart J* 1984;108(5):1347-1352.

16. Chew GT, Gan SK, Watts GF. Revisiting the metabolic syndrome. *Med J Aust* 2006;185(8):445-449.

17. Martins D, Tareen N, Zadshir A, et al. The association of poverty with the prevalence of albuminuria: data from the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2006;47(6):965–971.

18. Al-Qaoud TM, Nitsch D, Wells J, et al. Socioeconomic status and reduced kidney

function in the Whitehall II Study: role of obesity and metabolic syndrome. *Am J Kidney Dis* 2011;58(3):389-397.

19. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010;362(12):1090-1101.

20. Luepker RV EA, McKeigue P, Reddy KS. *Cardiovascular survey methods. 3rd ed.* Geneva: World Health Organization; 2004.

21. National Bureau of Statistics of China. China statistical yearbook — 2006. http://www.stats.gov.cn/tjsj/ndsj/2006/indexeh.htm. Accessed February 26, 2010.

22. Houlihan CA, Tsalamandris C, Akdeniz A, et al. Albumin to creatinine ratio:a screening test with limitations. Am J Kidney Dis. 2002;39(6):1183-9.

231. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006;29(5):1130-1139.

~~22. National Bureau of Statistics of China. China statistical yearbook — 2006. http://www.stats.gov.cn/tjsj/ndsj/2006/indexeh.htm. Accessed February 26, 2010.~~

24.Asselbergs FW, Diercks GF, Hillege HL,et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110(18):2809-16.

25. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348(5):383-93.

263. Pravenec M, Kajiya T, Zídek V, et al. Effects of human C-reactive protein on pathogenesis of features of the metabolic syndrome. *Hypertension* 2011;57(4):731-737.

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Figure legends

Figure 1. Prevalence of MAU in various categories in Chinese without diabetes

1A. ~~a~~Age and sex specific prevalence of MAU; 1B. ~~p~~Prevalence of MAU in different obesity, blood pressure and ISI groups; 1C. prevalence of MAU in different education level, income level, profession, and SES level groups. *P trend<0.001 among age groups,†*P* <0.001 men vs. women in ~~all~~ corresponding age subgroups; ~~†~~‡*P*<0.01 in different ~~sex,~~ ISI, BMI, blood pressure, ~~and~~ glucose tolerance ~~groups; ‡*P*<0.01 in different sex~~, economic developed areas, education level, incomes and profession groups;#*P*<0.01 men vs. women in corresponding subgroups.

Figure 2. Prevalence of MAU in individuals with different metabolic status and SES level

2A.Pprevalence of MAU in individuals with different numbers of components of metabolic risk factors~~status~~. †*P*-trend<0.001 for comparing different risk factor numbers; **P*<0.05 vs. under-developed~~ing~~ area; #*P*<0.05 vs. intermediate developing area.

2B. ~~p~~Prevalence of MAU in individuals with different numbers of low SES level. †*P*-trend<0.001 for comparing different low SES numbers; **P*<0.05 vs. under-developed~~ing~~ area ~~#*P*<0.05 vs. intermediate developing area.~~

2C.Number of low SES level and gender-specific prevalence of MAU. †*P*-trend<0.001 for comparing different low SES numbers;**P*<0.01 men vs. women。

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Tables

Table 1. Characteristics of participants presented by ACR quartiles in Chinese men and women

ACR (mg/g)	Men				Women			
	Q1 (0.5 to 6.8)	Q2 (6.9 to 12.5)	Q3 (12.6 to 26.3)	Q4 (≥26.4)	Q1 (0.5 to 6.8)	Q2 (6.9 to 12.5)	Q3 (12.6 to 26.3)	Q4 (≥26.4)
N=35,470	4,265	3,682	2,960	2,820	4,589	5,264	5,839	6,051
Age (year)	41.1(40.4,41.9)	42.8(41.9,43.7)*	45.2(44.2,46.2)*	48.3(47.3,49.3)*	41.6(40.8,42.4)	41.2(40.5,42.0)	43.2(42.4,44.0)*	47.6(46.4,48.9)*
Overweight	26.8(23.2,23.5)	27.9(23.4,23.8)	29.0(24.3,24.6)*	33.1(30.2,36.1)*	19.9(17.7,22.4)#	23.6(21.6,25.7)*#	21.7(20.0,23.5)#	27.3(25.1,29.7)*#
Obese	4.3(3.1,6.0)	5.5(4.4,6.8)*	4.5(3.6,5.7)	8.9(7.3,10.9)*	4.2(3.3,5.3)	3.3(2.7,4.1)*	3.9(3.2,4.8)	6.3(5.2,7.5)*#
Central obesity	24.2(22.0,26.6)	24.8(22.7,27.1)	24.7(22.3,27.3)	31.9(29.1,34.9)*	34.6(32.0,37.4)#	34.8(32.6,37.1)#	36.7(34.5,38.9)*#	45.9(42.8,48.9)*#
HTG	31.3(31.0,33.8)	29.7(28.8,34.0)	32.1(29.3,35.0)	38.0(35.0,41.1)*	21.1(18.9,23.4)#	18.9(17.1,20.8)#	20.6(18.9,22.5)#	27.0(24.4,29.8)*#
Hypertension	15.8(14.2,17.6)	24.0(21.8,26.3)*	29.9(27.2,32.7)*	43.0(39.9,46.3)*	13.3(11.4,15.5)	12.5(11.2,13.9)#	19.5(17.8,21.4)*#	36.1(33.0,39.4)*#
IGR	15.8(13.7,18.1)	17.2(15.2,19.4)	18.7(16.4,21.2)*	25.0(22.3,27.8)*	13.4(11.7,15.2)	13.8(13.9,16.9)#	15.4(13.9,16.9)*#	23.3(20.4,26.4)*
IR	24.0(21.8,26.4)	24.7(22.4,27.2)	22.8(20.4,25.4)	30.1(27.2,33.1)*	22.5(20.4,24.8)	23.4(21.5,25.5)	24.0(22.0,26.1)	28.0(25.6,30.5)*

*P<0.05 vs. ACR 0.5 to 6.8 mg/g; #P<0.05 vs. men at same ACR quartiles.HTG, serum triglyceride≥1.7 mmol/l; IGR, impaired glucose regulation, IR, insulin resistant.

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Table 2. Clinical characteristics for men and women presented by level of economic development

	Men			Women		
	Under-developed	Intermediate-Developed	Developed	Under-developed	Intermediate-developed	Developed
N=41,290	4,340	3,376	8,482	6,404	5,179	13,509
Age(year)	43.7(43.4,44.0)	43.8(43.0,44.5)	44.2(43.3,45.2)	43.7(43.1,44.2)	43.7(42.6,44.9)	43.7(43.2,44.3)
Body mass index (kg/m^2)	23.3(23.2,23.5)	23.6(23.4,23.8)	24.5(24.3,24.6)*#	22.9(22.8,23.1)	23.1(23.0,23.2)	23.5(23.4,23.6)*#
Waist circumference (cm)	82.1(81.6,82.6)	80.5(79.9,81.1)*	85.2(84.9,85.6)*#	77.2(76.8,77.6)	76.2(75.5,76.9)*	78.2(77.9,78.5)*#
Systolic BP (mmHg)	119.1(118.2,120.0)	121.6(120.5,122.7)*	125.8(125.2,126.4)*#	115.4(114.5,116.3)	118.5(117.3,119.7)*	120.6(120.1,121.1)*#
Fasting PG (mmol/L)	4.9(4.9,5.0)	4.9(4.9,5.0)	5.1(5.0,5.1)*#	4.9(4.9,4.9)	4.8(4.8,4.9)	5.0(5.0,5.1)*#
PG at 30' (mmol/L)	8.1(8.0,8.2)	8.6(8.5,8.7)*	9.0(8.9,9.1)*#	7.5(7.5,7.7)	8.1(8.0,8.2)*	8.4(8.4,8.5)*#
PGat 120' (mmol/L)	5.8(5.7,5.8)	6.2(6.1,6.3)*	6.1(6.1,6.2)*	5.9(5.8,6.0)	6.2(6.1,6.3)*	6.2(6.2,6.3)*
ACR (mg/g)	14.1(7.2,27.1)	10.4(6.6,19.7)*	9.8(6.0.18.8)*#	17.1(8.2,37.0)	15.4(9.3,33.6)*	13.3(7.6,25.1)*#
Fasting serumIRI (mU/L)	6.4(4.8,8.7)	6.4(4.4,9.1)	7.3(5.1,10.4)*#	6.6(4.9,8.8)	6.5(4.6,9.1)	7.1(5.1,10.0)*#
SerumIRI at 30' (mU/L)	28.0(16.6,47.4)	30.2(16.7,49.4)	39.1(22.4,67.7)*#	31.5(19.4,50.4)	30.9(20.1,49.3)	39.5(24.7,61.9)*#
Serum IRI at 120' (mU/L)	21.1(11.8,35.1)	19.9(11.6,35.4)	26.6(15.3,47.0)*#	24.3(16.5,42.2)	25.9(11.8,37.3)	30.7(18.8,50.1)*#
Total cholesterol (mmol/L)	4.57(4.52,4.62)	4.62(4.57,4.67)	4.79(4.76,4.83)*#	4.55(4.51,4.59)	4.68(4.62,4.74)*	4.76(4.73,4.79)*#
Triglycerides (mmol/L)	1.23(0.91,1.89)	1.21(0.85,1.83)	1.37(0.93,2.16)*	1.17(0.85,1.66)	1.05(0. 78,1.55)*	1.09(0.78,1.63)*
HDL-cholesterol (mmol/L)	1.25(1.24,1.27)	1.24(1.22,1.26)	1.26(1.25,1.27)	1.33(1.32,1.35)	1.32(1.30,1.33)	1.40(1.38,1.41)*#
HOMA-IR	1.36(1.00,1.88)	1.38(0.94,2.01)	1.64(1.15,2.38)*#	1.40(1.03,1.95)	1.39(0.95,2.00)	1.59(1.15,2.26)*#
Matsuda ISI	9.3(6.5,12.3)	8.8(6.0,12.8)	6.9(4.7,10.0)*#	8.6(6.2,11.8)	8.5(5.8,11.7)	7.1(4.9,9.5)*#

SI conversion factors: To convert insulin to pmol/L, multiple values by 6.945.BP, blood pressure; PG, plasma glucose; IRI, immunoreactive insulin.

* Significant difference compared with developed area, $P<0.01$.

Significant difference compared with intermediate developed area, $P<0.01$.

Table 3. Results from multivariate logistic regression analyses for individuals with ACR≥30 mg/g *

	Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI)
Sex (women vs. men)	1.81 (1.62,2.03)	1.66 (1.44,1.92)
Age (per 10ys increment)	1.16 (1.11,1.22)	1.11 (1.06,1.18)
BMI (per 2 kg/m^2 increment)	1.06 (1.03,1.09)	1.05 (1.01,1.08)
Blood pressure (hypertension vs. normotension)	2.38 (2.08,2.72)	2.30 (2.00,2.65)
Insulin sensitivity † (IS. vs. IR)	1.14 (1.01,1.28)	1.07 (0.94,1.21)
2 hour plasma glucose (per 2 mmol/L increase)	NI	1.16 (1.08,1.26)
Education (less than college vs. college)	NI	1.21 (1.02,1.45)
Occupation (workers vs. officials or intellectuals)	NI	1.20 (1.01,1.42)
Occupation (farmers vs. officials or intellectuals)	NI	1.24 (1.01,1.52)
Development ‡ (developed vs. underdeveloped)	0.50 (0.44,0.57)	0.49 (0.43,0.55)
Development ‡ (intermediated- vs. under-developed)	0.73 (0.63,0.84)	0.71 (0.61,0.83)

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~~Residence (rural vs. urban)~~	~~1.07 (0.97,1.19)~~	~~1.00 (0.89-1.14)~~

~~* Odds ratios were calculated using multivariate logistic models. All covariates listed were included in the model simultaneously.~~

~~† Insulin resistance was defined as Matsuda ISI <25th percentile in individuals with normal glucose tolerance~~

~~‡ Economic development levels were placed into 3 categories (under-developed, intermediate-developed, and developed).~~

~~NI: not included in the model 1.~~

Table 3. Results from multivariate logistic regression analyses for individuals with ACR≥22.1 mg/g in men 30.9 mg/g in women *

	Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI)	Model 3 (OR, 95% CI)
Sex (women vs. men)	1.06 (0.95,1.17)	1.03 (0.90,1.17)	1.02 (0.89,1.17)
Age (per 10ys increment)	1.15 (1.10,1.21)	1.12 (1.07,1.18)	1.12 (1.07,1.18)
BMI (per 2 kg/m^2 increment)	1.02 (0.99,1.05)	1.02 (0.99,1.06)	1.03 (1.00,1.06)
Blood pressure (hypertension vs. normotension)	2.09 (1.84,2.37)	2.10 (1.85,2.40)	2.17 (1.90,2.48)
Insulin sensitivity † (IS. vs. IR)	1.04 (0.93,1.17)	1.09 (0.96,1.23)	1.11 (0.98,1.25)
2 hour plasma glucose (per 2 mmol/L increase)	1.13 (1.05,1.21)	1.10 (1.02,1.19)	1.14 (1.06,1.23)
Education (less than college vs. college)	NI	1.37 (1.18,1.60)	1.34 (1.15,1.55)
Annual family income (<30,000 vs.>=30,000 CNY)	NI	1.26 (1.07,1.49)	1.08 (0.91,1.27)
Occupation (workers vs. officials or intellectuals)	NI	0.79 (0.69,0.90)	0.88 (0.77,1.01)
Occupation (farmers vs. officials or intellectuals)	NI	1.06 (0.93,1.22)	1.03 (0.89,1.20)
Development ‡ (developed vs. under-developed)	NI	NI	0.52 (0.46,0.60)

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Development ‡ (intermediate- vs. under-developed)	NI	NI	0.65 (0.57,0.76)
Residence (rural vs. urban)	NI	NI	1.01 (0.90 -1.14)

* Odds ratios were calculated using multivariate logistic models. All covariates listed were included in the model simultaneously. Serum triglycerides, smoking status included the 3 models without significant difference not presented.

† Insulin resistance was defined as Matsuda ISI <25th percentile in individuals with normal glucose tolerance

‡ Economic development levels were placed into 3 categories (under-developed, intermediate-developed, and developed).

NI: not included in the model~~.~~.

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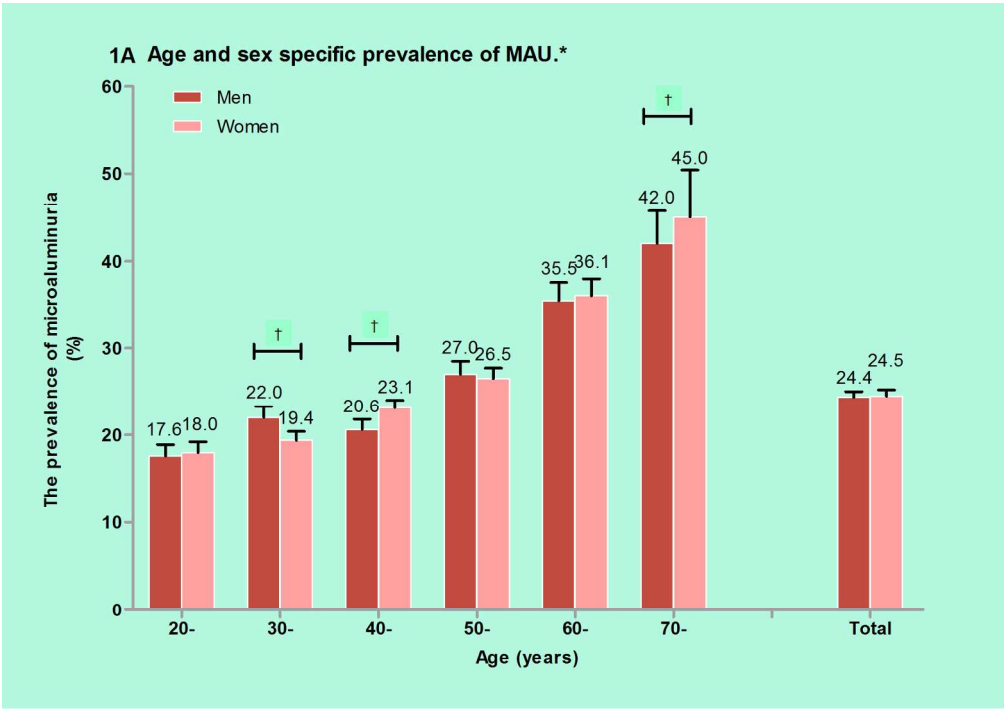

Figure 1A. Age and sex specific prevalence of MAU.
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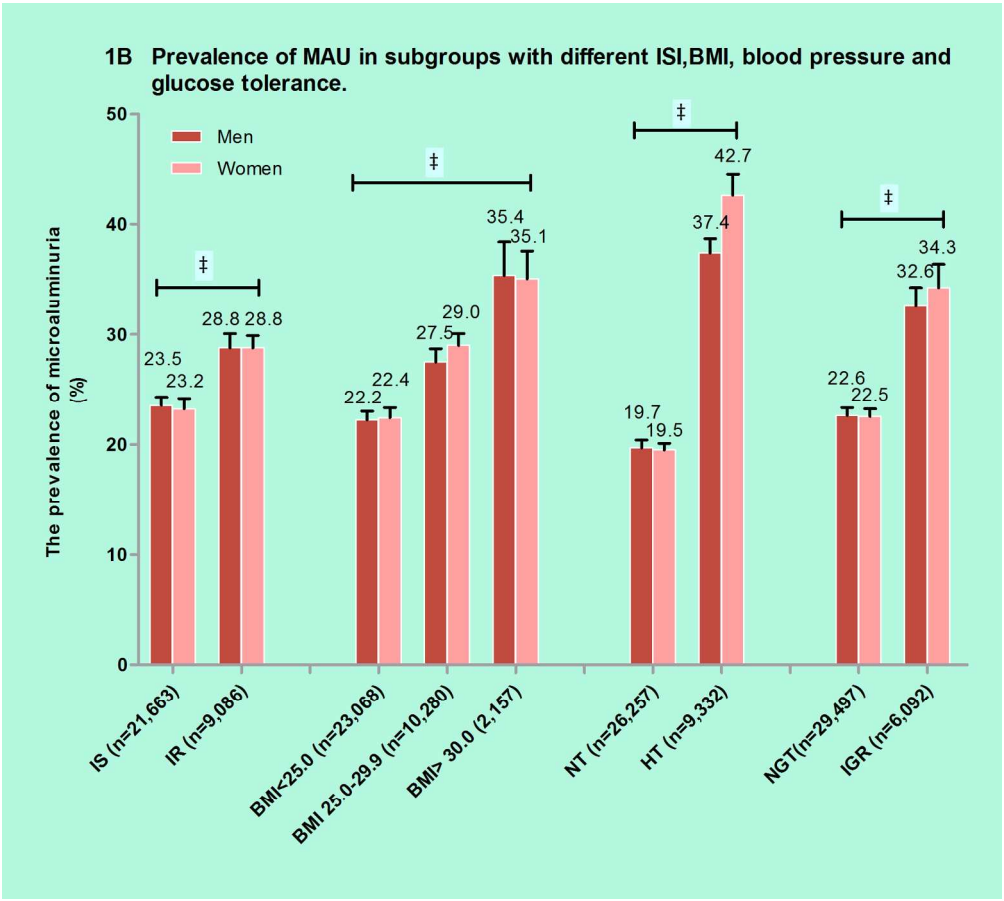

Figure 1B. Prevalence of MAU in different obesity, blood pressure and ISI groups.
172x154mm (300 x 300 DPI)

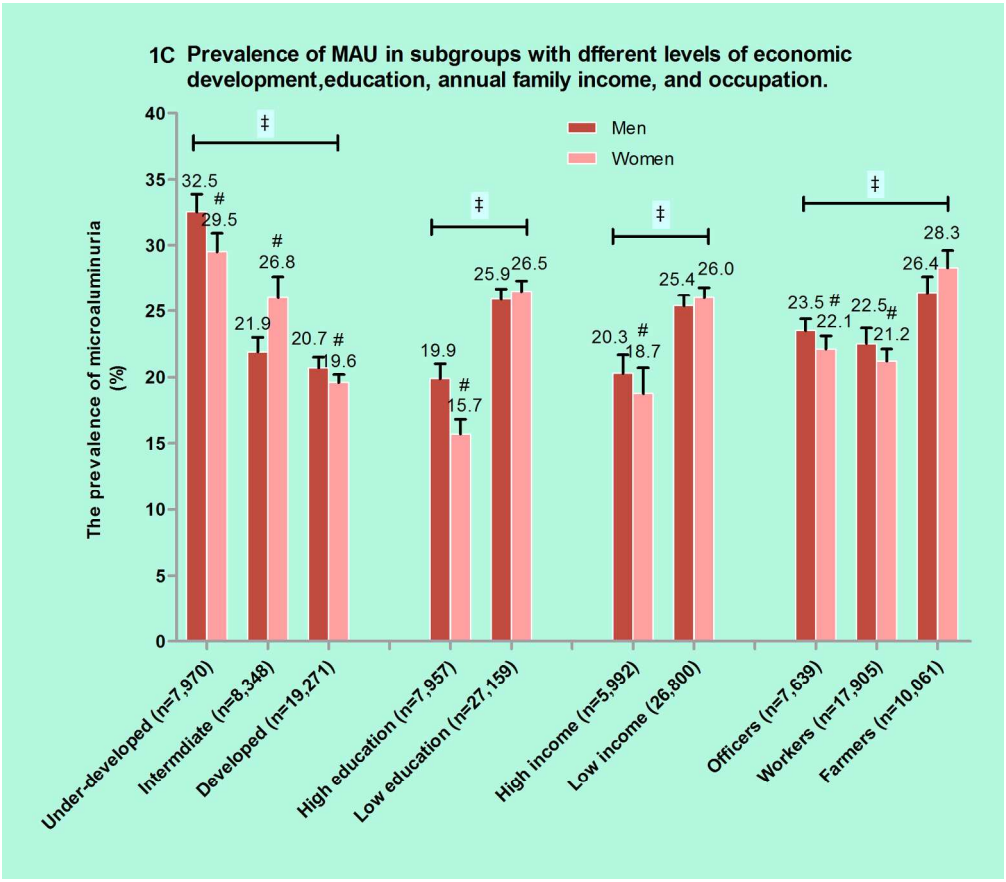

Figure 1C. prevalence of MAU in different education level, income level, profession, and SES level groups.
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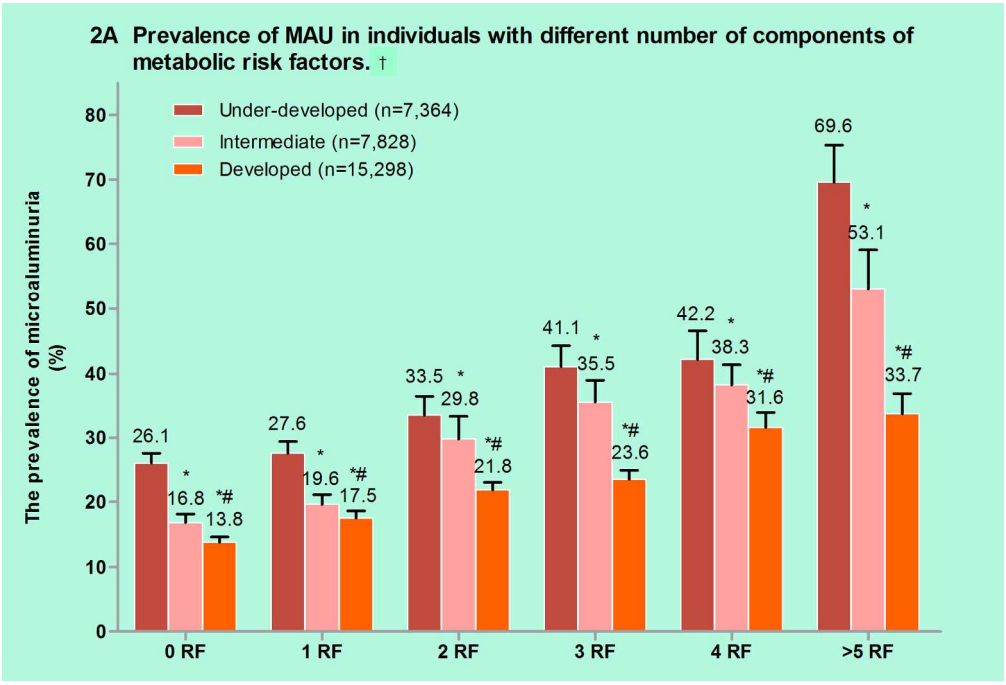

Figure 2A.Prevalence of MAU in individuals with different numbers of components of metabolic risk factors.
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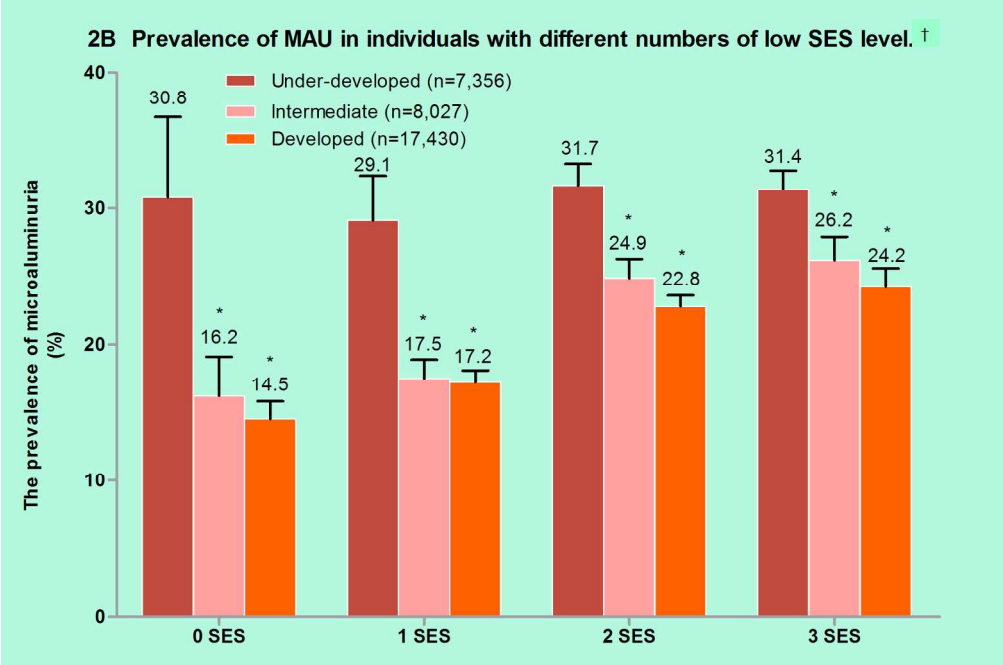

Figure 2B. Prevalence of MAU in individuals with different numbers of low SES level.
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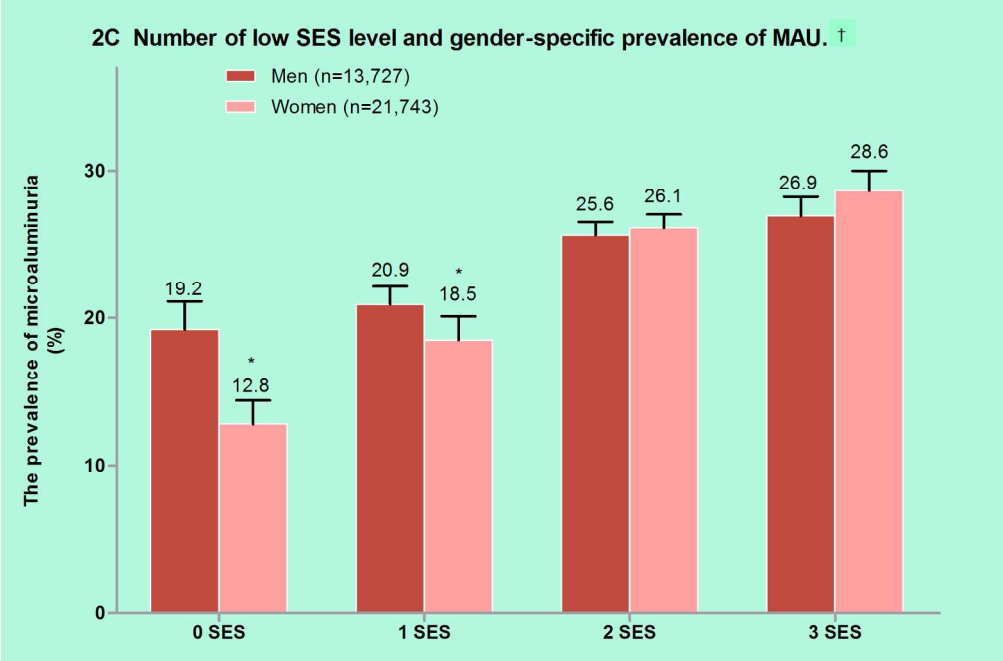

Figure 2C.Number of low SES level and gender-specific prevalence of MAU.
185x122mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7,8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	na

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1,2
		(b) Indicate number of participants with missing data for each variable of interest	Table 1,2
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Na
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Na
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Na
		Cross-sectional study—Report numbers of outcome events or summary measures	Table 1,2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 1,2
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.