

Microalbuminuria in Nondiabetic Adults

Relation of Blood Pressure, Body Mass Index, Plasma Cholesterol Levels, and Smoking: The Gubbio Population Study

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Background: Evidence exists that cardiovascular risk factors influence progression toward end-stage renal failure. We tested the hypothesis that in nondiabetic middle-aged adults without macroalbuminuria, cardiovascular risk factors are related to urinary albumin excretion and prevalence of microalbuminuria, a sign of early nephropathy.

Methods: Cross-sectional analysis of data for 1567 participants in The Gubbio Population Study (677 men and 890 women), aged 45 to 64 years, without macroalbuminuria, without diabetes mellitus, and with fasting plasma glucose levels of less than 7.8 mmol/L (140 mg/dL). Data collection included albumin and creatinine excretion in timed overnight urine collection; levels of fasting plasma cholesterol, glucose, triglycerides, creatinine, and uric acid; creatinine clearance; red blood cell sodium-lithium countertransport; blood pressure; weight; height; medical history; smoking status; and alcohol intake. Urinary albumin excretion and prevalence of microalbuminuria were the dependent variables.

Results: Blood pressure, plasma cholesterol levels, smoking, and body mass index significantly related to urinary albumin excretion and prevalence of microalbuminuria. In analyses with control for multiple variables, relative risk for microalbuminuria (urinary albumin excretion, 20-199 $\mu\text{g}/\text{min}$) in men and women was 2.51 and 1.62, respectively, with 18 mm Hg higher (1 SD) systolic blood pressure; 2.25 and 2.10, respectively, with 1.0 mmol/L (40 mg/dL) higher plasma cholesterol level; 1.99 and 1.91, respectively, for smokers vs nonsmokers; and 1.83 and 1.33, respectively, with 4 kg/m² higher body mass index. Findings were similar for microalbuminuria defined as urinary albumin excretion of at least 25 $\mu\text{g}/\text{dL}$ glomerular filtration rate.

Conclusion: Major cardiovascular risk factors are independent correlates of microalbuminuria in nondiabetic middle-aged adults.

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IN HEALTHY individuals, urinary protein excretion ranges below 150 mg/d, with albumin excretion lower than 30 mg/d. Elevation in urinary albumin excretion generally reflects renal glomerular damage. It is designated microalbuminuria if in the range that can be missed with routine laboratory techniques (30-299 mg/d or 20-199 $\mu\text{g}/\text{min}$), and macroalbuminuria if more severe. In diabetic individuals, onset of microalbuminuria—judged to be an important sign of early nephropathy¹—is related to major cardiovascular risk factors (ie, blood pressure, plasma cholesterol levels, cigarette smoking)²⁻⁴ and is predictive of risk for end-stage renal failure,⁵⁻⁹ a major and mounting public health problem. There is growing evidence that, in other diseases, the process leading to end-stage renal failure is influenced by major cardiovascular risk factors.¹⁰⁻¹⁴ In this light, a relation between cardiovascular risk factors and microal-

buminuria in nondiabetic persons could support the idea (of potential importance for medical care and public health if validated) of a continuing relationship of these factors to development and progression of renal damage, from early to ultimate stages.

Determinants of microalbuminuria have not been extensively investigated in population-based research. Three studies reported conflicting data on the association of microalbuminuria with blood pressure, body mass index (BMI), and blood lipid levels¹⁵⁻¹⁷; 3 others reported data on albumin concentration, not excretion, as urine flow rate was not measured.¹⁸⁻²⁰ We herein report on prevalence of microalbuminuria, urinary albumin excretion rate, and their correlates in a population sample of nondiabetic middle-aged adult men and women. We test the prior hypothesis that major cardiovascular risk factors (ie, plasma cholesterol level, blood pressure,

PARTICIPANTS AND METHODS

COHORT

The Gubbio Population Study is a population-based, on-going investigation in the hill town of Gubbio, in north central Italy.²¹⁻²⁸ The cohort for our analysis is based on 1684 persons (740 men and 944 women), aged 45 to 64 years, who participated in the second examination. From this cohort, 110 individuals (57 men and 53 women) were excluded for previous diagnosis of diabetes mellitus ($n = 101$) or fasting plasma glucose levels of at least 7.8 mmol/L (140 mg/dL) ($n = 9$); 7 more individuals (6 men and 1 woman), for macroalbuminuria (albuminuria ≥ 200 $\mu\text{g}/\text{min}$) in timed overnight urine collection. Thus, the cohort for our study is 1567 individuals (677 men and 890 women).

DATA COLLECTION

At the second examination, data were collected on sex, age, weight, height, medical history, systolic (SBP) and diastolic blood pressure (DBP), antihypertensive treatment status, alcohol intake, and smoking habit, using methods as in the baseline examination.²¹⁻²⁸ Weight (in kilograms) was divided by height (in square meters) to calculate BMI. Body surface area (BSA) was calculated in square meters using the following equation:

$$\text{BSA} = 71.84 \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$$

where weight is given in kilograms and height in centimeters. Participants were instructed on collecting a timed overnight urine specimen for measurement of urinary albumin and creatinine levels. After overnight fast, blood samples were drawn for measurement of levels of plasma glucose, total and high-density lipoprotein (HDL) cholesterol (used to calculate non-HDL cholesterol levels as

total cholesterol - HDL cholesterol), triglycerides, uric acid, and creatinine and for determination of red blood cell activity of sodium-lithium countertransport (Na-Li CT). Creatinine clearance was taken as index of glomerular filtration rate (GFR) (milliliters per minute) and calculated as creatininuria (millimoles per day) divided by plasma creatinine level (micromoles per liter). Urinary albumin level was measured using a commercial immunoturbidimetric assay; urine samples were concentrated using ultrafiltration²⁹ when urinary albumin concentration was below 7 $\mu\text{g}/\text{mL}$. Automated biochemical analysis was used for other determinations in urine and plasma, as previously reported.²¹⁻²⁸ For urine and plasma determinations, 10% of samples were processed as blind duplicates. The intra-assay technical error was 8.8% for urinary albumin level and less than 5% for other plasma and urine variables. The Na-Li CT in red blood cells was measured as described^{21,22,27,28}; assays were considered valid only for days with technical error of less than 20%. Valid determinations of Na-Li CT were available for 1160 (506 men and 654 women) of the 1567 individuals included in the analysis. For analyses using reported alcohol intake and reported number of cigarettes smoked per day as continuous variables, both variables were logarithm-transformed; the logarithm-transformed number of cigarettes smoked per day and alcohol intake were coded as zero for nonsmokers and nondrinkers, respectively.^{27,28}

STATISTICAL METHODS

Univariate product moment and rank order correlation analysis, χ^2 analysis with correction for continuity, univariate logistic regression analysis, and multivariate linear and logistic regression analysis were used. Exponentiated logistic regression coefficients and SEs were used to calculate relative risks and 95% confidence intervals (CIs).

cigarette smoking) relate independently to microalbuminuria. Individuals with diabetes mellitus or macroalbuminuria were excluded from analyses to focus on correlates of early glomerular damage independent of diabetes mellitus.

RESULTS

DESCRIPTIVE STATISTICS

Descriptive statistics are shown in **Table 1** for data on urinary albumin levels and in **Table 2** for other variables. Compared with women, men had higher urinary albumin concentration and excretion per minute, similar excretion per deciliter of GFR, and lower albumin-creatinine ratio. Urinary albumin excretion per minute and per deciliter of GFR were logarithm-transformed in correlation analyses, as they were positively skewed in men and women (skewness >4). Logarithm-transformed albumin excretion per minute and per deciliter of GFR were highly correlated (men and women, $r = 0.936$ and 0.940 , respectively; $P < .001$).

The percentage of individuals with urinary albumin above cutoff points commonly used to define microalbuminuria^{1,30} varied from 4.7% to 7.1% in men and from 2.4% to 11.1% in women. Prevalence of urinary albumin concentration of at least 30 mg/L and of urinary albumin excretion of at least 25 $\mu\text{g}/\text{dL}$ GFR were similar in men and women. In contrast, prevalence of urinary albumin-creatinine ratio of at least 2.5 mg/mmol was more than twice as high for women than men; the opposite was the case for prevalence of urinary albumin excretion of at least 20 $\mu\text{g}/\text{min}$.

There were significant inverse relationships of urine flow rate to prevalence of urinary albumin concentration of at least 30 mg/L (for men and women, 12.9 and 15.1 times higher prevalence, respectively, for 0.5 mL/min lower urine flow rate; $P < .001$) and of creatininuria to prevalence of urinary albumin-creatinine ratio of at least 2.5 mg/mmol (for men and women, 2.11 and 3.88 times higher, respectively, for 2 $\mu\text{mol}/\text{min}$ lower creatininuria; $P < .001$). Therefore, data for urinary albumin concentration and urinary albumin-creatinine ratio were not used for analysis, to avoid confounding by urine flow rate and creatininuria.

Table 1. Urinary Albumin Levels and Related Indices*

Variable	Men	Women
No. of persons	677	890
Urinary albumin concentration, mean \pm SD, mg/L	13.3 \pm 13.7	11.6 \pm 11.4
Urinary albumin-creatinine ratio, mean \pm SD, mg/mmol	1.15 \pm 1.15	1.39 \pm 1.37
Urinary albumin excretion, mean \pm SD μ g/min	10.4 \pm 10.1	8.9 \pm 8.5
μ g/dL GFR	10.7 \pm 10.9	11.0 \pm 11.2
Urinary albumin \geq 30 mg/L, No. (%)	48 (7.1)	55 (6.2)
Urinary albumin-creatinine ratio \geq 2.5 mg/mmol, No. (%)	32 (4.7)	99 (11.1)
Urinary albumin excretion \geq 20 μ g/min, No. (%)	38 (5.6)	21 (2.4)
Urinary albumin excretion \geq 25 μ g/dL GFR, No. (%)	33 (4.9)	35 (3.9)

*GFR indicates glomerular filtration rate (ie, creatinine clearance, milliliters per minute).

RELATIONSHIP OF OTHER VARIABLES TO URINARY ALBUMIN EXCRETION RATE OR PREVALENCE OF MICROALBUMINURIA

Univariate Analyses

In simple correlation analyses of logarithm-transformed albumin excretion with other variables, findings for several variables were similar with use of both albumin excretion indices, per minute or per 100 mL GFR (**Table 3**). Thus, blood pressure and levels of plasma total and non-HDL cholesterol, triglycerides, and uric acid were positively related to both indices of urinary albumin excretion rate, with correlation coefficients larger for women than men. Creatinine clearance inversely related to albumin excretion per deciliter of GFR in men and women; expressed in micrograms per minute, the relation was positive for men and nil for women. The BMI of both sexes positively related to albumin excretion expressed as micrograms per minute; *r* values were small and nonsignificant with albumin excretion expressed per deciliter of GFR. This finding reflected the positive association between BMI and GFR (for men and women, *r* = 0.400 and 0.476, respectively; *P* < .001), ie, the higher the BMI, the higher the creatinine clearance and the lower the urinary albumin excretion per deciliter of GFR. For SBP and DBP, *r* values were larger when individuals receiving antihypertensive drugs were excluded from analyses (data not shown); logarithm- or quadratic-transformation of SBP and DBP did not increase *r* values (data not shown). For all variables, findings were similar to the foregoing when nontransformed albumin excretion or Spearman rank order correlation were used (data not shown).

In univariate logistic analyses (data not shown), SBP, DBP, and levels of plasma total and non-HDL cholesterol significantly and directly related to microalbuminuria defined as albumin excretion of at least 20 μ g/min or at least 25 μ g/dL GFR for both sexes; for SBP and DBP, findings were similar when individuals receiving antihypertensive drugs were excluded from analyses (data

not shown). Creatinine clearance for both sexes significantly and inversely related to microalbuminuria defined as albumin excretion of at least 25 μ g/dL GFR only. The BMI of both sexes significantly and positively related to microalbuminuria defined as albumin excretion of at least 20 μ g/min only. Cigarettes smoked per day for both sexes significantly and positively related to microalbuminuria defined as albumin excretion of at least 25 μ g/dL GFR; with microalbuminuria defined as albumin excretion of at least 20 μ g/min, logistic coefficients were borderline significant in men and nonsignificant in women. Within the group of participants with untreated hypertension, prevalence of microalbuminuria was not consistently different between those with SBP of 160 mm Hg or greater or DBP of 95 mm Hg or greater and those with SBP of 140 to 159 mm Hg and DBP of 90 to 94 mm Hg (data not shown).

Multivariate Linear Analyses

Table 4 shows linear regression coefficients with non-transformed urinary albumin excretion per minute and per deciliter of GFR regressed on other variables, for men and women separately (Na-Li CT was not included in these models as it was not available for all individuals). In models with use of albumin excretion per minute, coefficients were significant and positive for SBP and BMI in both sexes, for plasma total cholesterol levels in women, and for cigarettes smoked per day in men. In models with use of albumin excretion per deciliter of GFR, coefficients were significant in both sexes for SBP and plasma total cholesterol levels (positive) and for creatinine clearance (inverse); they were significant for men but not women for BMI and cigarettes smoked per day. Findings were similar from analyses with logarithm-transformed albumin excretion and from analyses with exclusion of 48 persons with plasma glucose levels of 6.4 to 7.7 mmol/L (115-139 mg/dL) (data not shown).

In sex-controlled analyses with men and women combined, SBP, BMI, plasma total cholesterol levels, and logarithm-transformed cigarettes smoked per day related significantly to both indices of albumin excretion (regression coefficients similar to those shown in Table 4); sex related to albumin excretion per minute (1.53 μ g/min higher in men than women; *P* = .01) but not per deciliter of GFR (*P* = .53). In sex-controlled analyses for men and women combined, with DBP instead of SBP, DBP related to albumin excretion per minute and per deciliter of GFR (regression coefficients, 0.107 and 0.111, respectively; *P* < .001); findings for other variables were similar to the foregoing.

Multivariate Logistic Analyses

Table 5 shows relative risk and 95% CI from multiple logistic analyses with prevalence of microalbuminuria regressed on other variables for men and women separately. Plasma total cholesterol level and SBP related directly to both indices of microalbuminuria in men and women; BMI related directly to both indices of microalbuminuria in men but not in women; cigarette smoking (directly) and creatinine clearance (inversely) related to

Table 2. Descriptive Statistics for Other Variables*

Variable	Men	Women
No. of persons	677	890
Volume of overnight urine collection, mL	439 ± 224	446 ± 237
Duration of overnight urine collection, min	494 ± 68	493 ± 61
Urine flow rate, mL/min	0.90 ± 0.46	0.91 ± 0.49
Urinary creatinine concentration, mmol/L	12.7 ± 5.3	9.2 ± 4.5
Urinary creatinine excretion, μmol/min	9.49 ± 2.24	6.67 ± 1.52
Plasma creatinine, μmol/L	93.7 ± 13.3	78.7 ± 10.6
Creatinine clearance, mL/min	103.0 ± 27.9	86.3 ± 22.6
Creatinine clearance, mL/min × 1.73 m ² of body surface area	94.5 ± 23.0	89.1 ± 20.5
Age, y	54.0 ± 5.5	54.4 ± 5.7
Systolic pressure, mm Hg	129.4 ± 17.9	129.8 ± 18.1
Diastolic pressure, mm Hg	79.0 ± 9.7	78.1 ± 9.5
Persons with hypertension, No. (%)†		
All	263 (38.8)	344 (38.7)
Receiving antihypertensive drug	113 (16.7)	163 (18.3)
Body mass index, kg/m ²	27.8 ± 3.6	27.9 ± 4.7
Persons with obesity, No. (%)‡	309 (45.6)	404 (45.4)
Plasma glucose, mmol/L (mg/dL)	5.1 ± 0.6 (92.7 ± 11.2)	5.0 ± 0.6 (89.7 ± 10.4)
Persons with mild hyperglycemia, No. (%)§	29 (4.3)	19 (2.1)
Plasma cholesterol, mmol/L (mg/dL)	5.9 ± 1.0 (226.7 ± 40.3)	6.0 ± 1.0 (231.2 ± 38.0)
Persons with hypercholesterolemia, No. (%)	248 (36.6)	356 (40.0)
Plasma HDL cholesterol, mmol/L (mg/dL)	1.2 ± 0.3 (46.1 ± 11.6)	1.4 ± 0.3 (53.8 ± 12.0)
Plasma non-HDL cholesterol, mmol/L (mg/dL)	4.7 ± 1.1 (180.7 ± 41.1)	4.6 ± 1.0 (177.4 ± 38.6)
Plasma triglycerides, mmol/L (mg/dL)	2.1 ± 1.5 (182.0 ± 131.6)	1.5 ± 0.8 (134.4 ± 68.7)
Plasma uric acid, μmol/L (mg/dL)	321 ± 79 (5.40 ± 1.33)	234 ± 67 (3.94 ± 1.12)
Smokers, No. (%)	252 (37.2)	232 (26.1)
Cigarettes per day, smokers	16.4 ± 10.8	10.7 ± 8.8
Logarithm-transformed cigarettes per day, all	0.41 ± 0.58	0.23 ± 0.43
Alcohol drinkers, No. (%)	587 (86.7)	523 (58.8)
Alcohol intake, drinkers, g/d	57.5 ± 36.3	21.3 ± 17.8
Logarithm-transformed alcohol intake, all g/d	1.45 ± 0.63	0.74 ± 0.64
Red blood cell activity of Na-Li CT, μmol/L × h ⁻¹ ¶	362 ± 141	305 ± 121

*Unless otherwise indicated, data are given as mean ± SD. HDL indicates high-density lipoprotein.

†Indicates systolic pressure of at least 140 mm Hg and/or diastolic pressure of at least 90 mm Hg and/or receiving antihypertensive drug.

‡Indicates body mass index of at least 28 kg/m².

§Indicates fasting plasma glucose level of 6.4 to 7.7 mmol/L (115-139 mg/dL).

||Indicates plasma cholesterol level of at least 6.2 mmol/L (240 mg/dL).

¶Indicates sodium-lithium countertransport, measured for 74.0% of individuals.

microalbuminuria defined as albumin excretion of at least 25 μg/dL GFR. Results were similar in analyses with exclusion of individuals with plasma glucose levels of 6.4 to 7.7 mmol/L (115-139 mg/dL) (data not shown).

In sex-controlled analyses with men and women combined, SBP, BMI, plasma total cholesterol level, and cigarette smoking related directly and significantly to both indices of microalbuminuria (differences in relative risk similar to those shown in Table 5); sex related significantly to microalbuminuria (men vs women, relative risk for albumin excretion ≥20 μg/min and ≥25 μg/dL GFR, 2.58 and 2.25, respectively; *P* < .03); and creatinine clearance related significantly (inversely) to microalbuminuria defined as albumin excretion of at least 25 μg/dL GFR. In sex-controlled analyses with DBP instead of SBP, DBP related directly to microalbuminuria (relative risk for 10 mm Hg higher DBP, albumin excretion ≥20 μg/min and ≥25 μg/dL GFR, 1.94 and 1.66, respectively; *P* < .001); in analyses with logarithm-transformed cigarettes smoked per day instead of cigarette smoking, logarithm-transformed cigarettes smoked per day related directly to both indices of microalbuminuria (*P* < .05); findings for other variables were similar to the foregoing.

COMMENT

The main findings of the study are that cardiovascular risk factors amenable to prevention and control (ie, blood pressure and plasma cholesterol levels, BMI, and cigarette smoking) are independent correlates of urinary albumin excretion rate and prevalence of microalbuminuria in nondiabetic middle-aged adults. Findings were similar with exclusion of individuals with fasting plasma glucose levels of 6.4 to 7.7 mmol/L (115-139 mg/dL), who are at high risk for diabetes and may have had glucose intolerance. For SBP, plasma cholesterol levels, and smoking, results were similar with both indices of microalbuminuria, but not for BMI. Low coefficients for BMI in analyses with use of albumin excretion per deciliter of GFR were due to associations among albumin excretion per deciliter of GFR, creatinine clearance, and BMI. In some sex-specific analyses, findings for smoking and BMI were not significant for women, possibly due to low statistical power; microalbuminuria was less prevalent in women than men. Use of a single measure of blood pressure and urinary albumin and plasma cholesterol levels

Table 3. Simple Correlation Coefficients of Logarithm-Transformed Urinary Albumin Excretion Rate With Other Variables*

Variable	Urinary Albumin Excretion, µg/min		Urinary Albumin Excretion, µg/dL GFR†	
	Men	Women	Men	Women
Age, y	-0.040	0.086‡	0.057	0.164§
Systolic pressure, mm Hg	0.118‡	0.201§	0.139§	0.193§
Diastolic blood pressure, mm Hg	0.090‡	0.210§	0.067	0.179§
Body mass index, kg/m ²	0.187§	0.179§	0.050	0.006
Plasma cholesterol, mmol/L				
Total	0.123‡	0.238§	0.123§	0.258§
HDL	-0.015	0.067	-0.011	0.095‡
Non-HDL	0.125§	0.216§	0.124§	0.227§
Plasma triglycerides, mmol/L	0.095‡	0.109§	0.092	0.103‡
Plasma uric acid, µmol/L	0.070	0.138§	0.069	0.125§
Plasma glucose, mmol/L	0.041	0.022	0.026	-0.030
Logarithm-transformed, cigarettes per day	0.057	0.011	0.062	0.026
Logarithm-transformed, alcohol intake, g/d	0.021	-0.130§	0.002	-0.123§
Creatinine clearance, mL/min¶	0.116‡	0.018	-0.216§	-0.304§
Na-Li CT#	0.045	-0.010	0.016	-0.048

*HDL indicates high-density lipoprotein.

†Indicates glomerular filtration rate, calculated as creatinuria (millimoles per day) divided by plasma creatinine level (micromoles per liter).

‡P < .01.

§P < .001.

||P < .05.

¶Measured as milliliters per minute times 1.73 m² of body surface area.

#Indicates sodium-lithium countertransport, measured for 73.8% of individuals.

Table 4. Multiple Linear Regression Coefficients by Sex: Relationship of Other Variables to Urinary Albumin Excretion*

Variable	Urinary Albumin Excretion, µg/min		Urinary Albumin Excretion, µg/dL GFR†	
	Men	Women	Men	Women
Systolic blood pressure, mm Hg	0.0754‡	0.0829§	0.0683‡	0.1015§
Body mass index, kg/m ²	0.526§	0.219‡	0.329§	0.117
Plasma total cholesterol, mmol/L	-0.000375	-0.001047§	0.000579	0.001231§
Logarithm-transformed cigarettes per day	1.587	1.073	1.347	1.359¶
Creatinine clearance, mL/min†	0.0303	-0.0062	-0.096§	-0.113§

*Also in models: age; use of antihypertensive drugs; levels of plasma glucose, uric acid, and triglycerides; and logarithm-transformed alcohol intake, all these not significantly related to urinary albumin excretion.

†Described in the second footnote to Table 3.

‡P < .01.

§P < .001.

||P < .05.

¶P < .10.

resulted in limitation in precision of classification of individuals (regression dilution bias) due to intraindividual variability in these variables; therefore, coefficients reported in the study probably underestimate the true association.

Cross-sectional data have to be interpreted cautiously. The association between blood pressure and urinary albumin excretion is in contrast with data from a previous epidemiological study¹⁵; this relation could indicate an effect of blood pressure on glomerular function, of glomerular dysfunction on blood pressure, or of a third factor favoring increase in blood pressure and albumin excretion. Among these not mutually exclusive possibilities, an effect of blood pressure on glomerular function may be interpreted as the main one, since reduction of high blood pressure is known to lower urinary albumin excretion.³⁰ For BMI and smoking, it seems reasonable to infer an effect on glomerular function. Such

effects, although difficult to explain in terms of mechanisms, are supported by observations in obese or diabetic patients with proteinuria.^{4,31} The association of plasma cholesterol levels with microalbuminuria is in contrast to data from a previous clinical study.³² This association could conceivably reflect increase in plasma cholesterol level secondary to microalbuminuria.³³ However, microalbuminuria represents negligible albumin loss without lower plasma protein level, which is considered one of the important stimuli for increased cholesterol synthesis with gross proteinuria.³³ The alternative possibility, that hypercholesterolemia contributes to glomerular dysfunction, is supported by clinical and experimental observations linking hyperlipidemia to renal dysfunction.³⁴⁻³⁸ In some individuals, particularly the obese, microalbuminuria could reflect an insulin-resistant syndrome with overweight, high blood pressure, and high plasma lipids grouped together.³⁹ Plasma insulin levels

Table 5. Multiple Logistic Regression Analyses by Sex: Relationship of Other Variables to Prevalence of Microalbuminuria*

Variable	Difference	Difference in Relative Risk (95% Confidence Interval)			
		Urinary Albumin Excretion, ≥20 µg/min		Urinary Albumin Excretion, ≥25 µg/dL GFR†	
		Men	Women	Men	Women
Body mass index	4 kg/m ²	1.83 (1.23-2.72)‡	1.33 (0.91-1.93)	1.76 (1.16-2.67)‡	1.07 (0.74-1.55)
Systolic blood pressure	18 mm Hg	2.51 (1.80-2.98)§	1.62 (1.04-2.53)	1.82 (1.31-2.52)§	1.98 (1.40-2.82)§
Plasma cholesterol level	1.0 mmol/L (40 mg/dL)	2.25 (1.53-3.31)§	2.02 (1.25-3.26)‡	1.89 (1.27-2.81)‡	2.21 (1.47-3.31)§
Cigarette smoking	Yes vs no	1.99 (0.97-4.07)	1.91 (0.73-4.96)	2.53 (1.13-5.67)	2.32 (1.08-4.98)
Creatinine clearance‡	20 mL/min	0.79 (0.55-1.40)	0.89 (0.53-1.47)	0.27 (0.16-0.43)§	0.29 (0.17-0.50)§

*Also in models: age; use of antihypertensive drugs; levels of plasma glucose, triglycerides, and uric acid; and logarithm-transformed alcohol intake, all these not significantly related to microalbuminuria.

†Described in the second footnote to Table 3.

‡P < .01.

§P < .001.

||P < .05.

¶P < .10.

or insulin resistance were not measured in our cohort; these variables were not related or related inversely to microalbuminuria in other studies.^{40,41}

A primary relation of blood pressure, plasma cholesterol level, cigarette smoking, and BMI to an index of early glomerular damage such as microalbuminuria is not surprising in view of the key role of the glomerular vascular structure. In keeping with this idea, significant associations have also been reported for cardiovascular risk factors with diabetic nephropathy,²⁻⁴ end-stage renal failure due to any cause,¹⁰⁻¹³ and particular primary renal diseases.¹⁴ On the basis of all these observations, the hypothesis is reasonable that a continuity of relationship exists between cardiovascular risk factors and the process from early to ultimate renal damage.

In the Gubbio cohort, risk for microalbuminuria was greater for men than for women. This could reflect an influence of sex hormones on glomerular function. As to other variables related to microalbuminuria in some univariate analyses (ie, age, levels of plasma uric acid and triglycerides, and alcohol intake), findings were not significant in multivariate analyses. This lack of significance could indicate that the relation of these variables to microalbuminuria reflected confounding, a weak association, or methodological limits; for plasma glucose level, lack of relation to microalbuminuria could reflect exclusion of diabetic individuals from the analysis. The study also shows that definitions of microalbuminuria based on urinary albumin concentration or albumin-creatinine ratio can be biased by low urine flow (ie, low hydration) and low creatininuria (ie, low skeletal muscle mass),⁴² respectively.

Our study shows that blood pressure, plasma cholesterol levels, cigarette smoking, and BMI relate positively to rate of urinary albumin excretion and prevalence of microalbuminuria independently of each other in nondiabetic middle-aged people. On the basis of these and related findings, it is reasonable to infer that control of these cardiovascular risk factors may have a favorable effect in preventing, delaying, and lessening microalbuminuria and, possibly, renal disease. Given the association of microalbuminuria with blood pres-

sure, cholesterol levels, smoking, and BMI, assessment is needed as to whether microalbuminuria is a predictor of cardiovascular risk^{9,40,41,43-47} independent of these risk factors.

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