

# Metabolic Syndrome and Kidney Disease: A Systematic Review and Meta-analysis

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## Summary

**Background and objectives** Observational studies have reported an association between metabolic syndrome (MetS) and microalbuminuria or proteinuria and chronic kidney disease (CKD) with varying risk estimates. We aimed to systematically review the association between MetS, its components, and development of microalbuminuria or proteinuria and CKD.

**Design, setting, participants and measurements and population** We searched MEDLINE (1966 to October 2010), SCOPUS, and the Web of Science for prospective cohort confidence interval (CI) studies that reported the development of microalbuminuria or proteinuria and/or CKD in participants with MetS. Risk estimates for eGFR <60 ml/min per 1.73 m<sup>2</sup> were extracted from individual studies and pooled using a random effects model. The results for proteinuria outcomes were not pooled because of the small number of studies.

**Results** Eleven studies ( $n = 30,146$ ) were included. MetS was significantly associated with the development of eGFR <60 ml/min per 1.73 m<sup>2</sup> (odds ratio, 1.55; 95% CI, 1.34, 1.80). The strength of this association seemed to increase as the number of components of MetS increased (trend  $P$  value = 0.02). In patients with MetS, the odds ratios (95% CI) for development of eGFR <60 ml/min per 1.73 m<sup>2</sup> for individual components of MetS were: elevated blood pressure 1.61 (1.29, 2.01), elevated triglycerides 1.27 (1.11, 1.46), low HDL cholesterol 1.23 (1.12, 1.36), abdominal obesity 1.19 (1.05, 1.34), and impaired fasting glucose 1.14 (1.03, 1.26). Three studies reported an increased risk for development of microalbuminuria or overt proteinuria with MetS.

**Conclusions** MetS and its components are associated with the development of eGFR <60 ml/min per 1.73 m<sup>2</sup> and microalbuminuria or overt proteinuria.

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## Introduction

Metabolic syndrome (MetS) includes the constellation of various metabolic abnormalities that have been associated with cardiovascular disease, stroke, and all-cause mortality in the general population (1). The components of MetS include central obesity, dyslipidemia (high triglycerides and low HDL cholesterol), elevated BP, and impaired fasting glucose. Although the definition of MetS proposed by various agencies such as the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) (2), the International Diabetes Federation (IDF) (3), and the World Health Organization (WHO) differ (4,5), insulin resistance and abdominal obesity are the common denominators for the development of this condition.

With an increasingly sedentary lifestyle and high rates of obesity exceeding 30% in most age and gender groups (6), the age-adjusted prevalence of MetS stands at 34% (7). The burden of chronic kidney disease (CKD) has also increased in the United States during the same period (8). Previous observational studies have reported an independent association be-

tween MetS and microalbuminuria or proteinuria and CKD (9–12). However, the risk estimates for development of CKD and proteinuria with MetS and its individual components differed among these studies, with some reporting a positive association, and a few showing statistically insignificant associations (10,13,14). Additionally, the reported studies used varying definitions for MetS and studied different populations, with different follow-up durations. Diabetes and hypertension are the leading causes for development of both CKD and ESRD. Because both impaired fasting glucose and elevated BP are included in the definition of MetS, exploring the independent associations between the other three components of MetS and the development of CKD in the context of MetS is important. Thus, in this systematic review and meta-analysis, we aimed to assess (1) whether MetS is associated with the risk for development of CKD (estimated GFR [eGFR], <60 ml/min per 1.73 m<sup>2</sup> and/or microalbuminuria or proteinuria), (2) whether the individual components of MetS have a differential effect on the development of

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CKD, and (3) whether the risks for CKD increase progressively as the number of components of MetS increase.

## Materials and Methods

We followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines while conducting this systematic review (15).

### Types of Studies

Only prospective cohort studies that reported the development of CKD (eGFR <60 ml/min per 1.73 m<sup>2</sup> and/or microalbuminuria or proteinuria) in adult participants with MetS were considered for inclusion. Cross-sectional studies that reported an association between MetS and kidney disease and non-English language studies were excluded.

### Definition of Metabolic Syndrome

We included studies that used the following definitions of metabolic syndrome: NCEP-ATP III criteria (2,16), modified NCEP-ATP III criteria (3,17), IDF definition (3), or WHO criteria (4,5) (see Supplementary Table 1).

### Search Strategy and Data Extraction

MEDLINE (1966 to October 2010), SCOPUS (October 2010), and Web of Science were searched using optimally sensitive search strategies for relevant studies (see Supplementary Search Strategy). We also reviewed reference lists of all included studies for any additional relevant studies. Two reviewers (G.T. and S.D.N.) independently reviewed the search results and extracted from included studies relevant data regarding study design and setting (such as country of origin, years of study, and follow-up duration), participant characteristics (age, gender, and race), and outcome measures (described below) using a standardized data extraction form. The authors of the included studies were contacted for additional details regarding their studies. Disagreements were resolved in consultation with an arbitrator (T.R.S.).

### Study Quality

Study quality was assessed according to previously published guidelines (18,19). We assessed the risk of bias among the included studies on the basis of the following six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) confounding measurement, and (6) statistical analysis. Each of these individual domains was rated as “Yes,” “Partly,” “No,” or “Unclear.” The individual quality domain was categorized as low risk for bias (Yes) when adequate data were reported to assess the study quality and the study met the criteria for that quality domain, intermediate risk (Partly) when the study reported incomplete data to assess that quality domain, and high risk (No) when the study reported adequate data but did not meet the criteria for that quality domain. Studies that did not report data to assess the quality were categorized as “Unclear” and thus potentially at high risk for bias. We also reported the individual confounding factors that were adjusted in the multivariate analyses of the included studies.

### Outcome Measures

The following outcome measures were considered for inclusion: (1) development of eGFR <60 ml/min per 1.73 m<sup>2</sup> using the Modified Diet in Renal Disease equation or Cockcroft–Gault equation or creatinine clearance <60 ml/min per 1.73 m<sup>2</sup> using 24-hour urinary studies and (2) development of microalbuminuria defined as urinary albumin-to-creatinine ratio (UACR) of 30 to 300 mg/g or 24-hour urine albumin excretion of 30 to 300 mg, and overt proteinuria defined as UACR >300 mg/g or 24-hour urine protein excretion >300 mg.

### Statistical Analyses

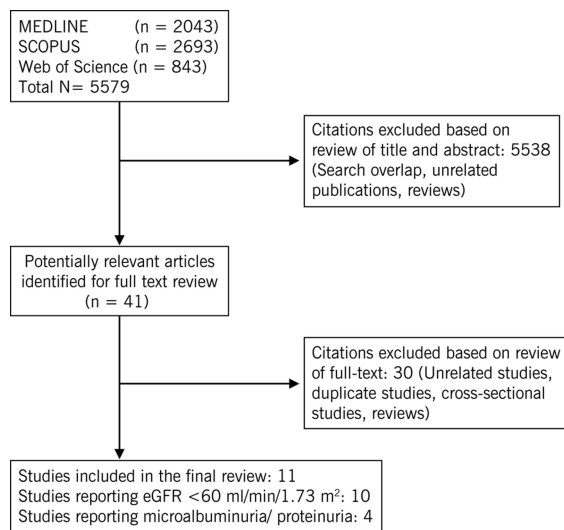
For dichotomous outcome measures such as the development of eGFR <60 ml/min per 1.73 m<sup>2</sup>, we pooled only the risk estimates (hazard ratio or relative risk [RR] or odds ratio [OR]) from individual cohort studies. Only the most adjusted risk estimates that were reported in the studies were extracted and included in the analysis. The data were pooled, and the OR were reported using the random effects model because of anticipated statistical heterogeneity, but the fixed effects model was also used to ensure robustness of the model chosen and susceptibility to outliers. Heterogeneity was analyzed using a chi-squared test on  $N-1$  degrees of freedom, with an alpha of 0.05 used for statistical significance and with the  $I^2$  test (20).

Subgroup analysis and univariate random-effects meta-regression were conducted to explore possible sources of heterogeneity including participant-specific characteristics such as age, gender, and race of study participants and study-specific characteristics such as duration of follow-up, sample size, and the definitions used. However, because of the lack of a sufficient number of studies providing relevant details, we conducted subgroup analysis on the basis of the definition of MetS, study duration, and study population alone. Univariate meta-regression included age of study participants, number of participants, duration of follow-up, and year of study publication. Separate analyses for the development of eGFR <60 ml/min per 1.73 m<sup>2</sup> and microalbuminuria or proteinuria were planned. We also examined the influence of each study by eliminating individual studies and assessing the effect on the cumulative risk estimate. The Cochrane–Armitage trend test was used to test the trend for dose-response relationship. We investigated the presence of publication bias graphically and used Egger’s regression test and its implications with the fail-safe  $n$  and the trim and fill method. Analyses were performed using Comprehensive Meta-analysis (Biostat, Englewood, NJ) and STATA/SE 10.1 (Stata Corporation, College Station, TX).

## Results

### Search Results

We identified 5579 citations with the combined search of the MEDLINE, SCOPUS, and Web of Science databases (Figure 1). We excluded 5538 studies after title and abstract review. Forty-one studies were reviewed in detail (full text), and 11 studies ( $n = 30,146$ ) that met our inclusion criteria were included in the meta-analysis (10–14,21–26).



**Figure 1. | Study flow diagram: included studies and reasons for exclusion of studies.**

### Study Characteristics

Table 1 summarizes the various characteristics of included studies. The sample size of included studies ranged from 176 to 17039 patients with MetS. Three studies included United States or European populations (10–12), whereas eight studies included Asian populations (13,14,21–26). Follow-up duration ranged from 3.5 to 12 years. Nine studies excluded participants with diabetes (10–12,14,22–26). Five studies used the modified NCEP-ATP III criteria for diagnosis of MetS (14,21,22,25,26); three studies used the NCEP-ATP III criteria (10,12,23); two studies examined both the modified NCEP-ATP III and IDF definitions (11,24); and one study classified patients as having MetS on the basis of modified NCEP-ATP III, NCEP-ATP III, and IDF definitions (13). For studies in Asian populations that reported more than one definition, we selected outcomes using the modified NCEP-ATP III criteria for this analysis. Three studies used body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> instead of waist circumference to assess obesity (14,25,26) because of a lack of data. Only four studies reported the use of creatinine calibration (10,13,14,25).

Ten studies reported MetS and the outcome of development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>, of which three studies also reported the outcome of microalbuminuria or proteinuria separately (12,14,26). One study reported MetS and the outcome of proteinuria alone (11). Sun *et al.* (24) reported CKD defined as eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> or proteinuria but did not report these separately. For our review, we included this study in the analysis of development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>.

### Study Quality

Study quality varied among the included studies, and the study quality for each individual domain is detailed in Table 2. Most studies were at low risk for bias for study participation and prognostic factor assessment. The included studies had different risk profiles (high risk, intermediate risk, or unclear risk) for other domains such as

study attrition, outcome assessment, confounding, and study analysis.

### Metabolic Syndrome and Development of eGFR $<60$ ml/min per 1.73 m<sup>2</sup>

Ten cohort studies reported risk estimates for the development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> in patients with MetS. In the pooled analysis, MetS was associated with the development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> (OR, 1.55; 95% confidence interval [CI], 1.34, 1.80) (Figure 2). We further examined the associations of individual components of MetS and the risk for eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>. All individual components of MetS showed a positive association with the development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> (Table 3). The strength of association between MetS and the development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> seems to increase as the number of components increased from 1 to 5 (trend *P*-value 0.02). Although patients with one component had no significant increase in the odds for development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>, patients with all five components of MetS had an OR of 1.96 (95% CI 1.71, 2.24) for development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup> (Table 4).

### Exploration of Heterogeneity

There was significant statistical heterogeneity between the included studies ( $I^2 = 80\%$ ) in the pooled analysis of MetS and development of eGFR  $<60$  ml/min per 1.73 m<sup>2</sup>. The risk estimates and the heterogeneity did not differ when individual studies were removed one at a time. Therefore, we conducted subgroup analyses and univariate metaregression. There was no difference in the risk estimates between the studies that used the NCEP ATP-III criteria and the modified NCEP ATP-III criteria. Similarly, there were no differences among studies that had follow-up for  $\geq 5$  years *versus*  $<5$  years and studies conducted in the United States and Europe *versus* Asian countries (see Supplementary Table 2). When examined as a continuous measure, age of study participants, number of participants, duration of follow-up, and year of study publication did not seem to explain the heterogeneity.

### Metabolic Syndrome and Development of Microalbuminuria or Proteinuria

We did not pool the results of individual studies because proteinuric outcomes were not consistently reported. After adjusting for demographics, education, and smoking status, Lucove *et al.* (12) reported an increased hazard (hazard ratio, 1.26; 95% CI, 0.99, 1.60) for the development of UACR  $>30$  mg/g among American Indians with MetS. Tozawa *et al.* (14) reported a two-fold increased risk for developing dipstick-positive proteinuria (RR, 2.09; 95% CI, 1.55, 2.81) in a Japanese population with MetS. In another Japanese cohort with MetS, Watanabe *et al.* (26) reported a 76% (95% CI, 1.57, 1.98) increased risk for developing  $\geq 1+$  dipstick proteinuria. Bonnet *et al.* (11) reported a higher risk for proteinuria only in men with MetS (RR, 1.87; 95% CI, 1.25, 2.81) using the IDF definition in a French cohort.

### Publication Bias

The funnel plot suggested the possible presence of publication bias. However, the Egger's test was NS ( $P = 0.09$ ).

**Table 1. Characteristics of prospective cohort studies that reported the development of chronic kidney disease (eGFR <60 ml/min per 1.73 m<sup>2</sup> or CrCl <60 ml/min per 1.73 m<sup>2</sup>) and/or proteinuria in patients with metabolic syndrome**

Study, Year (Reference)	Country	No. of Individuals with MetS/Study Sample Size	Men (%)	Mean Age ± SD or Range (Years); or Percentages	Duration of Follow-up (Years)	Definition of Metabolic Syndrome	Definition of CKD and/or Microalbuminuria
Bonnet <i>et al.</i> , 2006 (11)	France	176/2738	63.6	46.7 ± 9.8 (for men) and 48.4 ± 9.8 (for women)	6	Modified NCEP-ATP III, IDF	Proteinuria defined as urinary albumin concentration of >20 mg/ or dipstick positive for proteinuria
Kitiyakara <i>et al.</i> , 2007 (13)	Thailand	227/2067	87	43.0 ± 4.8	12	NCEP-ATP III, Modified NCEP-ATP III, IDF	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD)
Kurella <i>et al.</i> , 2005 (10)	United States	2110/10,096	45	54.5 ± 5.5	9	NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD)
Lucove <i>et al.</i> , 2008 (12)	United States (American Indians)	896/2386	34	Age 45 to 54 years, 51%; age 55 to 64 years, 29%; age ≥65 years, 17%	6.7	NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD) or albumin-to-creatinine ratio of 30 mg/g or greater; results for eGFR and proteinuria reported separately
Luk <i>et al.</i> , 2008 (21)	Hong Kong	2985/5829	43.7	55.6 ± 12.8	4.6	Modified NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD)
Ninomiya <i>et al.</i> , 2006 (22)	Japan	353/1440	32.9	60 ± 10	5	Modified NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD)
Rashidi <i>et al.</i> , 2007 (23)	Iran	1010/4607	47.6	48 ± 12	3	NCEP-ATP III	CKD defined as CrCl <60 ml/min per 1.73 m <sup>2</sup> (CG)
Ryu <i>et al.</i> , 2009 (25)	South Korea	787/10685	100	37.4 ± 4.8	3.8	Modified NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD)

Study, Year (Reference)	Country	No. of Individuals with MetS/Study Sample Size	Men (%)	Mean Age $\pm$ SD or Range (Years); or Percentages	Duration of Follow-up (Years)	Definition of Metabolic Syndrome	Definition of CKD and/or Microalbuminuria
Sun <i>et al.</i> , 2010 (24)	Taiwan	17,039/118,924	59.5	46.5 $\pm$ 12.1	3.5	Modified NCEP-ATP III, IDF	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD) or $\geq$ 1+ proteinuria
Tozawa <i>et al.</i> , 2007 (14)	Japan	884/6371	80	49 $\pm$ 9	5	Modified NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD) or dipstick proteinuria ( $\geq$ 1+); results for eGFR and proteinuria reported separately
Watanabe <i>et al.</i> , 2010 (26)	Japan	3679/34,986	34	61.1 $\pm$ 10.3	5.8	Modified NCEP-ATP III	CKD defined as eGFR <60 ml/min per 1.73 m <sup>2</sup> (MDRD), proteinuria defined as urine dipstick $\geq$ 1+

CKD, chronic kidney disease; NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III; IDF, International Diabetes Federation; MDRD, Modified Diet in Renal Disease; CG, Cockcroft-Gault; CrCl, creatinine clearance; eGFR, estimated GFR; MetS, metabolic syndrome.

**Table 2. Quality assessment of the prospective cohort studies included in the systematic review**

Study, Year (Reference)	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Confounding	Analysis	Variables That Were Adjusted For
Bonnet <i>et al.</i> , 2006 (11)	Yes	No	Yes	Yes	Partly	Partly	Age, use of angiotensin-converting enzyme inhibitors, smoking, fibrinogen levels
Kitiyakara <i>et al.</i> , 2007 (13)	Partly	No	Yes	Yes	No	Unclear	Age, gender, smoking status
Kurella <i>et al.</i> , 2005 (10)	Yes	Partly	Yes	Yes	Yes	Yes	Age, gender, race, education, body mass index, alcohol and tobacco use, coronary heart disease, and physical activity
Lucove <i>et al.</i> , 2008 (12)	Yes	No	Yes	Unclear	Partly	Partly	Age, gender, center, education, smoking
Luk <i>et al.</i> , 2008 (21)	Yes	Unclear	Yes	Unclear	Yes	Unclear	Age, gender, smoking status, duration of diabetes, HbA1C, body mass index, albuminuria
Ninomiya <i>et al.</i> , 2006 (22)	Yes	No	Yes	Partly	Yes	Yes	Age, gender, baseline GFR, proteinuria, serum albumin, serum total cholesterol, hemoglobin, alcohol and tobacco use, hyperinsulinemia
Rashidi <i>et al.</i> , 2007 (23)	Yes	Partly	Yes	Unclear	No	No	Age and gender
Ryu <i>et al.</i> , 2009 (25)	Yes	Yes	Yes	Yes	Yes	Yes	Age, baseline GFR, uric acid, $\gamma$ -glutamyltranspeptidase, incidental hypertension and incidental diabetes
Sun <i>et al.</i> , 2010 (24)	Yes	Partly	Yes	Partly	Partly	No	Age, gender, center, smoking status
Tozawa <i>et al.</i> , 2007 (14)	Yes	Partly	Yes	Yes	Partly	Unclear	Age, gender, current smoking and alcohol drinking habits
Watanabe <i>et al.</i> , 2010 (26)	Yes	No	Yes	Unclear	No	No	Age, gender

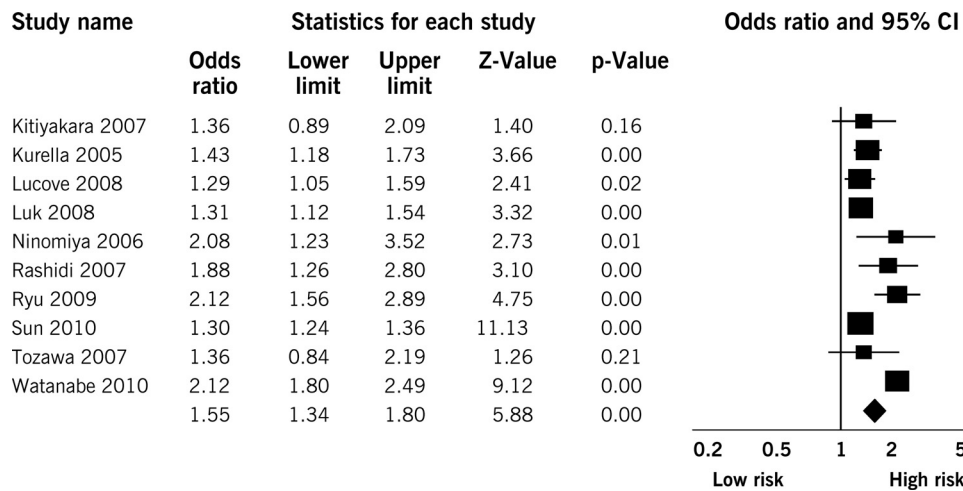


Figure 2. | Metabolic syndrome and risk for development of estimated GFR <60 ml/min per 1.73 m<sup>2</sup>.

Components of Metabolic Syndrome	Number of Studies/Patients	Odds Ratio (95% CI)	P
Elevated blood pressure	8/26,405	1.61 (1.29, 2.01)	<0.01
Impaired fasting glucose	8/26,405	1.14 (1.03, 1.26)	<0.01
Elevated triglycerides	8/28,721	1.27 (1.11, 1.46)	<0.01
Low HDL cholesterol	8/26,632	1.23 (1.12, 1.36)	<0.01
Obesity	9/28,897	1.19 (1.05, 1.34)	<0.01

eGFR, estimated GFR; CI, confidence interval.

Number of Components of Metabolic Syndrome	Number of Studies/Patients	Odds Ratio (95% CI) <sup>a</sup>	P
1	4/7460	1.42 (0.91, 2.22)	0.11
2	6/24,158	1.39 (1.09, 1.78)	<0.01
3	5/23,371	1.42 (1.22, 1.67)	<0.01
4	5/23,497	1.66 (1.53, 1.79)	<0.01
5	3/22,134	1.96 (1.71, 2.24)	<0.01

eGFR, estimated GFR; CI, confidence interval.  
<sup>a</sup>P for trend 0.02.

The fail-safe *n* for this pooled analysis was 470 (the number of studies reporting null effect that are needed to make our results insignificant), suggesting that the effect of unpublished studies is likely to be minimal. Using the trim and fill methods, the imputed OR for development of eGFR <60 ml/min per 1.73 m<sup>2</sup> was 1.30 (95% CI, 1.13, 1.51).

## Discussion

Our systematic review and meta-analysis of longitudinal studies including 30,146 patients from various ethnic groups found that the presence of MetS was associated with the development of eGFR <60 ml/min per 1.73 m<sup>2</sup> (OR, 1.55; 95% CI, 1.34, 1.79). The odds for eGFR <60

ml/min per 1.73 m<sup>2</sup> seem to vary for different components of MetS, and the risk estimate increased as the number of components of MetS increased from 1 to 5. The odds for development of eGFR <60 ml/min per 1.73 m<sup>2</sup> did not differ on the basis of the definition of MetS, duration of follow-up, or ethnicity of the population in which the study was conducted. Patients with MetS have a higher risk for development of higher urinary protein excretion (11,12,14,26).

The public health relevance of these results is underscored by the fact that the prevalence of MetS and its components are increasing over time, and findings suggest that the CKD burden might rise commensurately. A pre-

vious meta-analysis examining the association between obesity and kidney disease reported >60% increased risk for any kidney disease (including kidney stones, kidney cancer, CKD, and ESRD) (27). Because diabetes and hypertension are both addressed by the definition of MetS and are the leading causes of CKD and ESRD in the United States, the relative contribution of the individual components of MetS to CKD risk is of interest (28,29). In this analysis, apart from elevated BP and fasting glucose, we found an increased risk for development of eGFR <60 ml/min per 1.73 m<sup>2</sup> for each individual component of MetS. This meta-analysis of individual components was done to explore the differential effect of individual components in the presence of MetS, and thus the risk estimates should be interpreted in the context of MetS. Although hypertriglyceridemia and low HDL cholesterol levels have been previously associated with increased risk for CKD (30,31), these factors are often overlooked in clinical practice. Our results suggest that these could be potential targets for reducing the risk of CKD.

The relationship between MetS and CKD is biologically plausible. Visceral obesity is highly correlated with insulin resistance, and indices of visceral obesity may be more sensitive predictors of kidney disease than BMI (32). Adipose tissue is a significant source of inflammatory and immunomodulatory factors, and the interaction between adipocytes and macrophages may contribute to insulin resistance and many of the features that characterize MetS (33–35). Our review demonstrated a 19% higher risk of developing eGFR <60 ml/min per 1.73 m<sup>2</sup> with obesity. It should be noted that three of the five individual studies that reported obesity as a significant risk factor for eGFR <60 ml/min per 1.73 m<sup>2</sup> used waist circumference criteria (a better measure of central adiposity) rather than BMI (10,23,24). With the increasing problem of obesity across the globe, the burden of MetS is expected to rise rapidly, further underscoring the relevance of our findings (36,37).

Only three studies reported a significant risk for impaired fasting glucose and development of eGFR <60 ml/min per 1.73 m<sup>2</sup> (12,13,26), and the pooled estimate showed significant associations between eGFR <60 ml/min per 1.73 m<sup>2</sup> and impaired fasting glucose. There is evidence that hyperinsulinemia occurs well before the onset of glucose intolerance and indicates insulin resistance at the level of the muscle and liver that is not directly captured by the NCEP-ATP III criteria for MetS. Thus, insulin resistance and subsequent hyperinsulinemia in addition to mild hyperglycemia may underlie the association between impaired fasting glucose and CKD (38,39). Similarly, studies have confirmed the association between insulin resistance and microalbuminuria (40–43). We identified prospective studies that reported an increased risk for developing either microalbuminuria or dipstick-positive proteinuria among patients with MetS; however, we did not pool these results for analysis because of the small number of studies and the lack of consistently reported and quantifiable proteinuric outcomes. Individual components of MetS were reported to be independently associated with the development of higher urinary protein excretion in these studies.

In this analysis, the risk for eGFR <60 ml/min per 1.73 m<sup>2</sup> seems to increase as the number of components of MetS

increased, highlighting that the cluster of these risk factors might have some additive detrimental effects. In the general population, a two-fold increased risk for development of cardiovascular disease and stroke and a 1.5-fold increased risk for all-cause mortality among patients with MetS have been reported (44–48), which are similar to our risk estimates for development of eGFR <60 ml/min per 1.73 m<sup>2</sup>.

The major strength of this meta-analysis is that it is based on a prespecified study protocol that included a systematic search of MEDLINE, EMBASE, and Web of Science databases and included only prospective cohort studies. The main weakness of this analysis is that it involves individual observational studies that may be subject to unknown confounding factors, selection bias, and attrition bias. Study quality varied from low risk of bias to high risk for bias for each individual domain that was assessed. We noted significant clinical heterogeneity in the analysis that could not be explained on the basis of the definition used, duration of follow-up, or the country in which the study was conducted. The variables used in the risk estimate analyses varied among studies. This fact, along with the possible differences in the number of people who might have developed diabetes or hypertension during the study period, could have contributed to the heterogeneity noted in the cumulative analysis. Subgroup analyses by race and gender were not possible because of a lack of data, and only four studies reported details about calibration of serum creatinine.

As with any observational study, associations do not imply causality. However, the consistency of our results along with biologic plausibility as reviewed highlights their relevance to clinical practice and, more importantly, could serve as baseline data for future interventional studies.

Although some debate persists over its conceptual drawbacks, the definition of MetS is widely used as a simple and practical tool to identify and counsel patients at high risk for cardiovascular disease. CKD and microalbuminuria are established risk factors for cardiovascular disease. Studies targeting the interrelated individual risk factors included in MetS with either medications or life style interventions have been shown to slow the progression of CKD (49). Our results emphasize the need to identify individuals with the constellation of these metabolic risk factors earlier and consider multidisciplinary interventions, particularly life-style modifications, to retard the development of CKD.

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#### Disclosures

None.

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