



Metabolic syndrome is a predictor of decreased renal function among community-dwelling middle-aged and elderly Japanese

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Abstract

Purpose Metabolic syndrome (MetS) is increasing worldwide with the continuous increase in obesity prevalence. Chronic kidney disease (CKD) is also a major public health problem, but there is controversy over whether baseline MetS is a predictor of decreased renal function among Japanese community-dwelling middle-aged and elderly Japanese.

Methods We conducted a prospective cohort study designed as part of the Nomura study. We recruited a random sample of 410 men aged 68 ± 8 (mean \pm standard deviation; range, 50–95) years and 549 women aged 69 ± 7 (50–84) years during their annual health examination in a single community. We examined the relationship between baseline MetS and renal dysfunction after a 3-year evaluation based on estimated glomerular filtration rate (eGFR_{CKDEPI}) using the CKD-EPI equations modified by the Japan coefficient. CKD was defined as dipstick-positive proteinuria ($> \text{or} = 1+$) or a low eGFR_{CKDEPI} ($< 60 \text{ mL/min/1.73 m}^2$).

Results Of the 959 participants, 413 (43.1%) had MetS at baseline. Annual eGFR decline rate was significantly greater in those with MetS than in those without MetS, and the annual eGFR decline rate of $< -1.2 \text{ mL/min/1.73 m}^2/\text{year}$ increased significantly in relation to presence of baseline MetS, especially low HDL cholesterol (HDL-C). Moreover, the incidence rate of CKD after 3 years was 13.5% and increased significantly in relation to presence of baseline MetS, especially its components such as elevated HbA1c. The multivariate-adjusted odd ratio (OR) for CKD in participants with MetS versus those without MetS was 1.55 (0.99–2.43). The multivariate-adjusted ORs for rapid annual eGFR decline rate were significantly high in patients aged ≥ 65 years and presence of medication, regardless of gender and eGFR value.

Conclusions Low HDL-C and elevated HbA1c levels correlated significantly with eGFR decline in a short period of 3 years. MetS also showed a significant association with eGFR decline. This study suggests the importance of low HDL-C and elevated HbA1c in the effect of MetS on eGFR decline rather than obesity among Japanese community-dwelling middle-aged and elderly Japanese without CKD.

Keywords Metabolic syndrome · eGFR_{CKDEPI} · Decline rate · Chronic kidney disease

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Introduction

Metabolic syndrome (MetS), which is a cluster of cardiovascular risk factors, such as central obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) levels, and glucose intolerance, has insulin resistance as its underlying mechanism. It is known as a preconditioning state that leads to an increased risk of cardiovascular disease (CVD), all-cause mortality [1, 2], stroke [3], and type 2 diabetes [4–6], in the general population. However, the etiological role of MetS in CKD is not fully understood, and some authors have suggested that the relevant risk of CVD related to the presence of MetS is no greater than the contribution of the individual components [7].

CKD is an important public health problem worldwide with adverse outcomes of renal failure, CVD, and premature death. Based on clinical practice guidelines established by the Japanese Society of Nephrology, 18.7% of Japanese adults have CKD, which is defined as kidney damage or glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² over 3 months regardless of cause [8], and 10.6% of these had stage 3 + 4 + 5 CKD [9]. The increased incidence of CKD in recent years parallels the increasing prevalence of MetS [10]. The rapid increase in the prevalence of CKD suggests that a single known risk factor (e.g., diabetes or hypertension), cannot be fully explained and that there are other contributing factors [11]. Moreover, the most important factor for incident CKD in the general population without CKD is unknown. Therefore, it is important for us to investigate early detection of CKD progression in early stage CKD patients.

Previous observational studies have reported an independent association between MetS and microalbuminuria [12, 13] or proteinuria [14] and CKD [15, 16]. However, the risk of MetS and its components for CKD and proteinuria differed among these studies, some studies reported a positive association [17–19], and a few studies showed statistically insignificant associations [20]. Furthermore, these reported studies used varying definitions for MetS and studied different populations [19].

To address this hypothesis, we investigated the factors associated with an eGFR decline over 3 years, in particular baseline MetS and its components that are strongly affected by individual lifestyle, using prospective cohort data from community-dwelling middle-aged and elderly individuals.

Materials and methods

Subjects

The Nomura study is a prospective longitudinal study of cardiovascular disease risk factors. The population of this

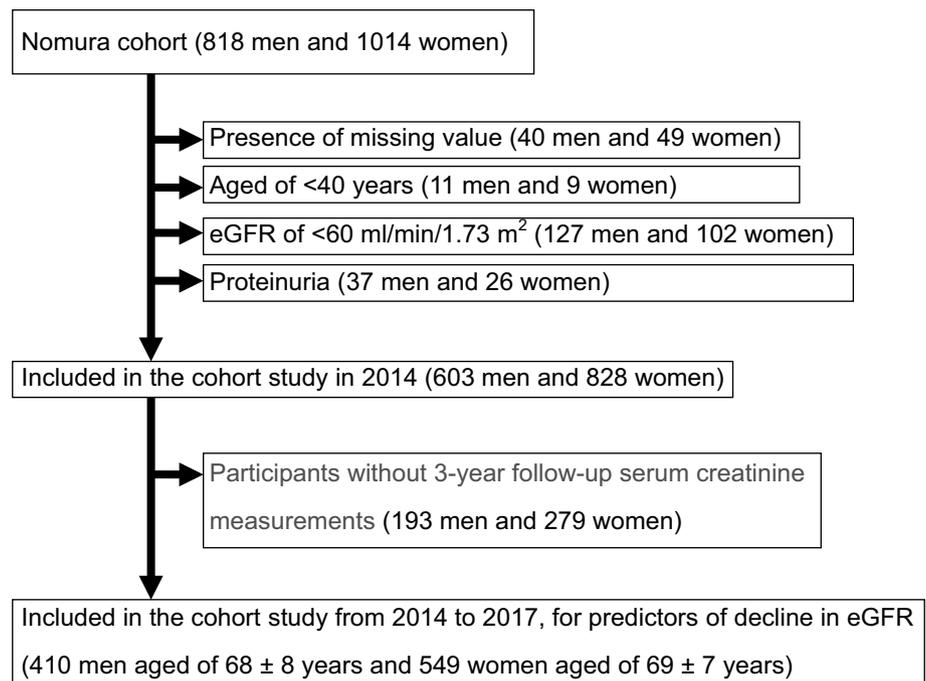
study consisted of individuals enrolled from the Nomura Health and Welfare Center in a rural town in Ehime, Japan through an annual health checkup process, and then returned for three follow-up visits at 3-year intervals. Serum creatinine (Cr) concentration was measured at visit 1 (baseline) and visit 2 (3 years after baseline). To better estimate kidney function, we calculated the estimated GFR (eGFR) using CKD-EPI equations modified by the coefficient of Japan (eGFR_{CKDEPI}): male, serum creatinine (Cr) ≤ 0.9 mg/dL, $141 \times (\text{Cr}/0.9)^{-0.411} \times 0.993^{\text{age}} \times 0.813$; Cr > 0.9 mg/dL, $141 \times (\text{Cr}/0.9)^{-1.209} \times 0.993^{\text{age}} \times 0.813$; female, Cr ≤ 0.7 mg/dL, $144 \times (\text{Cr}/0.7)^{-0.329} \times 0.993^{\text{age}} \times 0.813$; Cr > 0.7 mg/dL, $144 \times (\text{Cr}/0.7)^{-1.209} \times 0.993^{\text{age}} \times 0.813$. Figure 1 shows a flowchart of the inclusion of participants. For the analyses described here, we also excluded participants with missing data for components of the metabolic syndrome (*n* = 89). We excluded participants with a baseline age < 40 years (*n* = 20) and CKD [eGFR_{CKDEPI} < 60 mL/min/1.73 m² (*n* = 229) and/or proteinuria (*n* = 63)] and those without the 3-year follow-up serum creatinine measurements (*n* = 472).

In accordance with the Declaration of Helsinki, this study obtained written informed consent from each participant and was approved by the Ehime University Medical School Ethics Committee. All procedures carried out in the studies involving human participants followed the ethical standards of the in-facility research committee on which the study was conducted. (IRB Approval number: 1402009).

Evaluation of confounding factors

Demographic, anthropometric, and laboratory data were collected using clinical files at baseline and updated at each follow-up visit. Other characteristics such as exercise, smoking habit, alcohol consumption, and medication, were obtained by individual interviews conducted using a structured questionnaire. Body mass index (BMI) was calculated by dividing weight (kilograms) by the square of height (meters). Circumferential measurements of the waist measured at the umbilicus were performed with the participant standing and the values rounded to the nearest centimeter. Smoking habit was defined as the number of packs of cigarettes per day multiplied by the number of pack years (pack year) and participants were classified into nonsmokers, past smokers, light smokers (< 20 pack years), and heavy smokers (≥ 20 pack-year). Daily drinking condition was measured using the Japanese alcoholic beverage unit equivalent to 22.9 g of ethanol, and the participants were classified into never drinkers, occasional drinkers (< 1 unit/day), daily light drinkers (< 2 unit/day), and daily heavy drinkers (2–3 unit/day). After resting for at least 5 min, the participant's right brachial blood pressure (BP) was measured using an automatic oscillometric sphygmomanometer in the sitting position with an appropriately sized cuff, and the average of two measurements was recorded for analysis.

Fig. 1 Flowchart. For the longitudinal analyses, only participants aged ≥ 40 years and with an eGFR of ≥ 60 mL/min/1.73 m² in 2014 were included



For all these individuals, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1c), serum uric acid (SUA), and Cr were measured after an overnight fast of over 11 h. The annual eGFR decline rate was defined as $(\text{follow-up eGFR}_{\text{CKDEPI}} - \text{baseline eGFR}_{\text{CKDEPI}})/3$ years. We defined subjects with an annual eGFR decline rate over -1.2 mL/min/1.73 m²/year as rapid progressors (greater than the 90th percentile of an annual eGFR decline rate). CKD was defined as dipstick-positive proteinuria ($\geq 1+$) or a low eGFR_{CKDEPI} (< 60 mL/min/1.73 m²) [21]. Moreover, ischemic stroke, ischemic heart disease, and peripheral vascular disease were defined as cardiovascular diseases (CVD).

Criteria for clinical diagnosis of MetS

We defined metabolic syndrome as having three or more of the following criteria, according to the revised criteria of the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP) III report [22]: (1) abdominal obesity of waist circumference ≥ 85 cm for men and ≥ 80 cm for women based on the adjusted waist circumference criteria in Japan [23]; (2) high BP with a systolic BP (SBP) ≥ 130 mmHg and/or diastolic BP (DBP) ≥ 85 mmHg, and/or on drug treatment; (3) elevated TG with a TG level ≥ 150 mg/dL; (4) low HDL-C with a HDL-C < 40 mg/dL for men and < 50 mg/dL for women, and/or on drug treatment; and (5) impaired fasting glucose with a HbA1c $\geq 5.6\%$ (equivalent to FPG level = 100 mg/dL) [24] and/or on drug treatment.

Statistics

Unless otherwise specified, data are presented as the mean \pm standard deviation (SD) and for parameters with non-normal distributions (i.e., TG, FPG) data are shown as median (interquartile range) values. For all analyses, parameters with non-normal distributions were used after log-transformation. Statistical analysis was performed using IBM SPSS Statistics Version 21 (Statistical Package for Social Science Japan, Inc., Tokyo, Japan). Participants were divided into two groups based on the presence of baseline MetS. Differences in means and prevalence among baseline findings were analyzed by student's *t* test for continuous variables and χ^2 test for categorical variables. Multiple linear and logistic regression analysis was used to evaluate the contribution of each confounding factor to annual eGFR decline rate and CKD. Moreover, to control potential confounding factors by baseline gender, age, medication (e.g., antihypertensive, antilipidemic, and antidiabetic medication), and eGFR_{CKDEPI}, the data were further stratified based on gender (men, women), age (< 65 years, ≥ 65 years), medication (absence, presence), and eGFR_{CKDEPI} (< 70 mL/min/1.73 m², ≥ 70 mL/min/1.73 m²). Interaction between MetS and the subgroups was analyzed by a general linear model. When $p < 0.05$ the finding was considered statistically significant.

Results

Baseline characteristics of participants categorized by metabolic syndrome

Table 1 shows the value of the baseline characteristics of the participants categorized by MetS. The participants comprised 410 men aged 67 ± 9 (range, 40–95) years and 549 women aged 68 ± 8 (41–84) years. Prevalence of women, age, BMI, prevalence of obesity, waist circumference, history of CVD, SBP, DBP, presence of antihypertensive medication, TG, presence of antilipidemic medication, HbA1c, and presence of antidiabetic medication were significantly higher while prevalence of smoking status, presence of alcohol consumption, HDL-C, and $eGFR_{CKDEPI}$ were significantly lower among the participants with MetS (all $p < 0.05$). There were no inter-group differences regarding LDL-C and SUA.

Relationship between age and annual eGFR decline rate of participants categorized by baseline MetS

The incidence of MetS after 3 years was significantly high in the participants with baseline MetS (75.5%) compared with those without MetS (14.6%) ($p < 0.001$), and body weight after 3 years was significantly decreased in those with MetS (Supplement Table 1). Figure 2 shows the gender-adjusted relationships between age and annual eGFR decline rate categorized by baseline MetS. In participants with MetS, annual eGFR decline rate decreased significantly with age ($r = -0.104$, $p = 0.035$). There was a significant graded relationship between the number of MetS components present and annual eGFR decline rate (Table 2) ($p = 0.040$).

Table 1 Baseline characteristics of subjects categorized by metabolic syndrome

Baseline characteristics $N=959$	Metabolic syndrome		<i>p</i> value
	Absence $N=546$	Presence $N=413$	
Male gender (%)	49.1	34.4	< 0.001
Age (years)	67 ± 8	69 ± 8	< 0.001
Body mass index (kg/m^2)	21.4 ± 2.4	24.3 ± 2.9	< 0.001
Obesity. Body mass index $\geq 25 \text{ kg}/\text{m}^2$, %	6.6	37.0	< 0.001
Waist circumference (cm)	77.2 ± 6.7	85.9 ± 7.7	< 0.001
Smoking status ^a (%)	68.1/20.3/3.8/7.7	76.3/16.9/1.7/5.1	0.021
Alcohol consumption ^b (%)	44.0/22.5/10.6/22.9	55.4/22.5/6.8/15.3	0.001
History of cardiovascular disease (%)	3.1	7.5	0.003
Systolic blood pressure (mmHg)	130 ± 18	139 ± 14	< 0.001
Diastolic blood pressure (mmHg)	76 ± 10	80 ± 9	< 0.001
Antihypertensive medication (%)	25.5	58.1	< 0.001
Triglycerides (mg/dL)	78 (59–100)	107 (76–158)	< 0.001
HDL cholesterol (mg/dL)	70 ± 17	61 ± 15	< 0.001
LDL cholesterol (mg/dL)	120 ± 29	121 ± 30	0.577
Antilipidemic medication (%)	5.3	45.0	< 0.001
Hemoglobin A1c (%)	5.6 (5.3–5.8)	5.8 (5.6–6.1)	< 0.001
Antidiabetic medication (%)	5.1	9.7	0.007
Serum uric acid (mg/dL)	5.1 ± 1.3	5.2 ± 1.3	0.074
eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	76.1 ± 7.3	74.6 ± 6.6	0.001

Data for triglycerides and hemoglobin A1c were skewed and presented as median (interquartile range) values, and were log-transformed for analysis

Bold values indicate significance ($p < 0.05$)

HDL high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate

p value: Student's *t* test for continuous variables or the χ^2 test for categorical variables

^aSmoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack-year), and the participants were classified into never smokers, past smokers, light smokers (< 20 pack-year), and heavy smokers (≥ 20 pack-year)

^bAlcohol consumption was measured using the Japanese liquor unit in which a unit corresponds to 22.9 g of ethanol, and the participants were classified into never drinkers, occasional drinkers (< 1 unit/day), daily light drinkers (1–2 unit/day), and daily heavy drinkers (2–3 unit/day)

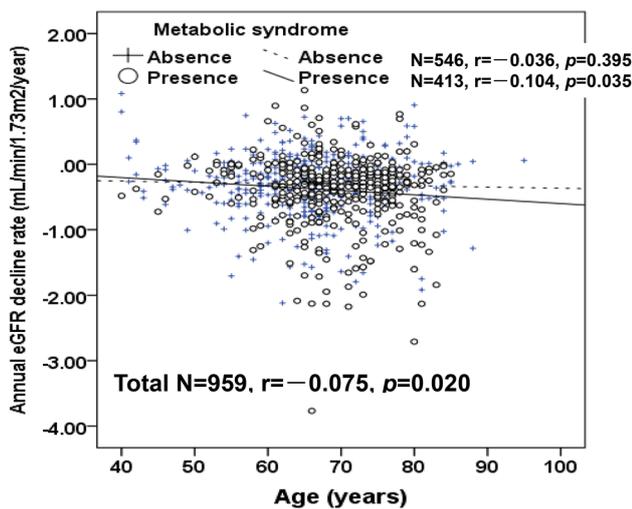


Fig. 2 Gender-adjusted relationship between age and annual eGFR decline rate categorized by baseline metabolic syndrome (absence, $r = -0.036$, $p = 0.395$; presence, $r = -0.104$, $p = 0.035$)

Table 2 Annual eGFR decline rate of subjects categorized by baseline metabolic syndrome and its components

Baseline characteristics N=959	N	Annual eGFR decline rate (mL/min/1.73 m ² /year)	p value
Metabolic syndrome			
Absence	546	-0.31 ± 0.43	0.004
Presence	413	-0.39 ± 0.53	
Component model			
Central obesity			
Absence	556	-0.33 ± 0.45	0.325
Presence	403	-0.36 ± 0.51	
Elevated blood pressure			
Absence	261	-0.33 ± 0.41	0.449
Presence	698	-0.35 ± 0.50	
Elevated triglycerides			
Absence	828	-0.34 ± 0.48	0.683
Presence	131	-0.36 ± 0.46	
Lowering HDL cholesterolemia			
Absence	688	-0.33 ± 0.46	0.077
Presence	271	-0.39 ± 0.51	
Elevated hemoglobin A1c			
Absence	245	-0.29 ± 0.46	0.059
Presence	714	-0.36 ± 0.48	
Number of metabolic syndrome			
0–1	255	-0.31 ± 0.43	0.040
2	291	-0.31 ± 0.42	
3	242	-0.40 ± 0.57	
4–5	171	-0.38 ± 0.47	

Bold values indicate significance ($p < 0.05$)

p value: Student's *t* test

Annual eGFR decline rate and the incidence of CKD of participants categorized by baseline MetS and its components

As shown in Table 2, Annual eGFR decline rate was significantly greater in participants with MetS than in those without MetS ($p = 0.004$). As shown in Table 3, the MetS group had a higher prevalence of participants with incident CKD. In the component model, participants with low HDL-C had a greater annual eGFR decline rate ($p = 0.043$), and those with elevated HbA1c also had a greater prevalence of proteinuria ($p = 0.019$) and incident CKD ($p = 0.019$).

Relationships between various risk factors including baseline MetS and its components and annual eGFR decline rate

Table 4 shows the relationships between various risk factors including the baseline MetS components and annual eGFR decline rate. A multiple regression analysis using annual eGFR decline rate as the objective variable, and gender, age, BMI, smoking status, alcohol consumption, history of CVD, BP, antihypertensive medication, lipids, antilipidemic medication, HbA1c, antidiabetic medication, SUA, and eGFR_{CKDEPI} as the explanatory variables, showed that age ($\beta = -0.164$, $p < 0.001$), HbA1c ($\beta = -0.086$, $p = 0.008$), and eGFR_{CKDEPI} ($\beta = -0.173$, $p = 0.001$) were independently associated with annual decline in eGFR rate.

Non-adjusted and multivariate-adjusted odds ratios of baseline MetS for the incidence of rapid annual eGFR decline rate and CKD

Table 5 shows the incidence and the risk for annual eGFR decline rate and CKD in relation to presence of baseline MetS. As shown in Table 5, after adjustments for the baseline parameters: gender, age, prevalence of obesity, smoking status, alcohol consumption, prevalence of CVD, LDL-C, and eGFR_{CKDEPI}, the incidence of annual eGFR decline rate of < -1.20 mL/min/1.73 m²/year and the incidence of CKD defined as proteinuria and an eGFR_{CKDEPI} of < 60 mL/min/1.73 m² or < 45 mL/min/1.73 m² increased significantly in relation to presence of baseline MetS. The non-adjusted odds ratios (OR) [95% confidence interval (CI)] were 2.36 (1.34–4.16), 1.63 (1.12–2.36), and 1.93 (1.17–3.19), respectively, and the multivariate-adjusted ORs (95% CI) were 2.76 (1.50–5.07), 1.67 (1.12–2.50), and 2.51 (1.49–4.12), respectively.

Table 3 The incidence of rapidly annual eGFR decline rate and CKD of subjects categorized by baseline metabolic syndrome and its components

Baseline characteristics <i>N</i> = 959	<i>N</i>	Rapidly annual eGFR decline rate		Incidence of chronic kidney disease					
		<− 1.2 mL/min/1.73 m ² /year		Proteinuria		eGFR < 60 mL/min/1.73 m ²		eGFR < 45 mL/min/1.73 m ²	
		Prevalence (%)	<i>p</i> value	Prevalence (%)	<i>p</i> value	Prevalence (%)	<i>p</i> value	Prevalence (%)	<i>p</i> value
Metabolic syndrome									
Absence	546	3.7	0.003	5.1	0.015	11.0	0.013	5.1	0.010
Presence	413	8.2		9.2		16.7		9.4	
Component model									
Central obesity									
Absence	556	5.4	0.777	6.1	0.302	12.9	0.632	6.3	0.369
Presence	403	6.0		7.9		14.1		7.9	
Elevated blood pressure									
Absence	261	3.8	0.158	6.1	0.668	10.3	0.090	6.1	0.572
Presence	698	6.3		7.2		14.6		7.3	
Elevated triglycerides									
Absence	828	5.3	0.306	6.5	0.266	13.0	0.337	6.6	0.273
Presence	131	7.6		9.2		16.0		9.2	
Lowering HDL cholesterolemia									
Absence	688	4.7	0.043	6.5	0.483	12.1	0.058	6.5	0.400
Presence	271	8.1		7.7		17.0		8.1	
Elevated hemoglobin A1c									
Absence	245	4.5	0.425	3.7	0.019	10.2	0.103	3.7	0.019
Presence	714	6.0		8.0		14.6		8.1	

Data for triglycerides and hemoglobin A1c were skewed and were log-transformed for analysis

Bold values indicate significance ($p < 0.05$)

p value: χ^2 test

Multivariate-adjusted odds ratios of baseline MetS for rapid annual eGFR decline rate within selected subgroups

To control potential confounding factors, the data were further stratified based on gender, age (< 65 years, \geq 65 years), medication (absence, presence), HbA1c (< 5.8%, \geq 5.8%), and eGFR_{CKDEPI} (< 70 mL/min/1.73 m², \geq 70 mL/min/1.73 m²) as shown in Table 6. The multivariate-adjusted ORs of baseline MetS for annual eGFR decline rate (< − 1.2 mL/min/1.73 m²/year) were significant in participants aged \geq 65 years, and presence of medication, regardless of gender and eGFR. However, there was no significant interaction between the two groups regarding those parameters.

Discussion

In the present study, we investigated metabolic factors associated with an annual eGFR decline rate and incident CKD in a Japanese population undergoing a health checkup. All

participants in this study were without CKD at baseline. Our results showed that the presence of MetS, especially low HDL-C, related significantly to rapid development of annual eGFR decline rate in a population with health checkups at an interval of 3 years. Among individuals with MetS, especially its components such as elevated HbA1c, the incidence of CKD defined as proteinuria and an eGFR_{CKDEPI} of < 45 mL/min/1.73 m² was high. In participants with baseline MetS, the multivariate-adjusted OR for incident CKD was significantly increased compared to those without MetS, independent of obesity. The identification of MetS with low HDL-C and elevated HbA1c is important in patients with a high risk of developing end-stage renal disease (ESRD).

Several previous studies have shown that MetS is significantly associated with an increased risk of renal dysfunction and is an essential predictor of incident CKD. However, it is difficult to elucidate whether the renal dysfunction is due to the syndrome itself or the individual risk factors. From a total of 57 studies, 44 were on albuminuria and 13 on proteinuria, with a total sample size of 10,603,067 participants, MetS components such as obesity, elevated BP, elevated TG,

Table 4 Relationships between various risk factors including baseline metabolic syndrome and annual eGFR decline rate

Baseline characteristics <i>N</i> =959	Multiple regression analysis	
	Forced entry method β (<i>p</i> -value)	Backward elimination method β (<i>p</i> -value)
Gender (male=0, female=1)	0.001 (0.987)	–
Age	–0.133 (0.006)	–0.164 (<0.001)
Body mass index	–0.024 (0.708)	–
Waist circumference	0.016 (0.808)	–
Smoking status (never=0, past=1, light=2, heavy=3)	–0.013 (0.733)	–
Alcohol consumption (never=0, light=1, daily light=2, daily heavy=3)	–0.055 (0.212)	–
History of cardiovascular disease (no=0, yes=1)	–0.058 (0.077)	–0.056 (0.083)
Systolic blood pressure	–0.052 (0.318)	–
Diastolic blood pressure	0.005 (0.917)	–
Antihypertensive medication (no=0, yes=1)	–0.013 (0.722)	–
Triglycerides	0.016 (0.674)	–
HDL cholesterol	0.069 (0.082)	0.054 (0.092)
LDL cholesterol	0.031 (0.388)	0.059 (0.068)
Antilipidemic medication (no=0, yes=1)	0.002 (0.951)	–
Hemoglobin A1c	–0.070 (0.065)	–0.086 (0.008)
Antidiabetic medication (no=0, yes=1)	0.035 (0.362)	–
Serum uric acid	0.064 (0.116)	–
eGFR	–0.153 (0.001)	–0.173 (0.001)
<i>R</i> ²	0.045 (0.001)	0.036 (<0.001)

Data for triglycerides and hemoglobin A1c were skewed and were log-transformed for analysis

Bold values indicate significance (*p*<0.05)

r Pearson's correlation coefficient

low HDL-C, and impaired fasting glucose, were significantly associated with increases in proteinuria and albuminuria risk [14]. In addition, Rashidbeygi et al. [14] showed that MetS contributed to higher risks of proteinuria (OR = 2.08, 95% CI 1.85–2.34) and albuminuria (1.92, 1.71–2.15) independent of diabetes status, and the total impact of MetS on proteinuria was more remarkable than each component of the syndrome. In a nationally representative sample of 4248 Chinese adults in Taiwan, the multivariate-adjusted HR (95% CI) of CKD in participants with MetS compared with those without MetS was 1.42 (1.03–1.73), and there was a significant relationship between the number of the MetS components and risk of CKD [25]. From 11 prospective cohort studies (*n*=30,146), MetS was significantly associated with the development of eGFR < 60 mL/min/1.73 m² (1.55, 1.34–1.80). In patients with MetS, the ORs (95% CI) for the development of eGFR < 60 mL/min/1.73 m² for its components of MetS were: central obesity 1.19 (1.05–1.34), elevated BP 1.61 (1.29–2.01), elevated TG 1.27 (1.11–1.46), low HDL-C 1.23 (1.12–1.36), and impaired fasting glucose 1.14 (1.03–1.26) [26]. In our study, MetS per se was more important as a risk factor than the individual components.

Therefore, therapeutic strategies that targeted MetS per se as well as its components seem highly reasonable for preventing CKD.

The mechanisms by which presence of MetS induce the development of CKD are biologically plausible. Previous studies reported that obesity [27–30], waist circumference, and waist to hip ratio [31], BMI [32] are significant risk factors for developing CKD and proteinuria. However, in our study, obesity per se was not significantly associated with incident CKD. Among parameters included in the criteria for MetS, low HDL-C and elevated HbA1c were risk predictors for progression of CKD.

The role of insulin resistance linked with the MetS establishment may explain the observed significant association between presence of the MetS and cause of renal dysfunction. Insulin resistance is a significant source of inflammation (i.e., C-reactive protein) [33, 34], increased oxidative stress [35], activation of the renin-angiotensin system [36], increased sympathetic activity [37], and cytokine expression [34]. These risk factors all cause endothelial dysfunction and reduced synthesis of endothelial nitric oxide, and induce atherosclerosis, which could contribute to CKD, and

Table 5 Non-adjusted and multivariate-adjusted odds ratios of baseline metabolic syndrome for the incidence of rapidly annual eGFR decline rate and chronic kidney disease

Baseline characteristics N=959	N	Incidence of rapid annual eGFR decline rate		Incidence of chronic kidney disease (proteinuria + eGFR decline)			
		<−1.2 mL/min/1.73 m ² /year	p-value	<60 mL/min/1.73 m ²	p-value	<45 mL/min/1.73 m ²	p-value
Metabolic syndrome: absence/presence	546/413	20 (3.7%)/34 (8.2%)	0.003	60 (11.0%)/69 (16.7%)	0.013	28 (5.1%)/39 (9.4%)	0.010
Non-adjusted odds ratio (95% CI)		2.36 (1.34–4.16)	0.003	1.63 (1.12–2.36)	0.011	1.93 (1.17–3.19)	0.011
Age-adjusted odds ratio (95% CI)		2.18 (1.23–3.87)	0.008	1.45 (0.99–2.12)	0.054	1.86 (1.12–3.08)	0.017
Age, gender, BMI, waist circumference-adjusted odds ratio (95% CI)		2.53 (1.28–4.99)	0.008	1.37 (0.87–2.18)	0.177	2.08 (1.13–3.83)	0.019
Multivariate-adjusted odds ratio (95% CI) ^a		2.71 (1.45–5.09)	0.002	1.55 (0.99–2.43)	0.056	2.31 (1.30–4.12)	0.004
Multivariate-adjusted odds ratio (95% CI) ^b		2.76 (1.50–5.07)	0.001	1.67 (1.12–2.50)	0.012	2.51 (1.49–4.12)	0.001

Bold values indicate significance ($p < 0.05$)

CI confidence interval

p value: χ^2 test or logistic regression analysis

^aMultivariate-adjusted for the baseline parameters: gender, age, prevalence of obesity, smoking status, alcohol consumption, prevalence of CVD, LDL-cholesterol, serum uric acid, and eGFR (forced entry method)

^bBackward elimination method

Table 6 Multivariate-adjusted odds ratios of baseline metabolic syndrome for rapidly annual eGFR decline rate within selected subgroups

Baseline characteristics N=959	N	Baseline metabolic syndrome	
		Odds ratio (95% CI) ^a	p-interaction
Gender			
Men	410	2.78 (1.16–6.66)	0.960
Women	549	2.71 (1.06–6.95)	
Age (years)			
<65	293	1.22 (0.29–5.16)	0.484
≥65	666	3.46 (1.66–7.22)	
Medication (e.g., antihypertensive, antilipidemic, and antidiabetic medication)			
Absence	389	2.00 (0.80–5.04)	0.527
Presence	570	3.93 (1.40–11.1)	
eGFR			
<70 mL/min/1.73 m ²	212	3.09 (1.06–8.96)	0.215
≥70 mL/min/1.73 m ²	747	2.06 (1.19–5.97)	

Bold values indicate significance ($p < 0.05$)

CI confidence interval

p-interaction was estimated using a general linear model

^aMultivariate-adjusted for the baseline parameters: gender, age, prevalence of obesity, smoking status, alcohol consumption, prevalence of CVD, LDL-cholesterol, serum uric acid, and eGFR

vice versa. These results stress the importance of low HDL-C and elevated HbA1c on the effect of metabolic syndrome on eGFR decline in a non-CKD population. In this analysis, the risk for annual eGFR decline 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 a previous study, a twofold increased risk for developing CVD and a 1.5-fold increased risk for all-cause mortality among patients with MetS were reported [2, 38] and are similar to our risk estimates for Incidence of CKD.

There are some limitations of this study. First, estimating GFR using the CKD-EPI equation tends to be less accurate in participants with normal renal function and CKD compared to when inulin clearance is used, but is more accurate than serum creatinine or eGFR when the modification of diet in renal disease (MDRD) formula [39] is used. In a general population, CKD-EPI is the most appropriate, but in an obese population it is not so obvious. Second, because there are several risk factors in the study population, such as gender, old age, hypertension, dyslipidemia, diabetes, etc., we could not eliminate the possible effect of underlying diseases and medications used for these diseases on the present findings. Third, confounding factors and eGFR are based on a single assessment of blood, which may result in a misclassification bias. Thus, the demographics and referral source may limit generalization.

In conclusion, the present study suggests the importance of low HDL-C and elevated HbA1c in the effect of the MetS on eGFR decline rather than obesity in a non-CKD population. The underlying mechanism behind this relationship is unknown. Based on these results, monitoring of metabolic factors, especially HDL-C and HbA1c, is important for the prevention of a rapid decline in eGFR and the occurrence of CKD in a non-CKD population. For healthy community residents, prospective population-based studies are necessary to investigate mechanisms such as an effective lifestyle improvement and other interventions.

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Author contributions RK participated in the design of the study, performed the statistical analysis, and drafted the manuscript. RK, TA, DN, TK, and AK, contributed to the acquisition and interpretation of data. RK, DN, and AK contributed to the conception and design of the statistical analysis. All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at which the studies conducted (IRB Approval Number: 1402009).

Informed consent We obtained consent through an opt-out procedure from all individual participants included in the study.

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