

The Metabolic Syndrome and Chronic Kidney Disease in U.S. Adults

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Background: The metabolic syndrome is a common risk factor for cardiovascular disease.

Objective: To examine the association between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria.

Design: Cross-sectional study.

Setting: The Third National Health and Nutrition Examination Survey.

Patients: Participants 20 years of age or older were studied in the chronic kidney disease ($n = 6217$) and microalbuminuria ($n = 6125$) analyses.

Measurements: The metabolic syndrome was defined as the presence of 3 or more of the following risk factors: elevated blood pressure, low high-density lipoprotein cholesterol level, high triglyceride level, elevated glucose level, and abdominal obesity. Chronic kidney disease was defined as a glomerular filtration rate less than 60 mL/min per 1.73 m², and microalbuminuria was defined as a urinary albumin-creatinine ratio of 30 to 300 mg/g.

Results: The multivariate-adjusted odds ratios of chronic kidney disease and microalbuminuria in participants with the metabolic syndrome compared with participants without the metabolic syndrome were 2.60 (95% CI, 1.68 to 4.03) and 1.89 (CI, 1.34 to 2.67), respectively. Compared with participants with 0 or 1 component of the metabolic syndrome, participants with 2, 3, 4, and 5 components of chronic kidney disease had multivariate-adjusted odds ratios of 2.21 (CI, 1.16 to 4.24), 3.38 (CI, 1.48 to 7.69), 4.23 (CI, 2.06 to 8.63), and 5.85 (CI, 3.11 to 11.0), respectively. The corresponding multivariate-adjusted odds ratios of microalbuminuria for participants with 3, 4, and 5 components were 1.62 (CI, 1.10 to 2.38), 2.45 (CI, 1.55 to 3.85), and 3.19 (CI, 1.96 to 5.19), respectively.

Conclusions: These findings suggest that the metabolic syndrome might be an important factor in the cause of chronic kidney disease.

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Chronic kidney disease has become an important public health challenge in the United States. According to data from the third National Health and Nutrition Examination Survey (NHANES III), 8.3 million (4.6%) U.S. adults 20 years of age or older have chronic kidney disease (1). Chronic kidney disease is a major risk factor for end-stage renal disease, cardiovascular disease, and premature death (1–7). Identifying and treating risk factors for early chronic kidney disease may be the best approach to prevent and delay adverse outcomes (1).

The metabolic syndrome, characterized by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol level, high blood pressure, and high fasting glucose level, is a common disorder in the United States (8). For example, 47 million (23.7%) U.S. residents 20 years of age or older have the metabolic syndrome, according to data from NHANES III (9). With the continuous increase in the prevalence of obesity in the United States, the metabolic syndrome is expected to be even more common in the future (10). The metabolic syndrome has been associated with an increased risk for diabetes mellitus and cardiovascular disease, as well as increased mortality from cardiovascular disease and all causes (11–13). However, there are sparse data on the relationship between the metabolic syndrome and risk for chronic kidney disease (14). We examined the association between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria in a large representative sample of U.S. adults who participated in the NHANES III.

METHODS

Study Participants

The NHANES III was conducted by the National Center for Health Statistics between 1988 and 1994. A detailed description of the study participants and methods has been published elsewhere (15, 16). In brief, a stratified, multistage probability design was used to obtain a representative sample of the civilian noninstitutionalized U.S. general population (15, 16). A subsample of 7832 NHANES III participants who were 20 years of age and older was randomly selected to participate in morning visits at which fasting blood specimens were obtained. Persons without a fasting blood sample ($n = 503$), women who were pregnant ($n = 120$) or menstruating ($n = 275$), and 1 person with kidney failure (estimated glomerular filtration rate <15 mL/min per 1.73 m²) were excluded from the current analysis. Furthermore, persons who were missing measurements for any component of the metabolic syndrome (plasma glucose level, HDL cholesterol level, serum triglyceride level, waist circumference, or blood pressure measurements) were excluded ($n = 621$). In addition, 95 persons with missing creatinine measurements were excluded from the chronic kidney disease analyses and 94 persons with missing data on urinary albumin and 93 persons with clinical proteinuria (urinary albumin-creatinine ratio >300 mg/g) were excluded from the microalbuminuria analyses. After these exclusions, 6217 persons were included in the chronic kidney disease analyses and 6125 persons were included in the microalbuminuria analyses.

Context

People with the metabolic syndrome (hypertension, low high-density lipoprotein cholesterol level, high triglyceride level, high glucose level, and obesity) are at high risk for cardiovascular disease, and cardiovascular disease is associated with chronic kidney disease. However, it is unknown whether the metabolic syndrome is independently associated with chronic kidney disease.

Contribution

In this population-based study of more than 6000 adults, the risks for chronic kidney disease and microalbuminuria both increased progressively as the number of components of the metabolic syndrome increased from 0 or 1 to 5.

Cautions

It is difficult to disentangle the effects of the metabolic syndrome from those of hypertension and abnormal glucose metabolism. It is unclear whether treating the metabolic syndrome will prevent chronic kidney disease.

—The Editors

Exposure Measurements

Data from NHANES III were collected during a home interview followed by a detailed physical examination at a mobile examination center or at the participant's home. Information on age; race or ethnicity; sex; years of education completed; history of smoking and hypertension; use of antihypertensive medication, diabetes medication, insulin, and nonsteroidal anti-inflammatory drugs (NSAIDs); alcohol consumption; and physical activity were obtained during the home interview (15, 16). Blood pressure was measured 3 times during the home interview and 3 times during the subsequent evaluation at the mobile examination center by trained observers using a standard protocol (15, 16). Blood pressure for an individual participant was calculated as the average of all available systolic and diastolic readings. Waist circumference was measured according to a standard protocol by a trained NHANES III staff member.

For NHANES III participants who were assigned to a physical examination during a morning session, a blood sample was collected after an overnight fast of 8 hours or more. Plasma glucose level was measured with a hexokinase enzymatic reference method (COBAS MIRA, Roche Diagnostics Corp., Indianapolis, Indiana) (15, 16). Serum HDL cholesterol and triglyceride levels were measured enzymatically by using a commercially available reagent mixture (Cholesterol/HP, Boehringer Mannheim, Indianapolis, Indiana), and creatinine was analyzed by the modified kinetic Jaffe reaction method using a Hitachi 737 analyzer (Boehringer Mannheim) (15, 16).

The metabolic syndrome was defined by using criteria recommended in the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines (8).

Specifically, elevated blood pressure was defined as an average systolic or diastolic blood pressure of 130/85 mm Hg or higher. Low HDL cholesterol level was defined as less than 1.036 mmol/L (40 mg/dL) in men or less than 1.295 mmol/L (50 mg/dL) in women. High serum triglyceride level was defined as 1.695 mmol/L (150 mg/dL) or more. Elevated fasting plasma glucose level was defined as 6.10 mmol/L (110 mg/dL) or more. Finally, abdominal obesity was defined as a waist circumference of 102 cm or more in men or 88 cm or more in women. Participants who reported current use of antihypertensive or antidiabetic medication (insulin or oral agents) were classified as having elevated blood pressure or elevated fasting plasma glucose level, respectively. The metabolic syndrome was defined as the presence of 3 or more of these components (8). Diabetes was defined as a self-reported history of a previous diagnosis of diabetes or a fasting plasma glucose level of 7.0 mmol/L (126 mg/dL) or more.

Outcome Measures

Two outcomes, chronic kidney disease and microalbuminuria, were used in this analysis. Glomerular filtration rate was calculated by using the abbreviated equation developed by the Modification of Diet in Renal Disease (MDRD) study (17): Estimated glomerular filtration rate = $186.3 \times (\text{serum creatinine level})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$. Serum creatinine level was calibrated for measurement variance between NHANES III and MDRD clinical laboratories (18). Chronic kidney disease was defined as a glomerular filtration rate less than 60 mL/min per 1.73 m². In addition, we conducted a sensitivity analysis by using serum creatinine level to define chronic kidney disease ($\geq 132.6 \mu\text{mol/L}$ [$\geq 1.5 \text{ mg/dL}$] for men and $\geq 114.9 \mu\text{mol/L}$ [$\geq 1.3 \text{ mg/dL}$] for women). During the physical examination, a random untimed urine sample was obtained from all adults. Urinary albumin concentration was measured by solid-phase fluorescent immunoassay on thawed urine specimens (15, 16). Urinary albumin level was not measured on visibly hematuric specimens or those testing positive for hemoglobin by using qualitative test strips. Urinary creatinine level was analyzed by the modified kinetic Jaffe reaction method by using SYNCHRON AS/ASTRA analyzer (Beckman Instruments, Inc., Brea, California). Microalbuminuria was defined as a urinary albumin-creatinine ratio of 30 to 300 mg/g, and clinical proteinuria was defined as a urinary albumin-creatinine ratio greater than 300 mg/g.

Statistical Analyses

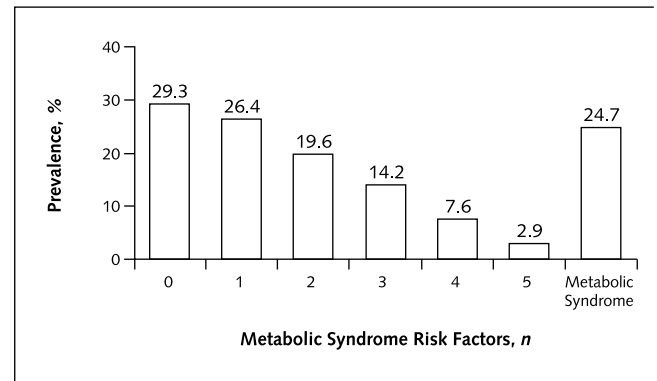
The prevalence of the metabolic syndrome and its individual components (elevated blood pressure level, high plasma glucose level, high triglyceride level, low HDL cholesterol level, and abdominal obesity) as well as the number of the metabolic syndrome components present (0, 1, 2, 3, 4, or 5) was determined for the overall study sample. Mean values of continuous variables and percentages of categor-

ical variables for exposures, covariates, and outcomes were calculated by metabolic syndrome status. The statistical significance of differences in these characteristics across those with and without the metabolic syndrome was examined by using the Z test (continuous variables) and the Wald chi-square test (categorical variables) in multivariate regression models after adjustment for age, sex, and race or ethnicity.

The prevalence of chronic kidney disease and microalbuminuria was determined for participants with and without each of the 5 components of the metabolic syndrome. The prevalence of chronic kidney disease and microalbuminuria was also calculated by the number of metabolic syndrome components present. Logistic regression analysis, adjusted for age, sex, and race or ethnicity, was used to determine the statistical significance of the differences in prevalence.

The crude; age-, sex-, and race- or ethnicity-adjusted; and multivariate-adjusted odds ratios of chronic kidney disease and microalbuminuria, separately, were calculated by using logistic regression models with each component of the metabolic syndrome as an exposure of interest. The crude and adjusted odds ratios of chronic kidney disease and microalbuminuria were also determined by clustering the components of the metabolic syndrome. In these analyses, the odds ratios of chronic kidney disease and microalbuminuria were calculated by comparing participants with 2, 3, 4, and 5 components of the metabolic syndrome with persons with 0 or 1 component of the metabolic syndrome because only 13 persons with no components of the metabolic syndrome had chronic kidney disease. Finally,

Figure 1. Prevalence of the metabolic syndrome and number of the metabolic syndrome components.



the crude and adjusted odds ratios of chronic kidney disease and microalbuminuria were calculated by comparing participants with the metabolic syndrome (≥ 3 components) and without the metabolic syndrome (< 3 components). In the multivariate models, age, sex, race or ethnicity, NSAID use in the past month, a high school education, physical inactivity, and current and former smoking were adjusted. Because body mass index was highly related to the metabolic syndrome, 2 sets of multivariate models with and without adjustment for body mass index were conducted. Age-, sex-, and race- or ethnicity-adjusted odds ratios were similar to multivariate-adjusted odds ratios. Therefore, only multivariate-adjusted odds ratios are presented.

Hypertension and diabetes are the most important es-

Table 1. Characteristics of the Study Participants with and without the Metabolic Syndrome*

Characteristic	Participants with the Metabolic Syndrome (n = 1173)	Participants without the Metabolic Syndrome (n = 4444)	P Value†
Age, y	55.0 ± 0.7	42.1 ± 0.6	<0.001
Men, %	49.3 ± 1.9	50.7 ± 1.2	>0.2
Non-Hispanic white, %	80.0 ± 1.8	76.4 ± 1.5	0.020
Non-Hispanic black, %	7.9 ± 0.8	10.6 ± 0.6	<0.001
High school education, %	67.3 ± 1.9	78.9 ± 1.3	0.020
Physically inactive, %	51.6 ± 2.0	34.3 ± 1.6	0.002
Current smoking, %	25.4 ± 1.6	28.4 ± 1.1	0.172
NSAID use in the past month, %	78.7 ± 1.2	77.6 ± 0.9	0.008
Systolic blood pressure, mm Hg	134.0 ± 0.5	118.4 ± 0.5	<0.001
Body mass index, kg/m ²	31.0 ± 0.2	25.1 ± 0.1	<0.001
Plasma glucose level, mmol/L (mg/dL)	6.57 ± 0.07 (118.2 ± 1.3)	5.23 ± 0.01 (94.4 ± 0.2)	<0.001
Serum HDL cholesterol level, mmol/L (mg/dL)	1.064 ± 0.013 (41.0 ± 0.5)	1.373 ± 0.010 (53.0 ± 0.5)	<0.001
Serum triglyceride level, mmol/L (mg/dL)	2.530 ± 0.076 (223.8 ± 6.7)	1.217 ± 0.021 (107.7 ± 1.9)	<0.001
Waist circumference, cm	105.3 ± 0.4	87.8 ± 0.3	<0.001
Serum insulin level, pmol/L	115.29 ± 3.47	60.42 ± 1.39	<0.001
Serum creatinine level, μmol/L (mg/dL)	72.5 ± 0.62 (0.82 ± 0.0007)	67.2 ± 0.44 (0.76 ± 0.005)	<0.001
Estimated GFR, mL/min per 1.73 m ²	100.5 ± 0.9	114.1 ± 10.9	<0.001
Chronic kidney disease, %	6.0 ± 0.8	1.2 ± 0.2	<0.001
Urinary albumin level, g/L	0.375 ± 0.047	0.151 ± 0.011	<0.001
Albumin-creatinine ratio, mg/g	37.0 ± 5.0	14.2 ± 2.2	0.043
Microalbuminuria, %‡	12.3 ± 1.5	4.7 ± 0.5	0.004
Clinical proteinuria, %‡	1.6 ± 0.4	0.4 ± 0.1	0.011

* All values are expressed as means ± SE. GFR = glomerular filtration rate; HDL = high-density lipoprotein; NSAID = nonsteroidal anti-inflammatory drug.

† Adjusted for age, race or ethnicity, and sex.

‡ Microalbuminuria was defined as a urinary albumin-creatinine ratio of 30 to 300 mg/g, and clinical proteinuria was defined as a urinary albumin-creatinine ratio greater than 300 mg/g.

Table 2. Prevalence of Chronic Kidney Disease and Microalbuminuria among Persons with and without Components of the Metabolic Syndrome*

Component	Chronic Kidney Disease			Microalbuminuria		
	Participants	Prevalence ± SE	P Value†	Participants	Prevalence ± SE	P Value†
	n	%		n	%	
Blood pressure ≥ 130/85 mm Hg						
Yes	2580	6.1 ± 0.6	<0.001	2507	13.2 ± 0.9	<0.001
No	3637	0.5 ± 0.1		3618	3.2 ± 0.5	
Serum HDL cholesterol level < 1.036 mmol/L (<40 mg/dL) in men or < 1.295 mmol/L (<50 mg/dL) in women						
Yes	2279	3.3 ± 0.5	0.002	2240	6.9 ± 1.0	>0.2
No	3938	1.9 ± 0.3		3885	6.4 ± 0.6	
Serum triglyceride level ≥ 1.695 mmol/L (≥150 mg/dL)						
Yes	1890	4.1 ± 0.5	0.004	1845	9.0 ± 1.1	0.039
No	4327	1.7 ± 0.3		4280	5.6 ± 0.5	
Plasma glucose level ≥ 6.10 mmol/L (≥110 mg/dL)						
Yes	1124	6.3 ± 0.9	0.044	1078	16.1 ± 1.6	<0.001
No	5093	1.8 ± 0.2		5047	5.2 ± 0.5	
Waist circumference ≥ 102 cm in men or ≥ 88 cm in women						
Yes	2687	4.1 ± 0.5	<0.001	2632	9.2 ± 1.0	0.109
No	3530	1.4 ± 0.2		3493	5.0 ± 0.5	

* HDL = high-density lipoprotein.

† Adjusted for age, race or ethnicity, and sex.

established risk factors for chronic kidney disease. We examined the association of 3 or more components of the metabolic syndrome, other than high blood pressure level and high plasma glucose level, separately, with chronic kidney disease. In addition, the analyses were repeated after excluding persons with diabetes. All statistical analyses were performed by using Stata software (Stata Corp., College Station, Texas) that included functions for analyzing complex survey data.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to publish the manuscript.

RESULTS

Overall, 34.1%, 13.4%, 30.1%, 37.3%, and 38.1% of the study sample had elevated blood pressure, high plasma glucose levels, high triglyceride levels, low HDL cholesterol levels, and abdominal obesity, respectively. **Figure 1** shows the distribution of the study participants by number of metabolic syndrome components present. Overall, 24.7% of the study participants had the metabolic syndrome.

Table 1 presents the general characteristics of study participants by metabolic syndrome status. On average, persons with the metabolic syndrome were older, more likely to be of non-Hispanic white ethnicity, and less likely to be of non-Hispanic black ethnicity compared with persons without the metabolic syndrome. The percentage of persons with a high school education was lower, while the percentage of persons who were physically inactive and taking NSAIDs was higher in those with the metabolic

syndrome than those without the metabolic syndrome. The mean serum creatinine level and urinary albumin-creatinine ratio were higher, while estimated glomerular filtration rate was lower among persons with the metabolic syndrome compared with those without the metabolic syndrome. The percentage of persons with chronic kidney disease or microalbuminuria was significantly higher among those with the metabolic syndrome compared with those without the metabolic syndrome.

Table 2 compares the proportion of participants with chronic kidney disease and microalbuminuria among those with and without each component of the metabolic syndrome. Elevated levels of blood pressure, serum triglyceride, and plasma glucose were significantly associated with an increased prevalence of both chronic kidney disease and microalbuminuria. In addition, a low HDL cholesterol level and abdominal obesity were significantly associated with an increased prevalence of chronic kidney disease.

Figure 2 presents the prevalence of chronic kidney disease and microalbuminuria by number of components of the metabolic syndrome. There was a significant graded relationship between the number of components present and the corresponding prevalence of chronic kidney disease or microalbuminuria ($P < 0.001$ for each comparison).

Table 3 shows the crude and multivariate-adjusted odds ratios of chronic kidney disease associated with individual and several components of the metabolic syndrome. In the multivariate models, elevated blood pressure level, low HDL cholesterol level, high triglyceride level, and abdominal obesity were all significantly associated with an increased odds ratio of chronic kidney disease ($P < 0.05$).

Participants with 2, 3, 4, and 5 components of the metabolic syndrome had increased odds of 2.21, 3.38, 4.23, and 5.85, respectively, for chronic kidney disease, compared with that of those with 0 or 1 component. Persons with the metabolic syndrome had 2.60-fold increased odds of chronic kidney disease compared with their counterparts without the metabolic syndrome. The results were consistent after additional adjustment for body mass index.

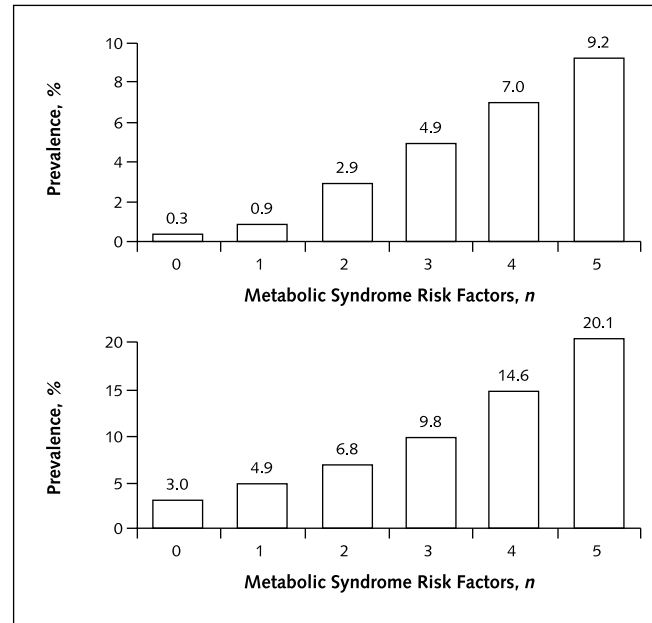
Elevated blood pressure and plasma glucose levels were significantly associated with increased odds ratios of microalbuminuria (Table 4). Participants with 3, 4, and 5 components of the metabolic syndrome had increased odds of 1.62, 2.45, and 3.19, respectively, for microalbuminuria, compared with those with 0 or 1 component. Persons with the metabolic syndrome had a 1.89-fold increased odds of microalbuminuria compared with those without the metabolic syndrome.

Sensitivity Analysis

The analysis results were similar when chronic kidney disease was defined by increased serum creatinine levels alone. For example, the multivariate-adjusted odds ratio of chronic kidney disease was 3.95 (95% CI, 1.43 to 10.9), 2.45 (CI, 1.27 to 4.74), 2.10 (CI, 1.19 to 3.69), and 1.99 (CI, 1.11 to 3.57) for elevated blood pressure level, low HDL cholesterol level, high triglyceride level, and abdominal obesity, respectively. The multivariate-adjusted odds ratio of chronic kidney disease defined by increased serum creatinine levels associated with metabolic syndrome was 2.60 (CI, 1.40 to 4.81).

The multivariate-adjusted odds ratio of chronic kidney

Figure 2. Prevalence of chronic kidney disease (top) and microalbuminuria (bottom) by number of the metabolic syndrome components.



disease and microalbuminuria associated with 3 or more components of the metabolic syndrome, other than elevated blood pressure, was 1.99 (CI, 1.29 to 3.05) and 1.88 (CI, 1.29 to 2.75), respectively. The analogous multivariate-adjusted odds ratio of chronic kidney disease and mi-

Table 3. Crude and Multivariate-Adjusted Odds Ratios of Chronic Kidney Disease Associated with Individual or Several Components of the Metabolic Syndrome*

Variable	Odds Ratio of Chronic Kidney Disease (95% CI)					
	Crude	P Value	Multivariate-Adjusted†	P Value	Multivariate-Adjusted‡	P Value
Blood pressure ≥ 130/85 mm Hg	12.4 (7.66–20.2)	<0.001	2.66 (1.62–4.35)	<0.001	2.39 (1.43–4.01)	0.001
Serum HDL cholesterol level < 1.036 mmol/L (<40 mg/dL) in men or < 1.295 mmol/L (<50 mg/dL) in women	1.78 (1.21–2.63)	0.004	2.11 (1.37–3.27)	0.002	1.85 (1.16–2.95)	0.011
Serum triglyceride level ≥ 1.695 mmol/L (≥150 mg/dL)	2.55 (1.72–3.79)	<0.001	1.80 (1.20–2.69)	0.004	1.58 (1.04–2.40)	0.032
Plasma glucose level ≥ 6.10 mmol/L (≥110 mg/dL)	3.66 (2.61–5.12)	<0.001	1.40 (0.95–2.06)	0.092	1.16 (0.76–1.78)	>0.2
Waist circumference ≥ 102 cm in men and ≥ 88 cm in women	3.08 (2.14–4.42)	<0.001	2.07 (1.41–3.03)	<0.001	1.54 (0.94–2.53)	0.087
2 components§	4.86 (2.76–8.54)	<0.001	2.21 (1.16–4.24)	0.018	2.06 (1.10–3.86)	0.025
3 components§	8.52 (4.05–17.9)	<0.001	3.38 (1.48–7.69)	0.005	3.05 (1.31–7.07)	0.011
4 components§	12.2 (6.06–24.7)	<0.001	4.23 (2.06–8.63)	<0.001	3.67 (1.70–7.90)	0.001
5 components§	16.7 (9.55–29.1)	<0.001	5.85 (3.11–11.0)	<0.001	4.72 (2.31–9.64)	<0.001
Metabolic syndrome	5.34 (3.53–8.06)	<0.001	2.60 (1.68–4.03)	<0.001	2.21 (1.33–3.67)	0.003

* HDL = high-density lipoprotein.

† Adjusted for age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking.

‡ Adjusted for body mass index in addition to age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking.

§ Compared with those with 0 or 1 component of the metabolic syndrome.

|| Compared with those with < 3 components of the metabolic syndrome.

Table 4. Crude and Multivariate-Adjusted Odds Ratios (95% CI) of Microalbuminuria Associated with Individual and Several Components of the Metabolic Syndrome*

Variable	Odds Ratio of Microalbuminuria (95% CI)					
	Crude	P Value	Multivariate-Adjusted†	P Value	Multivariate-Adjusted‡	P Value
Blood pressure \geq 130/85 mm Hg	4.60 (3.37–6.27)	<0.001	2.93 (2.19–3.92)	<0.001	3.21 (2.30–4.47)	<0.001
Serum HDL cholesterol level < 1.036 mmol/L (<40 mg/dL) in men or < 1.295 mmol/L (<50 mg/dL) in women	1.09 (0.78–1.51)	>0.2	1.06 (0.78–1.43)	>0.2	1.08 (0.81–1.45)	>0.2
Serum triglyceride level \geq 1.695 mmol/L (\geq 150 mg/dL)	1.68 (1.27–2.22)	0.001	1.33 (0.99–1.79)	0.054	1.40 (1.06–1.85)	0.029
Plasma glucose level \geq 6.10 mmol/L (\geq 110 mg/dL)	3.53 (2.67–4.66)	<0.001	2.30 (1.78–2.98)	<0.001	2.53 (2.00–3.20)	<0.001
Waist circumference \geq 102 cm in men and \geq 88 cm in women	1.94 (1.48–2.55)	<0.001	1.27 (0.92–1.74)	0.144	1.73 (1.17–2.57)	0.007
2 components§	1.77 (1.26–2.49)	0.001	1.22 (0.88–1.69)	>0.2	1.58 (1.08–2.30)	0.015
3 components§	2.66 (1.86–3.79)	<0.001	1.62 (1.10–2.38)	0.016	2.37 (1.63–3.44)	<0.001
4 components§	4.17 (2.61–6.67)	<0.001	2.45 (1.55–3.85)	<0.001	3.86 (2.33–6.39)	<0.001
5 components§	6.14 (3.80–9.81)	<0.001	3.19 (1.96–5.19)	<0.001	5.89 (3.61–9.63)	<0.001
Metabolic syndrome	2.91 (2.09–4.05)	<0.001	1.89 (1.34–2.67)	0.001	2.40 (1.74–3.31)	<0.001

* HDL = high-density lipoprotein.

† Adjusted for age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking.

‡ Adjusted for body mass index in addition to age, race or ethnicity, sex, nonsteroidal anti-inflammatory drug use in the past month, high school education, physical inactivity, and current and former smoking.

§ Compared with those with 0 or 1 component of the metabolic syndrome.

|| Compared with those with < 3 components of the metabolic syndrome.

croalbuminuria associated with 3 or more components of the metabolic syndrome, other than high glucose level, was 2.94 (CI, 1.91 to 4.52) and 1.69 (CI, 1.17 to 2.44), respectively.

After study participants with diabetes were excluded, the analysis yielded similar findings. For example, in the multivariate models, elevated blood pressure, low HDL cholesterol level, high triglyceride level, and abdominal obesity were significantly associated with an increased odds ratio for chronic kidney disease of 2.92 (CI, 1.43 to 5.99), 2.25 (CI, 1.28 to 3.95), 1.85 (CI, 1.18 to 2.90), and 1.96 (CI, 1.23 to 3.11), respectively. Compared with persons with 0 or 1 risk factor, the multivariate-adjusted odds ratios for chronic kidney disease were 2.02 (CI, 1.07 to 3.79), 3.62 (CI, 1.54 to 8.50), 4.59 (CI, 2.10 to 10.0), and 5.45 (CI, 1.86 to 16.0) for those with 2, 3, 4, and 5 components, respectively. The multivariate-adjusted odds ratio for chronic kidney disease was 2.83 (CI, 1.66 to 4.85) in participants with compared with those without the metabolic syndrome.

DISCUSSION

Our study identified a strong, positive, and significant relationship between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria. The risk for chronic kidney disease and microalbuminuria increased progressively with a higher number of components of the metabolic syndrome. These relationships were independent of age, sex, race or ethnicity, and other potential risk factors for chronic kidney disease, such as NSAID use, education, physical inactivity, and cigarette smoking. Our findings are noteworthy because they are based on a large, representative sample of the U.S. general population. In

addition, careful measures of study exposure and outcome variables allowed precise estimation of the association.

Our study is the first to report a strong relationship between the metabolic syndrome, defined by the ATP III guidelines, and the risk for chronic kidney disease and microalbuminuria. These findings have important clinical and public health implications because the metabolic syndrome is a common disorder in the United States (9). Previous studies have documented that the metabolic syndrome is an important risk factor for diabetes, coronary heart disease, and stroke (11–13). Our study provides new and important information about the relationship between the metabolic syndrome and risk for chronic kidney disease and microalbuminuria in a representative sample of the U.S. general population.

Several studies have examined the association between insulin resistance and risk for chronic kidney disease (14, 19). A cross-sectional survey of 934 nondiabetic Native Americans found that the insulin resistance syndrome was associated with microalbuminuria (14). Hoehner and colleagues (14) found that persons with 3 or more traits for the insulin resistance syndrome (hypertension, impaired fasting glucose level, high fasting insulin level, high triglyceride level, and low HDL cholesterol level) had a 2.3-fold higher odds of microalbuminuria than persons with no traits. In a previous study, we reported that insulin resistance estimated by homeostasis model assessment was associated with an increased risk for chronic kidney disease in nondiabetic participants in NHANES III (19). Our study shows that serum insulin levels and the ATP III-defined metabolic syndrome are highly correlated. Among NHANES III participants with 0, 1, 2, 3, 4, and 5 components of the metabolic syndrome, age-, race- or ethnic-

ity-, and sex-standardized levels of insulin were, respectively, 43.75, 58.34, 78.48, 102.09, and 159.04 pmol/L. In addition, with a serum insulin level 1 SD (48.59 pmol/L) higher, the odds ratio of chronic kidney disease was 1.35 (CI, 1.16 to 1.57).

Epidemiologic studies have documented that diabetes and hypertension are the major risk factors for the development and progression of chronic kidney disease and microalbuminuria (20–23). Our findings are consistent with those from previous studies and suggest that even mildly elevated blood pressure ($\geq 130/85$ mm Hg) or serum glucose levels (≥ 6.1 mmol/L [≥ 110 mg/dL]) are associated with an increased risk for chronic kidney disease and microalbuminuria.

Only a few epidemiologic studies have found that a reduced HDL cholesterol or elevated triglyceride level relates to an increased risk for chronic kidney disease (24, 25). In the MDRD study, a low HDL cholesterol level was an independent predictor of kidney disease progression among 840 patients with diverse renal diseases (24). Muntner and colleagues (25) found that high serum triglyceride and low HDL cholesterol levels predicted an increased risk for renal dysfunction in 12 728 participants in the Atherosclerosis Risk in Communities study. A recent meta-analysis of clinical trials indicates that lipid lowering preserves glomerular filtration rate and decreases proteinuria level in patients with renal disease (26). Our study provides additional evidence that low HDL cholesterol and high triglyceride levels are associated with an increased risk for chronic kidney disease and microalbuminuria.

Experimental studies indicate that obesity is associated with decreased renal function in animals (27). However, few studies have examined this association in humans and those that have provide inconsistent findings (28, 29). In a cohort study of 101 516 Japanese men and women, body mass index was inversely related to risk for end-stage renal disease in women but not in men (28). In a cross-sectional analysis of the MDRD experience, percentage of body fat and body mass index was positively associated with glomerular filtration rate in patients with renal disease (29). Our analysis indicated that abdominal obesity, defined as a waist circumference of 102 cm or more in men or 88 cm or more in women, was associated with 2-fold increase in odds of chronic kidney disease. These data suggest that abdominal obesity might be an important modifiable risk factor for chronic kidney disease in addition to diabetes and cardiovascular disease, which have been documented in previous studies.

Potential limitations of our study should be noted. First, the cross-sectional study design in NHANES III makes it difficult to infer causality between the metabolic syndrome and risk for chronic kidney disease or microalbuminuria. In addition, serum creatinine levels and calculated glomerular filtration rates were used to define chronic kidney disease in our study. Although insulin or iothalamate clearance techniques may provide a more sensitive estimate

of renal function, serum creatinine has been used widely in large epidemiologic studies and in clinical practice for estimating renal function. Therefore, our findings are applicable to clinical and public health practice settings. Even in a large study, such as NHANES III, chronic kidney disease is uncommon among persons without any components of the metabolic syndrome. Therefore, persons with 0 or 1 risk factor were pooled as a reference group to provide more stable estimates of the odds ratio associated with number of components. This approach probably underestimated the association between the metabolic syndrome and chronic kidney disease.

In conclusion, we document that the metabolic syndrome is a strong and independent risk factor for chronic kidney disease and microalbuminuria. In addition, there is a graded relationship between the number of metabolic syndrome components and risk for chronic kidney disease or microalbuminuria. These findings warrant intervention studies to test the effect of preventing and treating the metabolic syndrome on the risk for chronic kidney disease and microalbuminuria.

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