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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059504
Article Type:	Original research
Date Submitted by the Author:	23-Nov-2021
Complete List of Authors:	Liu, Peijia; Third Affiliated Hospital of Sun Yat-Sen University, Tang, Leile; Third Affiliated Hospital of Sun Yat-Sen University, Department of Cardiology Fang, Jia; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology Liu, Xun; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology
Keywords:	Chronic renal failure < NEPHROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Keywords: chronic renal failure; lipid disorders; public health

Word count: 2924

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Abstract

Objectives Few studies have explored correlations between metabolic syndrome (MetS) alterations and renal deterioration in longitudinal cohorts. We sought to address this knowledge gap by investigating associations between MetS recovery/development and rapid estimated glomerular filtration rate (eGFR) decline in the China Health and Retirement Longitudinal Study (CHARLS).

Design longitudinal cohort study.

Setting This study is a secondary analysis of CHARLS.

Participants We analyzed 4142 participants ≥ 45 years old from the CHARLS cohort.

Results According to baseline MetS status and follow-up, participants were divided into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group, the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, P = 0.01). In contrast, when compared with the MetS-free group, the multivariable adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, P = 0.98). In addition, recovery from central obesity was associated with a reduced risk of rapid eGFR decline (OR: 0.31; 95% CI: 0.15–0.65, $P < 0.01$).

Conclusions Over a 4-year follow-up period, we found that MetS recovery, including central obesity recovery, was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS appeared to protect against a rapid decline in eGFR. Further follow-up studies are required to identify the relationship between MetS alterations and adverse renal events.

Strength and limitation of this study

This study investigated the association between altered metabolic syndrome

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status and rapid glomerular filtration rate decline in a nationwide cohort.

Metabolic syndrome scores were applied to evaluate the metabolic syndrome severity.

Blood tests related to metabolic syndrome and serum creatinine were performed only once.

Introduction

Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood pressure (BP) (1-3). As of 2017, there were approximately 1 billion individuals with MetS around the world, of which China accounted for 21.7% (4). In China, MetS prevalence has been undergoing a steady increase, concomitant with an increasingly aged population, an obesity epidemic, and increased diabetes and hypertension levels, which collectively pose a considerable threat to people's health and impose a heavy burden on healthcare systems (4-6).

While investigations of causality relationships between MetS and cardiovascular events have gained considerable traction in recent years (7-9), MetS also impacts the kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly include insulin resistance, increased oxidative stress, and a chronic inflammatory state, which may lead to kidney degeneration and chronic kidney disease (CKD) development (5, 6). Previously, it was confirmed that MetS and associated components (abdominal obesity, elevated BG, elevated BP, and lipid metabolic disorder) are strongly related to CKD and a decreased estimated glomerular filtration rate (eGFR) (10-14). Several longitudinal studies reported that MetS and its components were associated with incremental rapid eGFR decline and CKD incidence (15-18). However, these studies failed to articulate the relationship between MetS alterations and renal function changes. This dearth of information on this subject warrants further study, especially within a Chinese population context.

The China Health and Retirement Longitudinal Study (CHARLS) is a prospective cohort study conducted by the National School of Development, Peking University, China (19). The nationwide sample assesses the social, behavioral, and health status

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of individuals aged 45 and older (19). The CHARLS baseline survey was implemented in 2011 (Wave 1), and the samples were followed up every two years. Blood samples from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the current study, we explored the relationship between MetS recovery/occurrence and rapid eGFR decline in middle-aged and older populations in the 4-year follow-up cohort.

Methods

Study population

CHARLS is a nationally representative longitudinal survey on the social, economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the community (19). In total, 17,708 participants were registered at baseline (Wave 1), of which 11,847 had blood sample tests.

In this study, our exclusion criteria excluded participants with the following: 1) missing values; 2) without fasting blood values; 3) baseline eGFR < 60 ml/min/1.73m^2; 4) clinician-reported malignant tumor, heart disease, stroke or kidney disease; 5) < 45 years old; and 6) no follow-up records and related blood examinations in Wave 3. After applying these criteria, 4142 participants were finally included. The participant screening process is outlined (Fig. 1).

The Medical Ethics Review Committee of Peking University approved this study. All participants provided written informed consent before participating. This study is a secondary analysis of a public dataset and does not require ethics approval again.

Blood examinations

At baseline (Wave 1), blood measurements and hemoglobin were assayed by the Center for Disease Control and Prevention of the local county, whereas other biochemical indicators were analyzed by Youanmen Center for Clinical Laboratory of Capital Medical University, Beijing, China. Serum creatinine (Scr) was measured by the picric acid method; blood urea nitrogen (BUN) was determined by an enzymatic UV method with urease; blood glucose (BG), total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG) were assayed by enzymatic colormetric tests; glycosylated hemoglobin (GHbA1c) was determined by high

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performance liquid chromatography; high-sensitivity C-reactive protein (hs-CRP) was examined by immunoturbidimetric assay; and uric acid (UA) was determined by the UA plus method (20). Blood specimen testing in 2015 (Wave 3) was completed by KingMed Diagnostics, the leading third-party institution in China, which has testing laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were determined by the same methods as Wave 1, while HDL was determined by a direct method, TG by an oxidase method, and BG by a hexokinase method (21). The collection, storage, transport, processing, and other blood sample details are described elsewhere (20, 21). Of note, the models and manufacturer information of blood test instruments in Wave 1 and Wave 3 were not available. All inspections and calibrations were performed by trained personnel.

Definition and grouping of MetS

According to the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension definition, MetS is diagnosed when three of the following four conditions are met: 1) Central obesity: waist circumference (WC) ≥ 90 cm in men and ≥ 85 cm in women; 2) Elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or diagnosed as hypertension and treated; 3) Dyslipidemia: fasting TG ≥ 150 mg/dL, or HDL ≤ 40 mg/dL, or diagnosed as dyslipidemia and treated; and 4) Elevated BG: Fasting BG (FBG) ≥ 100 mg/dL, or 2 h postprandial BG ≥ 100 mg/dL, or diagnosed as diabetes and treated (2). Diabetes was defined as fasting BG ≥ 126 mg/dL, and/or HbA1c ≥ 6.5%, and/or a self-reported history of diabetes (22). Of note, we did not have 2 h postprandial BG data.

According to MetS baseline status and follow-up, participants were categorized into 1) MetS-free, 2) MetS-developed, 3) MetS-recovery, and 4) MetS-chronic groups.

MetS scores

MetS severity potentially affects the recovery/occurrence of MetS. Thus, individuals with high MetS severity may be less liable to recover. Similarly, for those without MetS, it is not straightforward to progress to severe MetS. Therefore, MetS

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scores were introduced to assess MetS severity (23, 24). These scores were calculated using principal component (PC) analysis of WC, mean arterial pressure (MAP), FBG, fasting TG, and the inverse HDL values. All MetS related variables were normalized by 0–1. According to the PC analysis results, PC1 and PC2 explained 38.9% and 20.9% of the variance, respectively. MetS scores were calculated as follows:

$$\mathrm{PC1} = 0.369 \times \mathrm{WC} + 0.378 \times \mathrm{FBG} + 0.585 \times \mathrm{TG} + 0.562 \times \left(\frac{1}{\mathrm{HDL}}\right) + 0.252 \times \mathrm{MAP},$$

$$\mathrm{PC2} = 0.503 \times \mathrm{WC} - 0.171 \times \mathrm{FBG} - 0.268 \times \mathrm{TG} - 0.274 \times \left(\frac{1}{\mathrm{HDL}}\right) + 0.755 \times \mathrm{MAP},$$

$$\mathrm{MetS\ score} = 0.389 \times \mathrm{PC1} + 0.209 \times \mathrm{PC2}$$

Study outcomes

We calculated eGFR values using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine levels (25). A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2 (16, 26). In this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR in Wave 1, > 12 ml/min/1.73m^2.

Covariate assessments

Covariates included gender (male vs. female), age, marital status (married with spouse vs. others), education (illiterate, middle school and below, or high school and above), household per capita income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height, weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs. no), episodic memory scores, self-reporting disease (hypertension, diabetes, and dyslipidemia), and corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90. Grip strength was divided into three groups (T1, T2, and T3) according to the one-third percentile. BMI was calculated by weight (kg)/height squared (m^2). The BP of each participant was measured three times every 45–60 s with the OmronTM HEM-7112 sphygmomanometer (Omron Co. LTD， Dalian, China) at rest. Both SBP and DBP were averaged from three measurements. MAP was defined as MAP = 1/3 × SBP + 2/3 × DBP. Previous study demonstrated that depressive symptom was association with baseline eGFR (27). Thus, we should not overlook this variable. The 10-item

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Center for Epidemiological Studies Depression Scale (CESD-10) was applied in the study (28). A CESD-10 score ≥ 10 was grouped into the depressive symptom group, and < 10 into the non-depressive symptom group. Self-reporting disease was disease diagnosed by a doctor. Medical interventions included taking Chinese traditional and Western modern medicines.

Statistical methods

The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Continuous variables were expressed by the median (interquartile range) and categorical variables by frequency (%). The Mann-Whitney U test was performed on continuous variables, and categorical variables between the rapid eGFR decline group and the non-rapid eGFR decline group were tested by the Chi-square test. In preliminary analyses, variables with P values < 0.15 were used to calibrate the logistic model. Continuous variables not presenting a linear relationship with the logit conversion value of the dependent variable were converted to categorical variables. Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This existed if the tolerance was < 0.1 or the VIF was > 10. Eventually, age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification and MetS scores were selected as confounding variables for model adjustments in this study. Most selected covariates have been reported to be related to renal events (23, 29-32). Logistic models were used to test the association between MetS recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding factors. Furthermore, logistic models were used to explore the relationship between the recovery/occurrence of central obesity, elevated BP, elevated BG, dyslipidemia (elevated TG and decreased HDL), and the rapid decline of eGFR using different adjustments of confounding factors. $P < 0.05$ was considered statistically significant (two-sided test). Statistics were generated in IBM SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software (StataCorp, Texas, USA).

Patient and public involvement

There were no participants involved in the development. The results of the survey are disseminated to the public through websites.

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Results

Participant characteristics

As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS recovery-group, and 822 (19.8%) in the MetS-chronic group.

Participant characteristics were grouped by the eGFR decline rate (Table 1). A rapid decline in eGFR developed in 711 (17.2%) participants during the 4-year follow-up. The median age was 58 (52~64) years and males accounted for 42.5% at baseline. In contrast to rapid eGFR decline group, the non-rapid eGFR decline group was significantly higher with respect to FBG, Scr, hemoglobin, eGFR, weight, BMI, WC, MetS scores, central obesity, and elevated BG (all $P < 0.05$). Those in non-rapid eGFR decline group were more likely to be female and younger when compared with the eGFR decline group (both $P < 0.05$).

Rapid eGFR decline risk based on Mets recovery or occurrence

As shown (Table 2), after adjustment for age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification, and MetS scores, the odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% CI: 0.45–0.90, $P = 0.01$) when compared with the MetS-chronic group. In contrast, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, $P = 0.98$) when compared with the MetS-free group.

MetS components and rapid eGFR decline risk

The association of changes in the composition of MetS groups with rapid eGFR decline is shown (Table 3). In the baseline MetS population, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the population recovered from central obesity was 0.31 (OR: 0.31; 95% CI: 0.15–0.65, $P < 0.01$) when compared with chronic central obesity, whereas recovery from elevated BP, dyslipidemia, and elevated BG did not show statistically significant differences when

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compared with the corresponding population (all $P > 0.05$). In the baseline population without MetS, we observed no statistical difference in the rapid decline of eGFR between the occurrence of all MetS component groups and corresponding contrast groups (all $P > 0.05$). This was consistent with the overall trend.

Discussion

We examined the relationship between MetS changes and rapid eGFR decline in a large nationwide cohort. At the 4-year follow-up, MetS recovery was significantly associated with a reduced risk of rapid eGFR decline in the middle-aged and elderly, with only WC recovery consistent with the overall trend. The occurrence of MetS and its components did not significantly increase the risk of rapid eGFR decline. Further follow-up is required to elucidate the relationship between MetS dynamics and the rapid decline in eGFR.

Longitudinal cohort studies in several Asian countries concluded that MetS increased the risk of CKD, although follow-up times variedy from study to study (15-18, 33). However, the effect of MetS on the rapid decline of eGFR remains controversial. In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and eGFR rapid decline in the elderly (33). However, other studies reported that MetS was associated with a decline in eGFR and even acted as an independent predictor of eGFR decline (16-18). We noted that none of the aforementioned studies accounted for the MetS status of participants during follow-up periods. Park *et al.* explored the relationship between MetS status change and CKD events and concluded that MetS recovery was associated with a decreased risk of CKD incidence, but the occurrence of MetS increased the risk of CKD incidence (34). Park *et al.* did not discuss the association with the rapid eGFR decline. In this study, we concluded that MetS recovery was associated with a reduced risk of rapid eGFR decline, while MetS occurrence was not related to rapid eGFR decline. Studies exploring the relationship between MetS dynamic changes and the rapid decline of eGFR in the Chinese population are rare. Our investigation of the relationship between MetS recovery/occurrence and eGFR rapid decline in a large nationwide cohort may support renal function management in individuals with MetS.

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The effect of MetS on renal function is complex, thus, no definitive mechanisms can explain our study observations. The evidence suggests that every component of MetS is associated with adverse renal events (10-14). It is accepted that hypertension and diabetes play pivotal roles in CKD development and progression (35-37). Also, lipid metabolism dysregulation and abnormal lipid distribution can lead to lipotoxicity-related renal damage (38, 39). Thus, MetS may result from the combined effects of central obesity, increased BP, insulin resistance, and blood lipid disorder, leading to physiopathological lipotoxicity, oxidative stress increments, endothelial dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney dysfunction (5, 38). However, the relationship between MetS components and the weight of each factor on kidney injury remain unclear.

Our study had some limitations. Firstly, MetS diagnoses were not comprehensively checked (using multiple tests). Secondly, CKD occurrence was not included as a study outcome. Also, urine test results were unavailable for this cohort, thus, we may have underestimated the CKD incidence. Thirdly, blood analyses from Wave 1 and Wave 3 were performed at a different testing center, with inconsistent HDL, TG, and BG measurement methods, therefore, measurement errors may have occurred. Fourthly, a large proportion of individuals with missing values were excluded and this may have biased some of our results.

Conclusions

Over a 4-year follow-up, we observed that MetS recovery, including recovery of central obesity, was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Further follow-up studies are required to observe the relationship between MetS alterations and adverse renal events.

Acknowledgements The authors are grateful to the China Health and Retirement Longitudinal Study (CHARLS) team for providing the data.

Contributors PL, LT and JF—analysis and interpretation of data and preparation of the manuscript.XL—study concept and design, and preparation and critical review of

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the manuscript. All authors have approved the final manuscript.

Funding This work was supported by Guangzhou Municipal Science and Technology Bureau (202002020047).

Competing interests All authors declared no competing interests.

Data availability statement CHARLS data of the study will be available to investigators at the CHARLS website (http://charls.pku.edu.cn/en).

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Table 1. Baseline characteristics of participants between rapid eGFR decline group and non-rapid eGFR decline group

Characteristics	Overall (*n* = 4142)	Rapid eGFR decline (*n* = 711)	Non-rapid eGFR decline (*n* = 3431)	*P* value
Male [*n* (%)]	1874 (45.2)	351 (49.4)	1523 (44.4)	0.02
Age (years)	58 (52~64)	59 (52~66)	58 (52~64)	0.02
Married with spouse [*n* (%)]	3548 (87.5)	610 (85.8)	2938 (85.6)	0.91
Education				
Illiterate [*n* (%)]	1206 (29.1)	191 (26.9)	1015 (29.6)	
Middle school and below [*n* (%)]	1770 (41.2)	309 (43.5)	1398 (40.7)	0.28
High school and above [*n* (%)]	1229 (29.7)	211 (29.7)	1018 (29.7)	
Household per capita income (yuan)	6461.0	6000.0	6560.0	0.20
M (*P*25~*P*75)	(2336.7~13487.5)	(1866.7~13490.0)	(2450.0~13486.7)	
Drink [*n* (%)]	1470 (32.2)	234 (32.9)	1173 (34.2)	0.51
Smoke [*n* (%)]	1567 (37.8)	272 (38.3)	1295 (37.7)	0.80
Blood urea nitrogen (mg/dl)	15.0 (12.5~17.8)	15.1 (12.6~18.2)	15.0 (12.5~17.7)	0.18
Fasting glucose (mg/dl)	102.4 (94.9~111.2)	100.6 (93.4~109.8)	102.4 (95.2~111.4)	0.001
Creatinine (mg/dl))	0.7 (0.6~0.8)	0.7 (0.6~0.8)	0.8 (0.6~0.9)	<0.001
Total cholesterol (mg/dl)	190.6 (168.6~215.8)	189.8 (164.7~215.3)	190.6 (169.3~216.1)	0.20
Triglyceride (mg/dl)	105.3 (74.3~148.7)	101.8 (71.7~146)	106.2 (74.3~148.7)	0.23

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HDL cholesterol (mg/dl)	49.1 (41.0~59.5)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	0.81
hs-CRP (mg/l)	1.0 (0.5~2.0)	1.0 (0.6~2)	1.0 (0.5~2.0)	0.43
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.36
Uric acid (mg/dl)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	0.83
Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.0 (12.8~15.1)	14.3 (13.1~15.5)	<0.001
eGFR (ml/min/1.73m^2)	95.9 (86.4~102.9)	97.0 (88.3~106.1)	95.6 (85.9~102.4)	<0.001
eGFR group				
60~89 ml/min/1.73m^2 [*n* (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	0.02
90~ ml/min/1.73m^2 [*n* (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
Grip strength group				
T1 [*n* (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	0.01
T2 [*n* (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	
T3 [*n* (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	
Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
Body mass index (kg/m^2)	23.2 (21~25.7)	22.9 (20.8~25.4)	23.3 (21.1~25.8)	0.01
Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
Depression symptom [*n* (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
Self-report hypertension [*n* (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
Self-report dyslipidemia [*n* (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
Self-report diabetes or HBG [*n* (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
Antihypertensive therapy [*n* (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
Lipid-lowering therapy [*n* (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
Hypoglycemic therapy [*n* (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
Metabolic syndrome [*n* (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
Metabolic syndrome components				
Central obesity [*n* (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
Elevated blood pressure [*n* (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
Dyslipidemia [*n* (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
Elevated blood glucose [*n* (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
Baseline non-MetS group				
MetS-free [*n* (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
MetS-developed [*n* (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
Baseline Mets group				
MetS-recovery [*n* (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
MetS-chronic [*n* (%)]	822 (19.8)	143 (20.1)	679 (19.8)	

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Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; LDL: low density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; HBG: high blood glucose; MetS: metabolic syndrome; grip strength is divided into T1, T2 and T3 groups by one-third percentile.

Table 2. Multivariate logistic regression of rapid eGFR decline between study groups

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Baseline MetS groups				
MetS-chronic	ref		ref	
MetS-recovery	0.68 (0.50-0.95)	0.02	0.64 (0.45-0.90)	0.01
Baseline non-MetS groups				
MetS-free	ref		ref	
MetS-developed	0.93 (0.69-1.25)	0.64	1.00 (0.73-1.38)	0.98

Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification; hemoglobin; MetS scores and body mass index.

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome.

Table 3. Multivariate logistic regression of rapid eGFR decline between study groups according the changes of MetS components

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Recovered components in baseline MetS groups (chronic MetS components as reference)				
Central obesity	0.29 (0.15-0.59)	0.01	0.31 (0.15-0.65)	<0.01
Elevated blood pressure	0.80 (0.50-1.26)	0.33	0.79 (0.49-1.27)	0.33
Elevated SBP	0.89 (0.61-1.31)	0.56	0.88 (0.59-1.30)	0.51
Elevated DBP	0.75 (0.46-1.23)	0.26	0.68 (0.41-1.15)	0.15
Dyslipidemia	1.09 (0.82-1.44)	0.57	1.05 (0.78-1.40)	0.77
Elevated TG	1.22 (0.87-1.72)	0.26	1.14 (0.79-1.36)	0.50
Decreased HDL	0.84 (0.59-1.12)	0.32	0.85 (0.59-1.22)	0.38
Elevated blood glucose	1.08 (0.87-1.34)	0.49	1.08 (0.86-1.36)	0.52
Elevated fasting glucose	1.14 (0.91-1.43)	0.25	1.13 (0.89-1.43)	0.32
Developed components in baseline non-MetS groups (free MetS components as reference)				
Central obesity	1.21 (0.92-1.59)	0.16	1.32 (0.97-1.77)	0.74
Elevated blood pressure	0.84 (0.63-1.13)	0.26	0.87 (0.64-1.18)	0.37
Elevated SBP	0.88 (0.66-1.17)	0.37	0.92 (0.68-1.23)	0.56
Elevated DBP	0.88 (0.62-1.24)	0.46	0.91 (0.63-1.30)	0.59
Dyslipidemia	0.92 (0.69-1.22)	0.54	0.96 (0.72-1.30)	0.81
Elevated TG	0.93 (0.70-1.25)	0.64	1.02 (0.75-1.37)	0.91
Decreased HDL	1.02 (0.65-1.59)	0.95	0.97 (0.61-1.55)	0.91
Elevated blood glucose	1.07 (0.76-1.50)	0.71	1.07 (0.75-1.52)	0.71
Elevated fasting glucose	1.06 (0.74-1.51)	0.76	1.09 (0.76-1.57)	0.64

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Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification; hemoglobin; MetS score and body mass index.

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high density lipoprotein.

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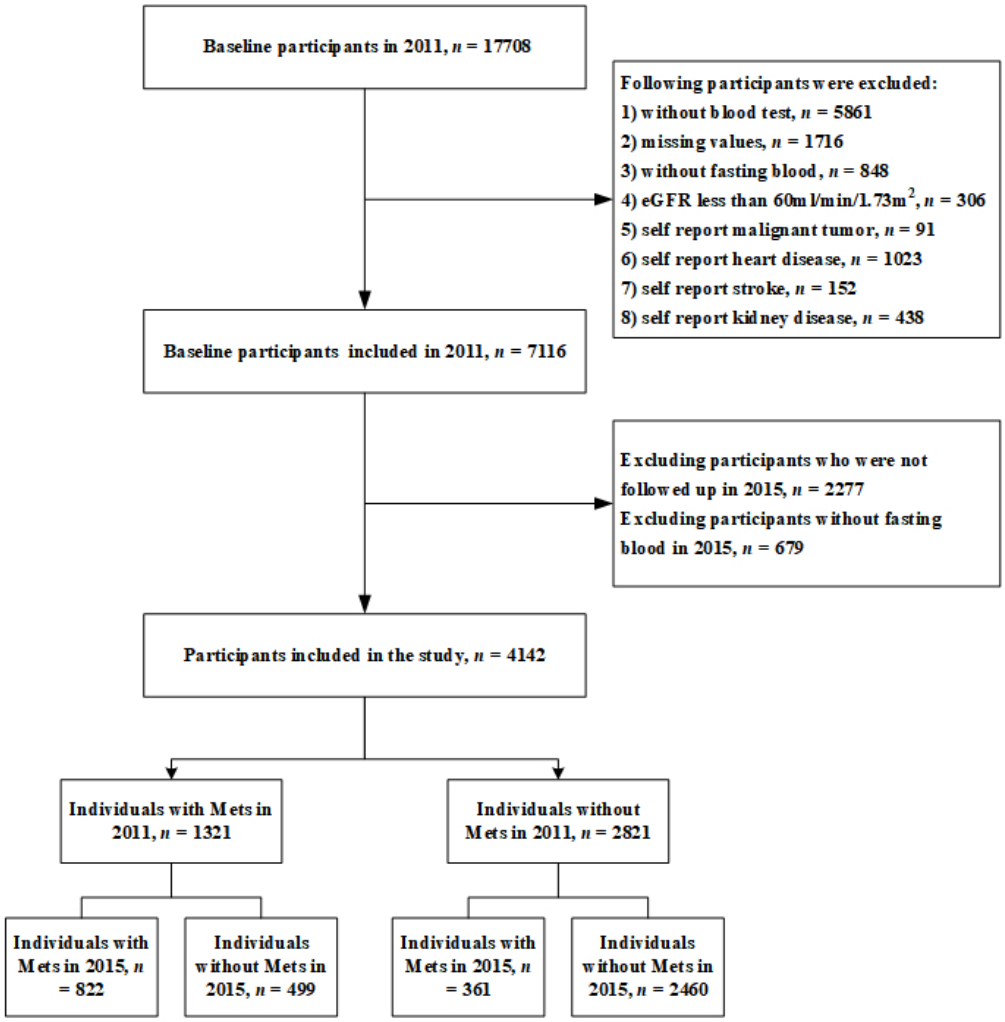

Fig.1 Flowchart of participants selection. eGFR: estimated glomerlular filtration rate; Mets: metabolic syndrome

flowchart of participants selection

180x197mm (96 x 96 DPI)

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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059504.R1
Article Type:	Original research
Date Submitted by the Author:	20-Apr-2022
Complete List of Authors:	Liu, Peijia; Third Affiliated Hospital of Sun Yat-Sen University, Tang, Leile; Third Affiliated Hospital of Sun Yat-Sen University, Department of Cardiology Fang, Jia; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology Chen, Chaojin; Third Affiliated Hospital of Sun Yat-Sen University Liu, Xun; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Urology, Diabetes and endocrinology, Public health
Keywords:	Chronic renal failure < NEPHROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Abstract

Objectives We sought to address this knowledge gap by investigating associations between metabolic syndrome (MetS) recovery/development and rapid estimated glomerular filtration rate (eGFR) decline in the China Health and Retirement Longitudinal Study (CHARLS).

Design Longitudinal cohort study.

Setting This study is a secondary analysis of CHARLS.

Participants After excluding individuals with age < 45 years old, eGFR < 60 ml/min/1.73m^2 and clinician-reported malignant tumor, heart disease, stroke or kidney disease at baseline, 4142 participants with complete data were selected from the CHARLS during the 4-year follow-up.

Outcome measures MetS were measured at both the beginning and the end of the 4-year follow-up. A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2. The associations between rapid eGFR decline and MetS recovery/development were analyzed using multivariable adjusted logistic models.

Results According to MetS baseline status and follow-up, participants were divided into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group, the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, P = 0.01). In contrast, when compared with the MetS-free group, the multivariable adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, P = 0.98).

Conclusions Over a 4-year follow-up period, we found that MetS recovery was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS

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appeared to protect against a rapid decline in eGFR.

Keywords: chronic renal failure; lipid disorders; public health;

Strength and limitation of this study

This study investigated the association between altered metabolic syndrome status and rapid glomerular filtration rate decline in a nationwide cohort.

Metabolic syndrome scores were applied to evaluate the metabolic syndrome severity.

Blood tests related to metabolic syndrome and serum creatinine were performed only once.

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Introduction

Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood pressure (BP) [1-3]. As of 2017, there were approximately 1 billion individuals with MetS around the world, of which China accounted for 21.7% [4]. In China, MetS prevalence has been undergoing a steady increase, concomitant with an increasingly aged population, an obesity epidemic, and increased diabetes and hypertension levels, which collectively pose a considerable threat to people's health and impose a heavy burden on healthcare systems [4-6].

While investigations of causality relationships between MetS and cardiovascular events have gained considerable traction in recent years [7-9], MetS also impacts the kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly include insulin resistance, increased oxidative stress, and a chronic inflammatory state, which may lead to kidney degeneration and chronic kidney disease (CKD) development [5 6]. Previously, it was confirmed that MetS and associated components (abdominal obesity, elevated BG, elevated BP, and lipid metabolic disorder) are strongly related to CKD and a decreased estimated glomerular filtration rate (eGFR) [10-14]. Several longitudinal studies reported that MetS and its components were associated with incremental rapid eGFR decline and CKD incidence [15-18]. However, these studies failed to articulate the relationship between MetS alterations and renal function changes. This dearth of information on this subject warrants further study, especially within a Chinese population context.

The China Health and Retirement Longitudinal Study (CHARLS) is a prospective cohort study conducted by the National School of Development, Peking University, China [19]. The nationwide sample assesses the social, behavioral, and health status of individuals aged 45 and older [19]. The CHARLS baseline survey was implemented in 2011 (Wave 1), and the samples were followed up every two years. Blood samples from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the

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current study, we explored the relationship between MetS recovery/occurrence and rapid eGFR decline in middle-aged and older populations in the 4-year follow-up cohort.

Methods

Study population

CHARLS is a nationally representative longitudinal survey on the social, economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the community [19]. In total, 17,708 participants were registered at baseline (Wave 1), of which 11,847 had blood sample tests.

In this study, our exclusion criteria excluded participants with the following: 1) missing values; 2) without fasting blood values; 3) baseline eGFR < 60 ml/min/1.73m^2; 4) clinician-reported malignant tumor, heart disease, stroke or kidney disease; 5) < 45 years old; and 6) no follow-up records and related blood examinations in Wave 3. After applying these criteria, 4142 participants were finally included. The participant screening process is outlined (Fig. 1).

The Medical Ethics Review Committee of Peking University approved this study. All participants provided written informed consent before participating. This study is a secondary analysis of a public dataset and does not require ethics approval again.

Blood examinations

At baseline (Wave 1), blood measurements and hemoglobin were assayed by the Center for Disease Control and Prevention of the local county, whereas other biochemical indicators were analyzed by Youanmen Center for Clinical Laboratory of Capital Medical University, Beijing, China. Serum creatinine (Scr) was measured by the picric acid method; blood urea nitrogen (BUN) was determined by an enzymatic UV method with urease; blood glucose (BG), total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG) were assayed by enzymatic colormetric tests; glycosylated hemoglobin (GHbA1c) was determined by high performance liquid chromatography; high-sensitivity C-reactive protein (hs-CRP) was

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examined by immunoturbidimetric assay; and uric acid (UA) was determined by the UA plus method [20]. Blood specimen testing in 2015 (Wave 3) was completed by KingMed Diagnostics, the leading third-party institution in China, which has testing laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were determined by the same methods as Wave 1, while HDL was determined by a direct method, TG by an oxidase method, and BG by a hexokinase method [21]. The collection, storage, transport, processing, and other blood sample details are described elsewhere [20 21]. Of note, the models and manufacturer information of blood test instruments in Wave 1 and Wave 3 were not available. All inspections and calibrations were performed by trained personnel.

Definition and grouping of MetS

Currently, there was no unified definition for MetS. The World Health Origination (WHO) diagnostic criteria proposed in 1999, the National Cholesterol Education Program Adult Panel Ⅲ (ATP Ⅲ) diagnostic criteria proposed in 2005, and International Diabetes Federation (IDF) diagnostic criteria proposed in 2006 were commonly used for metabolic syndrome [22]. These diagnostic criteria basically related to abdominal obesity, dyslipidemia, glucose metabolism disorder, and elevated blood pressure. However, these diagnostic criteria had different views and cut-off values for some specific indicators. This study adopted the 2018 China Guidelines for the Prevention and Treatment of Hypertension (CGPTH) definition for MetS, which was similar to the ATP Ⅲ diagnostic criteria [2]. Compared with ATP Ⅲ diagnostic criteria, the cut points of waist circumference defined by CGPTH were smaller and more suitable for the Chinese population. According to the 2018 CGPTH definition, MetS was diagnosed when three of the following four conditions were met: 1) Central obesity: waist circumference (WC) ≥ 90 cm in men and ≥ 85 cm in women; 2) Elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or diagnosed as hypertension and treated; 3) Dyslipidemia:

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fasting TG ≥ 150 mg/dL, or HDL ≤ 40 mg/dL, or diagnosed as dyslipidemia and treated; and 4) Elevated BG: Fasting BG (FBG) ≥ 100 mg/dL, or 2 h postprandial BG ≥ 100 mg/dL, or diagnosed as diabetes and treated [2]. Diabetes was defined as fasting BG ≥ 126 mg/dL, and/or HbA1c ≥ 6.5%, and/or a self-reported history of diabetes [23]. Of note, we did not have 2 h postprandial BG data.

According to MetS baseline status and follow-up, participants were categorized into 1) MetS-free, 2) MetS-developed, 3) MetS-recovery, and 4) MetS-chronic groups.

Study outcomes

We calculated eGFR values using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine levels [24]. A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2 [16 25]. In this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR in Wave 1, > 12 ml/min/1.73m^2.

MetS scores

MetS severity potentially affects the recovery or occurrence of MetS. For instance, individuals with high MetS severity may be less liable to recover. Similarly, for those without MetS, it is not straightforward to progress to severe MetS. Therefore, MetS scores were introduced to assess MetS severity in the study, which was thought to be more sufficient and accurate than other ways using the number of symptoms and complications to reflect MetS severity [26 27]. These scores were calculated using principal component (PC) analysis of WC, mean arterial pressure (MAP), FBG, fasting TG, and the inverse HDL values. All MetS related variables were normalized by 0–1. According to the PC analysis results, PC1 and PC2 explained 38.9% and 20.9% of the variance, respectively. MetS scores were calculated as follows:

$$\mathrm{PC1} = 0.369 \times \mathrm{WC} + 0.378 \times \mathrm{FBG} + 0.585 \times \mathrm{TG} + 0.562 \times \left(\frac{1}{\mathrm{HDL}}\right) + 0.252 \times \mathrm{MAP},$$

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$$PC2 = 0.503 \times WC - 0.171 \times FBG - 0.268 \times TG - 0.274 \times \left(\frac{1}{HDL}\right) + 0.755 \times MAP,$$

$$MetS\ score = 0.389 \times PC1 + 0.209 \times PC2$$

Other covariates

All potential covariates were all collected at baseline in Wave 1, including gender (male vs. female), age, marital status (married with spouse vs. others), education (illiterate, middle school and below, or high school and above), household per capita income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height, weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs. no), self-reporting disease (hypertension, diabetes, dyslipidemia and), and corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90. Grip strength was divided into three groups (T1, T2, and T3) according to the one-third percentile. BMI was calculated by weight (kg)/height squared (m^2). The BP of each participant was measured three times every 45–60 s with the OmronTM HEM-7112 sphygmomanometer (Omron Co. LTD， Dalian, China) at rest. Both SBP and DBP were averaged from three measurements. MAP was defined as MAP = 1/3 × SBP + 2/3 × DBP. Previous study demonstrated that depressive symptom was association with baseline eGFR [28]. Thus, we should not overlook this variable. The 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was applied in the study [29]. A CESD-10 score ≥ 10 was grouped into the depressive symptom group, and < 10 into the non-depressive symptom group. Self-reporting disease was disease diagnosed by a doctor. Medical interventions included taking Chinese traditional and Western modern medicines.

Statistical methods

The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Continuous variables were expressed by the median (interquartile range) and categorical variables by frequency (%). The Mann-Whitney U test was performed on continuous variables, and categorical variables between the rapid eGFR decline group and the non-rapid eGFR decline group were tested by the Chi-square test. In

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preliminary analyses, variables with P values < 0.15 were used to calibrate the logistic model. Continuous variables not presenting a linear relationship with the logit conversion value of the dependent variable were converted to categorical variables. Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This existed if the tolerance was < 0.1 or the VIF was > 10. Eventually, age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification and MetS scores were selected as confounding variables for model adjustments in this study. Most selected covariates have been reported to be related to renal events [26 30-33]. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group were carried out. Logistic models were used to test the association between MetS recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding factors. Furthermore, alterations in MetS status were accompanied by changes of diagnostic conditions (elevated blood glucose, elevated blood pressure, central obesity and dyslipidemia). As a result, logistic models were used to explore the relationship between the recovery/occurrence of Mets components and the rapid decline of eGFR using different adjustments of confounding factors, respectively. $P < 0.05$ was considered statistically significant (two-sided test). Statistics were generated in IBM SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software (StataCorp, Texas, USA).

Patient and public involvement

There were no participants involved in the development. The results of the survey are disseminated to the public through websites.

Results

Participant characteristics

As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS recovery-group, and 822 (19.8%) in the MetS-chronic group. Comparison of the basic

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characteristics between the 4142 enrolled participants and 2974 ones that excluded during follow-up were shown in Supplemental Table 1.

Participant characteristics were grouped by the eGFR decline rate (Table 1). A rapid decline in eGFR developed in 711 (17.2%) participants during the 4-year follow-up. The median age was 58 (52~64) years and males accounted for 42.5% at baseline. In contrast to rapid eGFR decline group, the non-rapid eGFR decline group was significantly higher with respect to FBG, Scr, hemoglobin, eGFR, weight, BMI, WC, MetS scores, central obesity, and elevated BG (all $P < 0.05$). Those in non-rapid eGFR decline group were more likely to be female and younger when compared with the eGFR decline group (both $P < 0.05$).

Rapid eGFR decline odds based on Mets recovery or occurrence

Univariate analysis was conducted to select covariates for correction (Supplemental Table 2). As shown (Table 2), after adjustment for age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification, and MetS scores, the odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% CI: 0.45–0.90, $P = 0.01$) when compared with the MetS-chronic group. In contrast, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, $P = 0.98$) when compared with the MetS-free group.

MetS components and rapid eGFR decline odds

The association of changes in the composition of MetS groups with rapid eGFR decline is shown (Table 3). In the baseline MetS population, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the population recovered from central obesity was 0.31 (OR: 0.31; 95% CI: 0.15–0.65, $P < 0.01$) when compared with chronic central obesity, whereas recovery from elevated BP,

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dyslipidemia, and elevated BG did not show statistically significant differences when compared with the corresponding population (all $P > 0.05$). In the baseline population without MetS, we observed no statistical difference in the rapid decline of eGFR between the occurrence of all MetS component groups and corresponding contrast groups (all $P > 0.05$). This was consistent with the overall trend.

Discussion

We examined the relationship between MetS changes and rapid eGFR decline in a large nationwide cohort. At the 4-year follow-up, MetS recovery was significantly associated with a reduced risk of rapid eGFR decline in the middle-aged and elderly, with only WC recovery consistent with the overall trend. The occurrence of MetS and its components did not significantly increase the risk of rapid eGFR decline. Further follow-up is required to elucidate the relationship between MetS dynamics and the rapid decline in eGFR.

Longitudinal cohort studies in several Asian countries concluded that MetS increased the risk of CKD, although follow-up times varied from study to study [15-18, 34]. However, the effect of MetS on the rapid decline of eGFR remains controversial. In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and eGFR rapid decline in the elderly [34]. However, other studies reported that baseline MetS was associated with a decline in eGFR and even acted as an independent predictor of eGFR decline [16-18]. *Wu et al.* investigated the association between the MetS severity score and kidney function, and found that the MetS severity score was an independent risk factor for the CKD development and progressive eGFR decline, although the definition of rapid eGFR decline was different from this study [26]. Here, the Mets severity score was a continuous variable that was primarily used to calibrate the MetS (yes vs. no). We noted that none of the aforementioned studies accounted for the MetS status of participants during follow-up periods. In a 4-year follow-up cohort, Park *et al.* explored the relationship between MetS status change and CKD events and concluded that MetS recovery was associated with a decreased risk of

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CKD incidence, but the occurrence of MetS increased the risk of CKD incidence [35]. One of the highlights of the article was to observe the status of MetS three times over a 4-year period, thereby making the MetS diagnosis more robust. However, Park *et al.* did not discuss the association with the rapid eGFR decline. In this study, we concluded that MetS recovery was associated with a reduced risk of rapid eGFR decline, while MetS occurrence was not related to rapid eGFR decline. It should be emphasized that we need to be cautious about the conclusion between the MetS occurrence and the rapid eGFR decline in this study. Because the follow-up time was short and the timing of MetS onset was unknown, the impairment of renal function caused by MetS may not have occurred in some populations. To sum up, studies exploring the relationship between MetS dynamic changes and the rapid decline of eGFR in the Chinese population are rare. Our investigation of the relationship between MetS recovery/occurrence and eGFR rapid decline in a large nationwide cohort may support renal function management in individuals with MetS.

The effect of MetS on renal function is complex, thus, no definitive mechanisms can explain our study observations. The evidence suggests that every component of MetS is associated with adverse renal events (10-14). It is accepted that hypertension and diabetes play pivotal roles in CKD development and progression [36-38]. Also, lipid metabolism dysregulation and abnormal lipid distribution can lead to lipotoxicity-related renal damage [39 40]. Thus, MetS may result from the combined effects of central obesity, increased BP, insulin resistance, and blood lipid disorder, leading to physiopathological lipotoxicity, oxidative stress increments, endothelial dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney dysfunction [5 39]. However, the relationship between MetS components and the weight of each factor on kidney injury remain unclear.

Our study had some limitations. Firstly, MetS diagnoses were not comprehensively checked (using multiple tests), and the exact timing of the MetS alteration is unknown. Secondly, renal stone disease, epiculopathy, epiculoepicardial

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disease or acute urinary tract infection are related to the occurrence and development of renal disease. Unfortunately, urine or kidney ultrasound results were unavailable in CHARLS cohort. Thirdly, CKD occurrence was not included as a study outcome because of the lack of urine test results, which would underestimate the CKD incidence. Fourthly, blood analyses from Wave 1 and Wave 3 were performed at a different testing center, with inconsistent HDL, TG, and BG measurement methods, therefore, measurement errors may have occurred. Fifthly, a large proportion of individuals were excluded due to exclusion criteria or missing values and this may have biased some of our results. Sixthly, we did not establish a model with all 4 MetS change groups included in the study.

Conclusions

Over a 4-year follow-up, we observed that MetS recovery, including recovery of central obesity, was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Reversing MetS, especially central obesity, might benefit the kidney function in MetS population. But, further follow-up studies are required to observe the relationship between MetS alterations and adverse renal events.

Acknowledgements The authors are grateful to the China Health and Retirement Longitudinal Study (CHARLS) team for providing the data.

Contributors PL and LT contributed equally to this paper. PL, LT and JF—analysis and interpretation of data and preparation of the manuscript. XL—study concept and design, and preparation and critical review of the manuscript. CC—critical review and statistical guidance of the revised manuscript. All authors have approved the final manuscript.

Funding This work was supported by Guangzhou Municipal Science and Technology Bureau (202002020047).

Competing interests All authors declared no competing interests.

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Data availability statement CHARLS data of the study will be available to investigators at the CHARLS website (http://charls.pku.edu.cn/en).

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Table 1. Baseline characteristics of participants between rapid eGFR decline group and non-rapid eGFR decline group

Characteristics	Overall (*n* = 4142)	Rapid eGFR decline (*n* = 711)	Non-rapid eGFR decline (*n* = 3431)	*P* value
Male [*n* (%)]	1874 (45.2)	351 (49.4)	1523 (44.4)	0.02
Age (years)	58 (52~64)	59 (52~66)	58 (52~64)	0.02
Married with spouse [*n* (%)]	3548 (87.5)	610 (85.8)	2938 (85.6)	0.91
Education				
Illiterate [*n* (%)]	1206 (29.1)	191 (26.9)	1015 (29.6)	
Middle school and below [*n* (%)]	1770 (41.2)	309 (43.5)	1398 (40.7)	0.28
High school and above [*n* (%)]	1229 (29.7)	211 (29.7)	1018 (29.7)	
Household per capita income (yuan)	6461.0	6000.0	6560.0	0.20
M (*P*25~*P*75)	(2336.7~13487.5)	(1866.7~13490.0)	(2450.0~13486.7)	
Drink [*n* (%)]	1470 (32.2)	234 (32.9)	1173 (34.2)	0.51
Smoke [*n* (%)]	1567 (37.8)	272 (38.3)	1295 (37.7)	0.80
Blood urea nitrogen (mg/dl)	15.0 (12.5~17.8)	15.1 (12.6~18.2)	15.0 (12.5~17.7)	0.18
Fasting glucose (mg/dl)	102.4 (94.9~111.2)	100.6 (93.4~109.8)	102.4 (95.2~111.4)	0.001
Creatinine (mg/dl)	0.75 (0.64~0.84)	0.71 (0.60~0.84)	0.76 (0.64~0.86)	<0.001
Total cholesterol (mg/dl)	190.6 (168.6~215.8)	189.8 (164.7~215.3)	190.6 (169.3~216.1)	0.20
Triglyceride (mg/dl)	105.3 (74.3~148.7)	101.8 (71.7~146)	106.2 (74.3~148.7)	0.23
HDL cholesterol (mg/dl)	49.1 (41.0~59.5)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	0.81
hs-CRP (mg/l)	1.0 (0.5~2.0)	1.0 (0.6~2)	1.0 (0.5~2.0)	0.43
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.36
Uric acid (mg/dl)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	0.83
Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.0 (12.8~15.1)	14.3 (13.1~15.5)	<0.001
eGFR (ml/min/1.73m^2)	95.9 (86.4~102.9)	97.0 (88.3~106.1)	95.6 (85.9~102.4)	<0.001
eGFR group				
60~89 ml/min/1.73m^2 [*n* (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	0.02
90~ ml/min/1.73m^2 [*n* (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
Grip strength group				
T1 [*n* (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	0.01
T2 [*n* (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	
T3 [*n* (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	

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Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
Body mass index (kg/m^2)	23.2 (21~25.7)	22.9 (20.8~25.4)	23.3 (21.1~25.8)	0.01
Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
Depression symptom [*n* (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
Self-report hypertension [*n* (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
Self-report dyslipidemia [*n* (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
Self-report diabetes or HBG [*n* (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
Self-report arthritis or rheumatism [*n* (%)]	1345 (32.5)	235 (33.1)	1110 (32.4)	0.71
Antihypertensive therapy [*n* (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
Lipid-lowering therapy [*n* (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
Hypoglycemic therapy [*n* (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
Therapy for arthritis or rheumatism [*n* (%)]	643 (15.5)	116 (16.3)	527 (15.4)	0.52
Metabolic syndrome [*n* (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
Metabolic syndrome components				
Central obesity [*n* (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
Elevated blood pressure [*n* (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
Dyslipidemia [*n* (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
Elevated blood glucose [*n* (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
Baseline non-MetS group				
MetS-free [*n* (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
MetS-developed [*n* (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
Baseline Mets group				
MetS-recovery [*n* (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
MetS-chronic [*n* (%)]	822 (19.8)	143 (20.1)	679 (19.8)	

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome.

grip strength is divided into T1, T2 and T3 groups by one-third percentile.

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Table 2. Multivariate logistic regression of rapid eGFR decline between study groups

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Baseline MetS groups				
MetS-chronic	ref		ref	
MetS-recovery	0.68 (0.50-0.95)	0.02	0.64 (0.45-0.90)	0.01
Baseline non-MetS groups				
MetS-free	ref		ref	

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MetS-developed	0.93 (0.69-1.25)	0.64	1.00 (0.73-1.38)	0.98

Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification; hemoglobin; MetS scores and body mass index.

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome.

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Table 3. Multivariate logistic regression of rapid eGFR decline between study groups according the changes of MetS components

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Recovered components in baseline MetS groups (chronic MetS components as reference)				
Central obesity	0.29 (0.15-0.59)	0.01	0.31 (0.15-0.65)	<0.01
Elevated blood pressure	0.80 (0.50-1.26)	0.33	0.79 (0.49-1.27)	0.33
Elevated SBP	0.89 (0.61-1.31)	0.56	0.88 (0.59-1.30)	0.51
Elevated DBP	0.75 (0.46-1.23)	0.26	0.68 (0.41-1.15)	0.15
Dyslipidemia	1.09 (0.82-1.44)	0.57	1.05 (0.78-1.40)	0.77
Elevated TG	1.22 (0.87-1.72)	0.26	1.14 (0.79-1.36)	0.50
Decreased HDL	0.84 (0.59-1.12)	0.32	0.85 (0.59-1.22)	0.38
Elevated blood glucose	1.08 (0.87-1.34)	0.49	1.08 (0.86-1.36)	0.52
Elevated fasting glucose	1.14 (0.91-1.43)	0.25	1.13 (0.89-1.43)	0.32
Developed components in baseline non-MetS groups (free MetS components as reference)				
Central obesity	1.21 (0.92-1.59)	0.16	1.32 (0.97-1.77)	0.74
Elevated blood pressure	0.84 (0.63-1.13)	0.26	0.87 (0.64-1.18)	0.37
Elevated SBP	0.88 (0.66-1.17)	0.37	0.92 (0.68-1.23)	0.56
Elevated DBP	0.88 (0.62-1.24)	0.46	0.91 (0.63-1.30)	0.59
Dyslipidemia	0.92 (0.69-1.22)	0.54	0.96 (0.72-1.30)	0.81
Elevated TG	0.93 (0.70-1.25)	0.64	1.02 (0.75-1.37)	0.91
Decreased HDL	1.02 (0.65-1.59)	0.95	0.97 (0.61-1.55)	0.91
Elevated blood glucose	1.07 (0.76-1.50)	0.71	1.07 (0.75-1.52)	0.71
Elevated fasting glucose	1.06 (0.74-1.51)	0.76	1.09 (0.76-1.57)	0.64

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high density lipoprotein.

Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification, hemoglobin, MetS score and body mass index.

Each Mets components run in their own model to predict rapid eGFR decline

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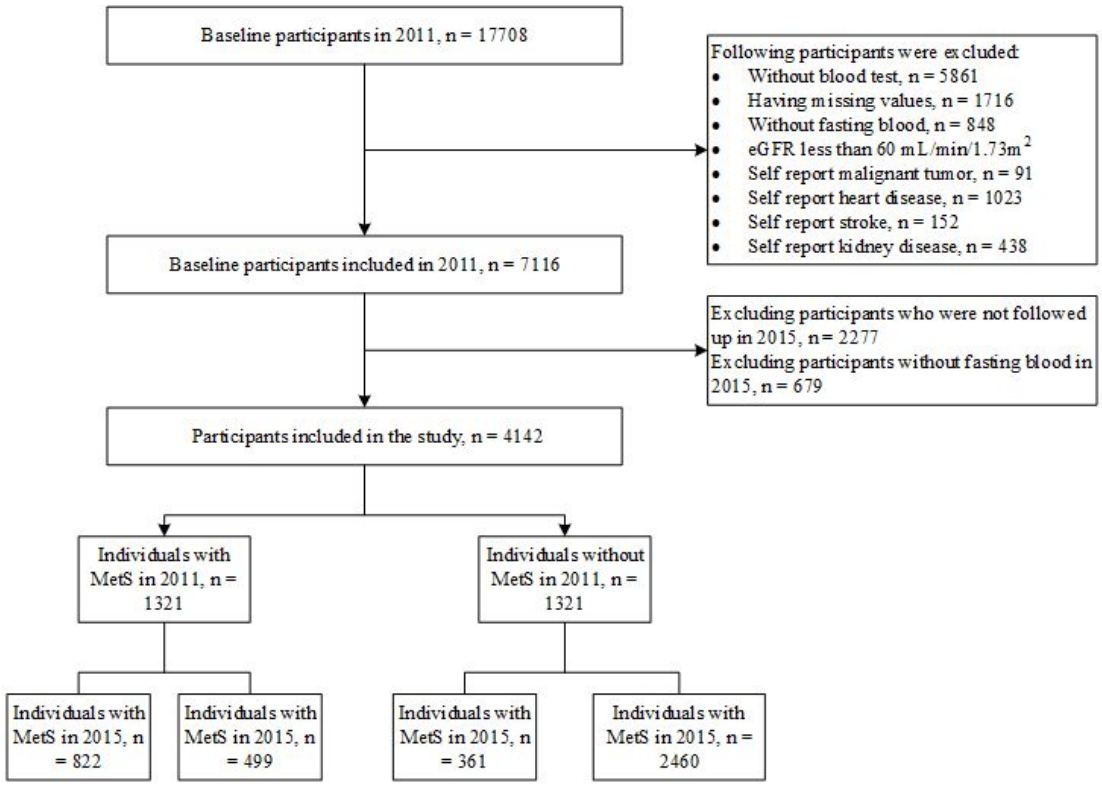

478 Fig 1. Flow chart of of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

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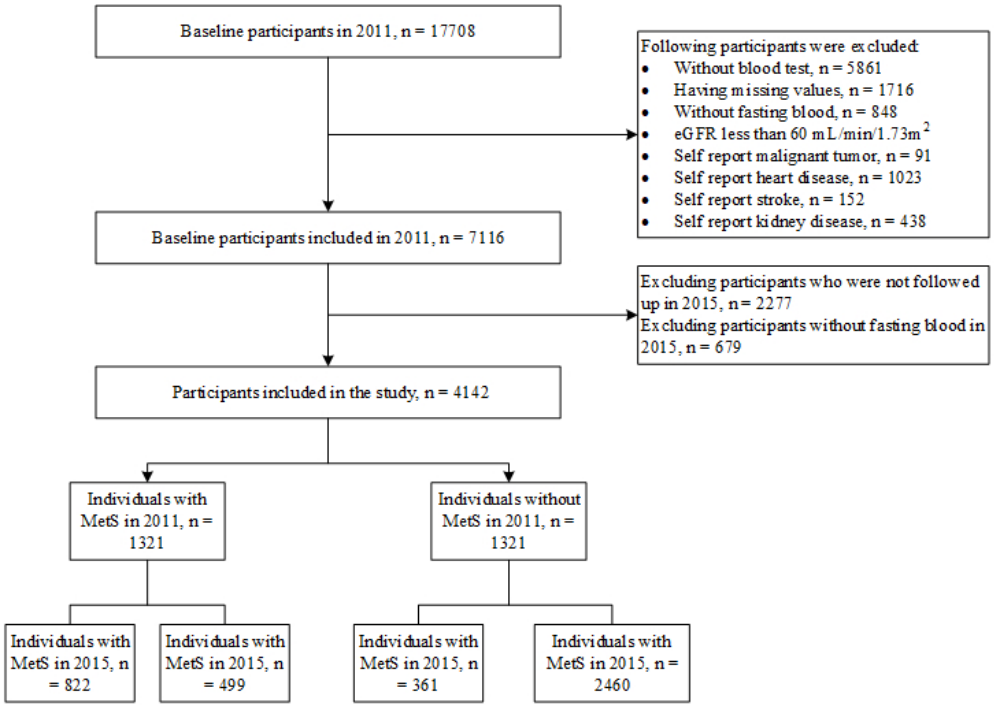

Fig 1. Flow chart of of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

Flow chart of of participants selection

193x148mm (96 x 96 DPI)

Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Supplemental Table 1. Baseline characteristics of participants included and excluded in the study

Characteristics	participants included in baseline (n=7116)	group 1 (n=2974)	group 2 (n=4142)	*P*-value
Age (years)	58 (52~65)	58 (52~64)	58 (51~66)	0.98
Male [*n* (%)]	3332 (46.8)	1458 (49.0)	1874 (45.2)	0.002
Married with spouse [*n* (%)]	5977 (84.0)	2974 (81.7)	3548 (87.5)	<0.001
Education				0.07
Illiterate [*n* (%)]	2106 (29.6)	900 (30.3)	1206 (29.1)	
Middle school and below [*n* (%)]	2853 (40.1)	1146 (38.5)	1770 (41.2)	
High school and above [*n* (%)]	2157 (30.3)	928 (31.2)	1229 (29.7)	
Household per capita income (yuan)	6748 (2417~14298)	6461 (2337~13487)	7276 (2500~15600)	0.02
Drink [*n* (%)]	2461 (34.6)	1054 (35.4)	1470 (32.2)	0.20
Smoke [*n* (%)]	2775 (39.0)	1208 (40.6)	1567 (37.8)	0.02
Blood urea nitrogen (mg/dl)	15.1 (12.52~17.90)	15.0 (12.5~17.8)	15.1 (12.8~18.0)	0.16
Fasting glucose (mg/dl)	102.4 (94.5~111.6)	102.4 (94.9~111.2)	102.1 (94.1~112.5)	0.72
Creatinine (mg/dl)	0.76 (0.64~0.86)	0.75 (0.64~0.85)	0.76 (0.66~0.88)	<0.001
Total cholesterol (mg/dl)	190.2 (168.2~215.3)	190.6 (168.6~215.7)	189.8 (167.4~214.9)	0.36
Triglyceride (mg/dl)	104.4 (74.34~147.8)	105.3 (74.34~148.7)	104.4 (73.46~147.8)	0.77
HDL cholesterol (mg/dl)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	49.9 (41.4~60.3)	0.02
hs-CRP (mg/l)	1.03 (0.54~2.04)	1.02 (0.54~1.97)	1.04 (0.55~2.17)	0.62
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.65
Uric acid (mg/dl)	4.3 (3.6~5.1)	4.2 (3.5~5.0)	4.4 (3.6~5.1)	<0.001
Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.2 (13.1~15.5)	14.2 (13.1~15.5)	0.75
Height (cm)	157.9 (152.0~164.1)	157.7 (152.0~163.8)	157.9 (152~164.5)	0.74
Weight (kg)	57.7 (51.0~65.4)	58.0 (51.3~65.5)	57.5 (50.3~65.2)	0.01
Waist (cm)	84.3 (77.6~91.4)	84.4 (78.0~92.0)	84.0 (77.0~91.0)	0.08
Body mass index (kg/m^2)	23.1 (20.8~25.6)	23.2 (21.0~25.7)	22.9 (20.6~25.5)	0.01
hand grip strength (kg)	29.3 (23.5~36.5)	29.1 (23.0~36.5)	29.3 (23.8~36.5)	0.59
Systolic blood pressure (mmHg)	127.3 (114.7~141.3)	127.0 (114.3~141.0)	127.7 (115.3~142.0)	0.32
Diastolic blood pressure (mmHg)	74.7 (67.3~83.0)	74.7 (67.0~82.7)	75.0 (67.3~83.0)	0.34
Mean arterial pressure (mmHg)	92.6 (83.7~102.0)	92.2 (83.4~101.7)	92.6 (84.0~102.6)	0.28
eGFR (ml/min/1.73m^2)	95.2 (85.5~102.7)	95.9 (86.4~102.9)	94.0 (84.3~102.3)	<0.001
Depression symptom [*n* (%)]	3172 (44.6)	1268 (42.6)	1904 (46.0)	0.005
Metabolic syndrome [*n* (%)]	2228 (31.3)	907 (30.5)	1321 (31.9)	0.21
Metabolic syndrome components				
Elevated blood pressure [*n* (%)]	3622 (50.9)	1523 (51.2)	2099 (50.7)	0.66
Elevated blood glucose [*n* (%)]	4179 (58.7)	1723 (57.9)	2456 (59.3)	0.25
Dyslipidemia [*n* (%)]	2673 (37.6)	1078 (36.2)	1595 (38.5)	0.052
Central obesity [*n* (%)]	2862 (40.2)	1136 (38.2)	1726 (41.7)	0.003

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR:estimated glomerular filtration rate; MetS: metabolic

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syndrome. Group 1: participants included in the baseline and exclueded after follow-up; Group 2: participants included in the study.

Supplemental Table 2. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group

Characteristics	Coef.	95% Conf.	*P*-value
Sex (female as ref)	0.200	0.038~0.362	0.02
Age (years)	0.011	0.002~0.021	0.02
Married status [*n* (%)]			
Other married status	ref	ref	
Married with spouse	0.013	-0.218~0.245	0.91
Education			
Illiterate	ref	ref	
Middle school and below	0.160	--0.037~0.359	0.11
High school and above	0.097	-0.118~0.311	0.34
Household per capita income (per 10000 yuan)	0.005	-0.053~0.062	0.88
Drink [*n* (%)]			
Smoke [*n* (%)]	0.022	-0.145~0.188	0.80
Blood urea nitrogen (mg/dl)	0.019	-0.001~0.038	0.06
Fasting glucose (mg/dl)	-0.002	-0.005~0.001	0.28
Creatinine (mg/dl))	-1.818	-2.368~-1.268	<0.001
Total cholesterol (mg/dl)	-0.001	-0.004~0.001	0.21
Triglyceride (mg/dl)	-0.0004	-	0.39
HDL cholesterol (mg/dl)	0.007	-0.005~0.006	0.80
hs-CRP (mg/l)	0.004	-0.013~0.020	0.66
GHbA1c (%)	-0.051	-0.167~0.066	0.40
Uric acid (mg/dl)	0.003	-0.066~0.072	0.93
Hemoglobin (mg/dl)	-0.102	-0.144~-0.060	<0.001
eGFR (ml/min/1.73m^2)	0.023	0.017~0.030	<0.001
eGFR group			
60~89 ml/min/1.73m^2 [*n* (%)]	ref	ref	
90~ ml/min/1.73m^2 [*n* (%)]	0.203	0.026~0.379	0.02
Grip strength (kg)	0.004	-0.005~0.012	0.38
Grip strength group			
T1 [*n* (%)]	ref	ref	
T2 [*n* (%)]	0.311	0.112~0.511	<0.01
T3 [*n* (%)]	0.148	-0.056~0.353	0.16
Height (cm)	0.003	-0.007~0.013	0.58
Weight (kg)	-0.008	-0.015~0.000	0.048
Body mass index (kg/m^2)	-0.032	-0.056~-0.009	0.01

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Waist circumference (cm)	-0.012	-0.018~-0.005	<0.001
Systolic blood pressure (mmHg)	0.002	-0.002~0.006	0.33
Diastolic blood pressure (mmHg)	-0.001	-0.008~0.005	0.76
Mean arterial pressure (mmHg)	0.001	-0.005~0.007	0.75
Depression symptom [*n* (%)]	-0.054	-0.216~0.109	0.52
Self-report hypertension [*n* (%)]	0.047	-0.148~0.243	0.63
Self-report dyslipidemia [*n* (%)]	0.019	-0.276~0.315	0.90
Self-report diabetes or HBG [*n* (%)]	-0.196	-0.065~0.213	0.35
Self-report arthritis or rheumatism [*n* (%)]	-0.032	-0.204~0.140	0.71
Antihypertensive therapy [*n* (%)]	0.062	-0.155~0.280	0.57
Lipid-lowering therapy [*n* (%)]	0.183	-0.186~0.552	0.33
Hypoglycemic therapy [*n* (%)]	-0.169	-0.663~0.326	0.50
Therapy for arthritis or rheumatism [*n* (%)]	0.072	-0.148~0.291	0.52
Metabolic syndrome [*n* (%)]	-0.158	-0.334~0.019	0.08
MetS scores	-0.138	-0.279~0.003	0.055
Metabolic syndrome components			
Central obesity [*n* (%)]	-0.229	-0.395~-0.062	0.01
Elevated blood pressure [*n* (%)]	0.052	-0.109~0.214	0.53
Dyslipidemia [*n* (%)]	0.030	-0.135~0.196	0.72
Elevated blood glucose [*n* (%)]	-0.268	-0.431~0.105	0.001

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR:

estimated glomerular filtration rate; MetS: metabolic syndrome.

grip strength is divided into T1, T2 and T3 groups by one-third percentile.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1-3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4	Explain the scientific background and rationale for the investigation being reported
Objectives	4-5	State specific objectives, including any prespecified hypotheses
Methods		
Study design		Present key elements of study design early in the paper
Setting		Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants.
Data sources/ measurement	5-6*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Variables	6-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Bias		Describe any efforts to address potential sources of bias
Study size		Explain how the study size was arrived at
Quantitative variables		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	8-9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	9*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	10*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	10*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	10	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

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		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10-11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11	Summarise key results with reference to study objectives
Limitations	12-13	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	11-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059504.R2
Article Type:	Original research
Date Submitted by the Author:	06-Aug-2022
Complete List of Authors:	Liu, Peijia; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology; Guangzhou Eighth People's Hospital, Guangzhou Medical University, Department of Nephrology Tang, Leile; Third Affiliated Hospital of Sun Yat-Sen University, Department of Cardiology Fang, Jia; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology Chen, Chaojin; Third Affiliated Hospital of Sun Yat-Sen University Liu, Xun; Third Affiliated Hospital of Sun Yat-Sen University, Department of Nephrology
Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Urology, Diabetes and endocrinology, Public health
Keywords:	Chronic renal failure < NEPHROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Abstract

Objectives Few studies have explored correlations between metabolic syndrome (MetS) alterations and renal deterioration in longitudinal cohorts. We aim to investigate associations between MetS recovery/development and rapid estimated glomerular filtration rate (eGFR) decline in the China Health and Retirement Longitudinal Study (CHARLS).

Design Longitudinal cohort study.

Setting This study is a secondary analysis of CHARLS.

Participants After excluding individuals with age < 45 years old, eGFR < 60 ml/min/1.73m^2 and clinician-reported malignant tumor, heart disease, stroke or kidney disease at baseline, 4142 participants with complete data were selected from the CHARLS during the 4-year follow-up period (2011-2015).

Outcome measures MetS were measured at 2011 and 2015 in CHARLS. A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2. The associations between rapid eGFR decline and MetS recovery/development were analyzed using multivariable adjusted logistic models.

Results According to MetS baseline status and follow-up, participants were divided into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group, the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, P = 0.01). In contrast, when compared with the MetS-free group, the multivariable adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, P = 0.98).

Conclusions Over the 4-year follow-up period, we found that MetS recovery was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS

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appeared to protect against a rapid decline in eGFR.

Keywords: chronic renal failure; lipid disorders; public health;

Strength and limitation of this study

This study investigated the association between altered metabolic syndrome status and rapid glomerular filtration rate decline in a nationwide cohort.

Metabolic syndrome scores were applied to evaluate the metabolic syndrome severity.

Blood tests related to metabolic syndrome and serum creatinine were performed only once.

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Introduction

Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood pressure (BP) [1-3]. As of 2017, there were approximately 1 billion individuals with MetS around the world, of which China accounted for 21.7% [4]. In China, MetS prevalence has been undergoing a steady increase, concomitant with an increasingly aged population, an obesity epidemic, and increased diabetes and hypertension levels, which collectively pose a considerable threat to people's health and impose a heavy burden on healthcare systems [4-6].

While investigations of causality relationships between MetS and cardiovascular events have gained considerable traction in recent years [7-9], MetS also impacts the kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly include insulin resistance, increased oxidative stress, and a chronic inflammatory state, which may lead to kidney degeneration and chronic kidney disease (CKD) development [5 6]. Previously, it was confirmed that MetS and associated components (abdominal obesity, elevated BG, elevated BP, and lipid metabolic disorder) are strongly related to CKD and a decreased estimated glomerular filtration rate (eGFR) [10-14]. Several longitudinal studies reported that MetS and its components were associated with incremental rapid eGFR decline and CKD incidence [15-18]. However, these studies failed to articulate the relationship between MetS alterations and renal function changes. This dearth of information on this subject warrants further study, especially within a Chinese population context.

The China Health and Retirement Longitudinal Study (CHARLS) is a prospective cohort study conducted by the National School of Development, Peking University, China [19]. The nationwide sample assesses the social, behavioral, and health status of individuals aged 45 and older [19]. The CHARLS baseline survey was implemented in 2011 (Wave 1), and the samples were followed up every two years. Blood samples from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the

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current study, we explored the relationship between MetS recovery/occurrence and rapid eGFR decline in middle-aged and older populations in the 4-year follow-up cohort.

Methods

Study population

CHARLS is a nationally representative longitudinal survey on the social, economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the community [19]. In total, 17,708 participants were registered at baseline (Wave 1 at 2011), of which 11,847 had blood sample tests.

In this study, our exclusion criteria excluded participants with the following: 1) missing values; 2) without fasting blood values; 3) baseline eGFR < 60 ml/min/1.73m^2; 4) clinician-reported malignant tumor, heart disease, stroke or kidney disease; 5) < 45 years old; and 6) no follow-up records and related blood examinations in Wave 3 at 2015. After applying these criteria, 4142 participants were finally included. The participant screening process is outlined (Fig. 1).

The Medical Ethics Review Committee of Peking University approved this study. All participants provided written informed consent before participating. This study is a secondary analysis of a public dataset and does not require ethics approval again.

Blood examinations

At baseline (Wave 1), blood measurements and hemoglobin were assayed by the Center for Disease Control and Prevention of the local county, whereas other biochemical indicators were analyzed by Youanmen Center for Clinical Laboratory of Capital Medical University, Beijing, China. Serum creatinine (Scr) was measured by the picric acid method; blood urea nitrogen (BUN) was determined by an enzymatic UV method with urease; blood glucose (BG), total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG) were assayed by enzymatic colormetric tests; glycosylated hemoglobin (GHbA1c) was determined by high performance liquid chromatography; high-sensitivity C-reactive protein (hs-CRP) was

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examined by immunoturbidimetric assay; and uric acid (UA) was determined by the UA plus method [20]. Blood specimen testing in 2015 (Wave 3) was completed by KingMed Diagnostics, the leading third-party institution in China, which has testing laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were determined by the same methods as Wave 1, while HDL was determined by a direct method, TG by an oxidase method, and BG by a hexokinase method [21]. The collection, storage, transport, processing, and other blood sample details are described elsewhere [20 21]. Of note, the models and manufacturer information of blood test instruments in Wave 1 and Wave 3 were not available. All inspections and calibrations were performed by trained personnel.

Definition and grouping of MetS

Currently, there was no unified definition for MetS. The World Health Origination (WHO) diagnostic criteria proposed in 1999, the National Cholesterol Education Program Adult Panel Ⅲ (ATP Ⅲ) diagnostic criteria proposed in 2005, and International Diabetes Federation (IDF) diagnostic criteria proposed in 2006 were commonly used for metabolic syndrome [22]. These diagnostic criteria basically related to abdominal obesity, dyslipidemia, glucose metabolism disorder, and elevated blood pressure. However, these diagnostic criteria had different views and cut-off values for some specific indicators. This study adopted the 2018 China Guidelines for the Prevention and Treatment of Hypertension (CGPTH) definition for MetS, which was similar to the ATP Ⅲ diagnostic criteria [2]. Compared with ATP Ⅲ diagnostic criteria, the cut points of waist circumference defined by CGPTH were smaller and more suitable for the Chinese population. According to the 2018 CGPTH definition, MetS was diagnosed when three of the following four conditions were met: 1) Central obesity: waist circumference (WC) ≥ 90 cm in men and ≥ 85 cm in women; 2) Elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or diagnosed as hypertension and treated; 3) Dyslipidemia:

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fasting TG ≥ 150 mg/dL, or HDL ≤ 40 mg/dL, or diagnosed as dyslipidemia and treated; and 4) Elevated BG: Fasting BG (FBG) ≥ 100 mg/dL, or 2 h postprandial BG ≥ 100 mg/dL, or diagnosed as diabetes and treated [2]. Diabetes was defined as fasting BG ≥ 126 mg/dL, and/or HbA1c ≥ 6.5%, and/or a self-reported history of diabetes [23]. Of note, we did not have 2 h postprandial BG data.

According to MetS baseline status and follow-up, participants were categorized into 1) MetS-free, 2) MetS-developed, 3) MetS-recovery, and 4) MetS-chronic groups.

Study outcomes

We calculated eGFR values using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine levels [24]. A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2 [16 25]. In this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR in Wave 1, > 12 ml/min/1.73m^2.

MetS scores

MetS severity potentially affects the recovery or occurrence of MetS. For instance, individuals with high MetS severity may be less liable to recover. Similarly, for those without MetS, it is not straightforward to progress to severe MetS. Therefore, MetS scores were introduced to assess MetS severity in the study, which was thought to be more sufficient and accurate than other ways using the number of symptoms and complications to reflect MetS severity [26 27]. These scores were calculated using principal component (PC) analysis of WC, mean arterial pressure (MAP), FBG, fasting TG, and the inverse HDL values. All MetS related variables were normalized by 0–1. According to the PC analysis results, PC1 and PC2 explained 38.9% and 20.9% of the variance, respectively. MetS scores were calculated as follows:

$$\mathrm{PC1} = 0.369 \times \mathrm{WC} + 0.378 \times \mathrm{FBG} + 0.585 \times \mathrm{TG} + 0.562 \times \left(\frac{1}{\mathrm{HDL}}\right) + 0.252 \times \mathrm{MAP},$$

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$$PC2 = 0.503 \times WC - 0.171 \times FBG - 0.268 \times TG - 0.274 \times \left(\frac{1}{HDL}\right) + 0.755 \times MAP,$$

$$MetS\ score = 0.389 \times PC1 + 0.209 \times PC2$$

Other covariates

All potential covariates were all collected at baseline in Wave 1, including gender (male vs. female), age, marital status (married with spouse vs. others), education (illiterate, middle school and below, or high school and above), household per capita income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height, weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs. no), self-reporting disease (hypertension, diabetes, dyslipidemia and), and corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90. Grip strength was divided into three groups (T1, T2, and T3) according to the one-third percentile. BMI was calculated by weight (kg)/height squared (m^2). The BP of each participant was measured three times every 45–60 s with the OmronTM HEM-7112 sphygmomanometer (Omron Co. LTD， Dalian, China) at rest. Both SBP and DBP were averaged from three measurements. MAP was defined as MAP = 1/3 × SBP + 2/3 × DBP. Previous study demonstrated that depressive symptom was association with baseline eGFR [28]. Thus, we should not overlook this variable. The 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was applied in the study [29]. A CESD-10 score ≥ 10 was grouped into the depressive symptom group, and < 10 into the non-depressive symptom group. Self-reporting disease was disease diagnosed by a doctor. Medical interventions included taking Chinese traditional and Western modern medicines.

Statistical methods

The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Continuous variables were expressed by the median (interquartile range) and categorical variables by frequency (%). The Mann-Whitney U test was performed on continuous variables, and categorical variables between the rapid eGFR decline group and the non-rapid eGFR decline group were tested by the Chi-square test. In

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preliminary analyses, variables with P values < 0.15 were used to calibrate the logistic model. Continuous variables not presenting a linear relationship with the logit conversion value of the dependent variable were converted to categorical variables. Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This existed if the tolerance was < 0.1 or the VIF was > 10. Eventually, age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification and MetS scores were selected as confounding variables for model adjustments in this study. Most selected covariates have been reported to be related to renal events [26 30-33]. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group were carried out. Logistic models were used to test the association between MetS recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding factors. Furthermore, alterations in MetS status were accompanied by changes of diagnostic conditions (elevated blood glucose, elevated blood pressure, central obesity and dyslipidemia). As a result, logistic models were used to explore the relationship between the recovery/occurrence of Mets components and the rapid decline of eGFR using different adjustments of confounding factors, respectively. $P < 0.05$ was considered statistically significant (two-sided test). Statistics were generated in IBM SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software (StataCorp, Texas, USA).

Patient and public involvement

There were no participants involved in the development. The results of the survey are disseminated to the public through websites.

Results

Participant characteristics

As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS recovery-group, and 822 (19.8%) in the MetS-chronic group. Comparison of the basic

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characteristics between the 4142 enrolled participants and 2974 ones that excluded during follow-up were shown in Supplemental Table 1.

Participant characteristics were grouped by the eGFR decline rate (Table 1). A rapid decline in eGFR developed in 711 (17.2%) participants during the 4-year follow-up. The median age was 58 (52~64) years and males accounted for 42.5% at baseline. In contrast to rapid eGFR decline group, the non-rapid eGFR decline group was significantly higher with respect to FBG, Scr, hemoglobin, eGFR, weight, BMI, WC, MetS scores, central obesity, and elevated BG (all $P < 0.05$). Those in non-rapid eGFR decline group were more likely to be female and younger when compared with the eGFR decline group (both $P < 0.05$).

Rapid eGFR decline odds based on Mets recovery or occurrence

Univariate analysis was conducted to select covariates for correction (Supplemental Table 2). As shown (Table 2), after adjustment for age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification, and MetS scores, the odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% CI: 0.45–0.90, $P = 0.01$) when compared with the MetS-chronic group. In contrast, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, $P = 0.98$) when compared with the MetS-free group.

MetS components and rapid eGFR decline odds

The association of changes in the composition of MetS groups with rapid eGFR decline is shown (Table 3). In the baseline MetS population, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the population recovered from central obesity was 0.31 (OR: 0.31; 95% CI: 0.15–0.65, $P < 0.01$) when compared with chronic central obesity, whereas recovery from elevated BP,

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dyslipidemia, and elevated BG did not show statistically significant differences when compared with the corresponding population (all $P > 0.05$). In the baseline population without MetS, we observed no statistical difference in the rapid decline of eGFR between the occurrence of all MetS component groups and corresponding contrast groups (all $P > 0.05$). This was consistent with the overall trend.

Discussion

We examined the relationship between MetS changes and rapid eGFR decline in a large nationwide cohort. At the 4-year follow-up, MetS recovery was significantly associated with a reduced risk of rapid eGFR decline in the middle-aged and elderly, with only WC recovery consistent with the overall trend. The occurrence of MetS and its components did not significantly increase the risk of rapid eGFR decline. Further follow-up is required to elucidate the relationship between MetS dynamics and the rapid decline in eGFR.

Longitudinal cohort studies in several Asian countries concluded that MetS increased the risk of CKD, although follow-up times varied from study to study [15-18, 34]. However, the effect of MetS on the rapid decline of eGFR remains controversial. In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and eGFR rapid decline in the elderly [34]. However, other studies reported that baseline MetS was associated with a decline in eGFR and even acted as an independent predictor of eGFR decline [16-18]. *Wu et al.* investigated the association between the MetS severity score and kidney function, and found that the MetS severity score was an independent risk factor for the CKD development and progressive eGFR decline, although the definition of rapid eGFR decline was different from this study [26]. Here, the Mets severity score was a continuous variable that was primarily used to calibrate the MetS (yes vs. no). We noted that none of the aforementioned studies accounted for the MetS status of participants during follow-up periods. In a 4-year follow-up cohort, Park *et al.* explored the relationship between MetS status change and CKD events and concluded that MetS recovery was associated with a decreased risk of

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CKD incidence, but the occurrence of MetS increased the risk of CKD incidence [35]. One of the highlights of the article was to observe the status of MetS three times over a 4-year period, thereby making the MetS diagnosis more robust. However, Park *et al.* did not discuss the association with the rapid eGFR decline. In this study, we concluded that MetS recovery was associated with a reduced risk of rapid eGFR decline, while MetS occurrence was not related to rapid eGFR decline. It should be emphasized that we need to be cautious about the conclusion between the MetS occurrence and the rapid eGFR decline in this study. Because the follow-up time was short and the timing of MetS onset was unknown, the impairment of renal function caused by MetS may not have occurred in some populations. To sum up, studies exploring the relationship between MetS dynamic changes and the rapid decline of eGFR in the Chinese population are rare. Our investigation of the relationship between MetS recovery/occurrence and eGFR rapid decline in a large nationwide cohort may support renal function management in individuals with MetS.

The effect of MetS on renal function is complex, thus, no definitive mechanisms can explain our study observations. The evidence suggests that every component of MetS is associated with adverse renal events (10-14). It is accepted that hypertension and diabetes play pivotal roles in CKD development and progression [36-38]. Also, lipid metabolism dysregulation and abnormal lipid distribution can lead to lipotoxicity-related renal damage [39 40]. Thus, MetS may result from the combined effects of central obesity, increased BP, insulin resistance, and blood lipid disorder, leading to physiopathological lipotoxicity, oxidative stress increments, endothelial dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney dysfunction [5 39]. However, the relationship between MetS components and the weight of each factor on kidney injury remain unclear.

Our study had some limitations. Firstly, MetS diagnoses were not comprehensively checked (using multiple tests), and the exact timing of the MetS alteration is unknown. Secondly, renal stone disease, epiculopathy, epiculoepicardial

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disease or acute urinary tract infection are related to the occurrence and development of renal disease. Unfortunately, urine or kidney ultrasound results were unavailable in CHARLS cohort. Thirdly, CKD occurrence was not included as a study outcome because of the lack of urine test results, which would underestimate the CKD incidence. Fourthly, blood analyses from Wave 1 and Wave 3 were performed at a different testing center, with inconsistent HDL, TG, and BG measurement methods, therefore, measurement errors may have occurred. Fifthly, a large proportion of individuals were excluded due to exclusion criteria or missing values, and the basic characteristics between the 4142 enrolled participants and 2974 ones that excluded during follow-up might have biased some of our results. Sixthly, we did not establish a model with all 4 MetS change groups included in the study.

Conclusions

Over a 4-year follow-up, we observed that MetS recovery, including recovery of central obesity, was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Reversing MetS, especially central obesity, might benefit the kidney function in MetS population. But, further follow-up studies are required to observe the relationship between MetS alterations and adverse renal events.

Contributors PL and LT contributed equally to this paper. PL, LT and JF—analysis and interpretation of data and preparation of the manuscript. XL—study concept and design, and preparation and critical review of the manuscript. CC—critical review and statistical guidance of the revised manuscript. All authors have approved the final manuscript.

Competing interests All authors declared no competing interests.

Funding This work was supported by Guangzhou Municipal Science and Technology Bureau (202002020047) and Legal and Ethical Compliance Standards for Data Use in Clinical Research on Major Chronic Diseases Based on Data Security (2018YFC1315403).

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Data availability statement CHARLS data of the study will be available to investigators at the CHARLS website (http://charls.pku.edu.cn/en).

Ethics statement The Medical Ethics Review Committee of Peking University approved this study and all participants provided written informed consent before participating. This study is a secondary analysis of a public dataset and does not require ethics approval again.

Acknowledgements The authors are grateful to the China Health and Retirement Longitudinal Study (CHARLS) team for providing the data.

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Table 1. Baseline characteristics of participants between rapid eGFR decline group and non-rapid eGFR decline group

Characteristics	Overall (*n* = 4142)	Rapid eGFR decline (*n* = 711)	Non-rapid eGFR decline (*n* = 3431)	*P* value
Male [*n* (%)]	1874 (45.2)	351 (49.4)	1523 (44.4)	0.02
Age (years)	58 (52~64)	59 (52~66)	58 (52~64)	0.02
Married with spouse [*n* (%)]	3548 (87.5)	610 (85.8)	2938 (85.6)	0.91
Education				
Illiterate [*n* (%)]	1206 (29.1)	191 (26.9)	1015 (29.6)	
Middle school and below [*n* (%)]	1770 (41.2)	309 (43.5)	1398 (40.7)	0.28
High school and above [*n* (%)]	1229 (29.7)	211 (29.7)	1018 (29.7)	
Household per capita income (yuan)	6461.0	6000.0	6560.0	0.20
M (*P*25~*P*75)	(2336.7~13487.5)	(1866.7~13490.0)	(2450.0~13486.7)	
Drink [*n* (%)]	1470 (32.2)	234 (32.9)	1173 (34.2)	0.51
Smoke [*n* (%)]	1567 (37.8)	272 (38.3)	1295 (37.7)	0.80
Blood urea nitrogen (mg/dl)	15.0 (12.5~17.8)	15.1 (12.6~18.2)	15.0 (12.5~17.7)	0.18
Fasting glucose (mg/dl)	102.4 (94.9~111.2)	100.6 (93.4~109.8)	102.4 (95.2~111.4)	0.001
Creatinine (mg/dl)	0.75 (0.64~0.84)	0.71 (0.60~0.84)	0.76 (0.64~0.86)	<0.001
Total cholesterol (mg/dl)	190.6 (168.6~215.8)	189.8 (164.7~215.3)	190.6 (169.3~216.1)	0.20
Triglyceride (mg/dl)	105.3 (74.3~148.7)	101.8 (71.7~146)	106.2 (74.3~148.7)	0.23
HDL cholesterol (mg/dl)	49.1 (41.0~59.5)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	0.81
hs-CRP (mg/l)	1.0 (0.5~2.0)	1.0 (0.6~2)	1.0 (0.5~2.0)	0.43
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.36
Uric acid (mg/dl)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	0.83

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Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.0 (12.8~15.1)	14.3 (13.1~15.5)	<0.001
eGFR (ml/min/1.73m^2)	95.9 (86.4~102.9)	97.0 (88.3~106.1)	95.6 (85.9~102.4)	<0.001
eGFR group				
60~89 ml/min/1.73m^2 [*n* (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	0.02
90~ ml/min/1.73m^2 [*n* (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
Grip strength group				
T1 [*n* (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	0.01
T2 [*n* (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	
T3 [*n* (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	
Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
Body mass index (kg/m^2)	23.2 (21~25.7)	22.9 (20.8~25.4)	23.3 (21.1~25.8)	0.01
Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
Depression symptom [*n* (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
Self-report hypertension [*n* (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
Self-report dyslipidemia [*n* (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
Self-report diabetes or HBG [*n* (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
Self-report arthritis or rheumatism [*n* (%)]	1345 (32.5)	235 (33.1)	1110 (32.4)	0.71
Antihypertensive therapy [*n* (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
Lipid-lowering therapy [*n* (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
Hypoglycemic therapy [*n* (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
Therapy for arthritis or rheumatism [*n* (%)]	643 (15.5)	116 (16.3)	527 (15.4)	0.52
Metabolic syndrome [*n* (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
Metabolic syndrome components				
Central obesity [*n* (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
Elevated blood pressure [*n* (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
Dyslipidemia [*n* (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
Elevated blood glucose [*n* (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
Baseline non-MetS group				
MetS-free [*n* (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
MetS-developed [*n* (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
Baseline Mets group				
MetS-recovery [*n* (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
MetS-chronic [*n* (%)]	822 (19.8)	143 (20.1)	679 (19.8)	

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome.

grip strength is divided into T1, T2 and T3 groups by one-third percentile.

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Table 2. Multivariate logistic regression of rapid eGFR decline between study groups

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Baseline MetS groups				
MetS-chronic	ref		ref	
MetS-recovery	0.68 (0.50-0.95)	0.02	0.64 (0.45-0.90)	0.01
Baseline non-MetS groups				
MetS-free	ref		ref	
MetS-developed	0.93 (0.69-1.25)	0.64	1.00 (0.73-1.38)	0.98

Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification; hemoglobin; MetS scores and body mass index.

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome.

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Table 3. Multivariate logistic regression of rapid eGFR decline between study groups according the changes of MetS components

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Recovered components in baseline MetS groups (chronic MetS components as reference)				
Central obesity	0.29 (0.15-0.59)	0.01	0.31 (0.15-0.65)	<0.01
Elevated blood pressure	0.80 (0.50-1.26)	0.33	0.79 (0.49-1.27)	0.33
Elevated SBP	0.89 (0.61-1.31)	0.56	0.88 (0.59-1.30)	0.51
Elevated DBP	0.75 (0.46-1.23)	0.26	0.68 (0.41-1.15)	0.15
Dyslipidemia	1.09 (0.82-1.44)	0.57	1.05 (0.78-1.40)	0.77
Elevated TG	1.22 (0.87-1.72)	0.26	1.14 (0.79-1.36)	0.50
Decreased HDL	0.84 (0.59-1.12)	0.32	0.85 (0.59-1.22)	0.38
Elevated blood glucose	1.08 (0.87-1.34)	0.49	1.08 (0.86-1.36)	0.52
Elevated fasting glucose	1.14 (0.91-1.43)	0.25	1.13 (0.89-1.43)	0.32
Developed components in baseline non-MetS groups (free MetS components as reference)				
Central obesity	1.21 (0.92-1.59)	0.16	1.32 (0.97-1.77)	0.74
Elevated blood pressure	0.84 (0.63-1.13)	0.26	0.87 (0.64-1.18)	0.37
Elevated SBP	0.88 (0.66-1.17)	0.37	0.92 (0.68-1.23)	0.56
Elevated DBP	0.88 (0.62-1.24)	0.46	0.91 (0.63-1.30)	0.59
Dyslipidemia	0.92 (0.69-1.22)	0.54	0.96 (0.72-1.30)	0.81
Elevated TG	0.93 (0.70-1.25)	0.64	1.02 (0.75-1.37)	0.91
Decreased HDL	1.02 (0.65-1.59)	0.95	0.97 (0.61-1.55)	0.91
Elevated blood glucose	1.07 (0.76-1.50)	0.71	1.07 (0.75-1.52)	0.71
Elevated fasting glucose	1.06 (0.74-1.51)	0.76	1.09 (0.76-1.57)	0.64

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome;

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SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high density lipoprotein.
Model 1: additional adjusted for age and sex.
Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification, hemoglobin, MetS score and body mass index.
Each Mets components run in their own model to predict rapid eGFR decline

Figure 1. Flowchart of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

Supplementary file

Table S1. Baseline characteristics of participants included and excluded in the study

Table S2. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group

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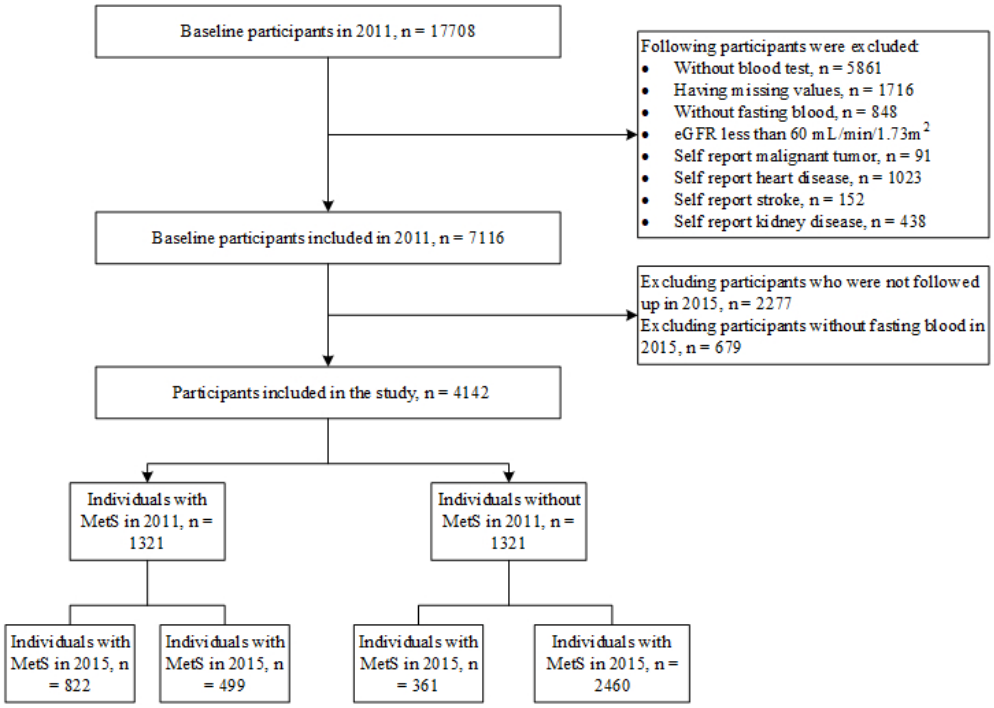

Flowchart of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

193x135mm (96 x 96 DPI)

Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Table S1. Baseline characteristics of participants included and excluded in the study

Characteristics	participants included in baseline (n=7116)	group 1 (n=2974)	group 2 (n=4142)	*P*-value
Age (years)	58 (52~65)	58 (52~64)	58 (51~66)	0.98
Male [*n* (%)]	3332 (46.8)	1458 (49.0)	1874 (45.2)	0.002
Married with spouse [*n* (%)]	5977 (84.0)	2974 (81.7)	3548 (87.5)	<0.001
Education				0.07
Illiterate [*n* (%)]	2106 (29.6)	900 (30.3)	1206 (29.1)	
Middle school and below [*n* (%)]	2853 (40.1)	1146 (38.5)	1770 (41.2)	
High school and above [*n* (%)]	2157 (30.3)	928 (31.2)	1229 (29.7)	
Household per capita income (yuan)	6748 (2417~14298)	6461 (2337~13487)	7276 (2500~15600)	0.02
Drink [*n* (%)]	2461 (34.6)	1054 (35.4)	1470 (32.2)	0.20
Smoke [*n* (%)]	2775 (39.0)	1208 (40.6)	1567 (37.8)	0.02
Blood urea nitrogen (mg/dl)	15.1 (12.52~17.90)	15.0 (12.5~17.8)	15.1 (12.8~18.0)	0.16
Fasting glucose (mg/dl)	102.4 (94.5~111.6)	102.4 (94.9~111.2)	102.1 (94.1~112.5)	0.72
Creatinine (mg/dl)	0.76 (0.64~0.86)	0.75 (0.64~0.85)	0.76 (0.66~0.88)	<0.001
Total cholesterol (mg/dl)	190.2 (168.2~215.3)	190.6 (168.6~215.7)	189.8 (167.4~214.9)	0.36
Triglyceride (mg/dl)	104.4 (74.34~147.8)	105.3 (74.34~148.7)	104.4 (73.46~147.8)	0.77
HDL cholesterol (mg/dl)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	49.9 (41.4~60.3)	0.02
hs-CRP (mg/l)	1.03 (0.54~2.04)	1.02 (0.54~1.97)	1.04 (0.55~2.17)	0.62
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.65
Uric acid (mg/dl)	4.3 (3.6~5.1)	4.2 (3.5~5.0)	4.4 (3.6~5.1)	<0.001
Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.2 (13.1~15.5)	14.2 (13.1~15.5)	0.75
Height (cm)	157.9 (152.0~164.1)	157.7 (152.0~163.8)	157.9 (152~164.5)	0.74
Weight (kg)	57.7 (51.0~65.4)	58.0 (51.3~65.5)	57.5 (50.3~65.2)	0.01
Waist (cm)	84.3 (77.6~91.4)	84.4 (78.0~92.0)	84.0 (77.0~91.0)	0.08
Body mass index (kg/m^2)	23.1 (20.8~25.6)	23.2 (21.0~25.7)	22.9 (20.6~25.5)	0.01
Hand grip strength (kg)	29.3 (23.5~36.5)	29.1 (23.0~36.5)	29.3 (23.8~36.5)	0.59
Systolic blood pressure (mmHg)	127.3 (114.7~141.3)	127.0 (114.3~141.0)	127.7 (115.3~142.0)	0.32
Diastolic blood pressure (mmHg)	74.7 (67.3~83.0)	74.7 (67.0~82.7)	75.0 (67.3~83.0)	0.34
Mean arterial pressure (mmHg)	92.6 (83.7~102.0)	92.2 (83.4~101.7)	92.6 (84.0~102.6)	0.28
eGFR (ml/min/1.73m^2)	95.2 (85.5~102.7)	95.9 (86.4~102.9)	94.0 (84.3~102.3)	<0.001
Depression symptom [*n* (%)]	3172 (44.6)	1268 (42.6)	1904 (46.0)	0.005
Metabolic syndrome [*n* (%)]	2228 (31.3)	907 (30.5)	1321 (31.9)	0.21
Metabolic syndrome components				
Elevated blood pressure [*n* (%)]	3622 (50.9)	1523 (51.2)	2099 (50.7)	0.66
Elevated blood glucose [*n* (%)]	4179 (58.7)	1723 (57.9)	2456 (59.3)	0.25
Dyslipidemia [*n* (%)]	2673 (37.6)	1078 (36.2)	1595 (38.5)	0.052
Central obesity [*n* (%)]	2862 (40.2)	1136 (38.2)	1726 (41.7)	0.003

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR:estimated glomerular filtration rate; MetS: metabolic syndrome. Group 1: participants included in the baseline and excluded after follow-up; Group 2: participants included in the study.

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Table S2. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group

Characteristics	Coef.	95% Conf.	*P*-value
Sex (female as ref)	0.200	0.038~0.362	0.02
Age (years)	0.011	0.002~0.021	0.02
Married status [*n* (%)]			
Other married status	ref	ref	
Married with spouse	0.013	-0.218~0.245	0.91
Education			
Illiterate	ref	ref	
Middle school and below	0.160	--0.037~0.359	0.11
High school and above	0.097	-0.118~0.311	0.34
Household per capita income (per 10000 yuan)	0.005	-0.053~0.062	0.88
Drink [*n* (%)]			
Smoke [*n* (%)]	0.022	-0.145~0.188	0.80
Blood urea nitrogen (mg/dl)	0.019	-0.001~0.038	0.06
Fasting glucose (mg/dl)	-0.002	-0.005~0.001	0.28
Creatinine (mg/dl))	-1.818	-2.368~-1.268	<0.001
Total cholesterol (mg/dl)	-0.001	-0.004~0.001	0.21
Triglyceride (mg/dl)	-0.0004	-	0.39
HDL cholesterol (mg/dl)	0.007	-0.005~0.006	0.80
hs-CRP (mg/l)	0.004	-0.013~0.020	0.66
GHbA1c (%)	-0.051	-0.167~0.066	0.40
Uric acid (mg/dl)	0.003	-0.066~0.072	0.93
Hemoglobin (mg/dl)	-0.102	-0.144~-0.060	<0.001
eGFR (ml/min/1.73m^2)	0.023	0.017~0.030	<0.001
eGFR group			
60~89 ml/min/1.73m^2 [*n* (%)]	ref	ref	
90~ ml/min/1.73m^2 [*n* (%)]	0.203	0.026~0.379	0.02
Grip strength (kg)	0.004	-0.005~0.012	0.38
Grip strength group			
T1 [*n* (%)]	ref	ref	
T2 [*n* (%)]	0.311	0.112~0.511	<0.01
T3 [*n* (%)]	0.148	-0.056~0.353	0.16
Height (cm)	0.003	-0.007~0.013	0.58
Weight (kg)	-0.008	-0.015~0.000	0.048
Body mass index (kg/m^2)	-0.032	-0.056~-0.009	0.01
Waist circumference (cm)	-0.012	-0.018~-0.005	<0.001
Systolic blood pressure (mmHg)	0.002	-0.002~0.006	0.33

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Diastolic blood pressure (mmHg)	-0.001	-0.008~0.005	0.76
Mean arterial pressure (mmHg)	0.001	-0.005~0.007	0.75
Depression symptom [*n* (%)]	-0.054	-0.216~0.109	0.52
Self-report hypertension [*n* (%)]	0.047	-0.148~0.243	0.63
Self-report dyslipidemia [*n* (%)]	0.019	-0.276~0.315	0.90
Self-report diabetes or HBG [*n* (%)]	-0.196	-0.065~0.213	0.35
Self-report arthritis or rheumatism [*n* (%)]	-0.032	-0.204~0.140	0.71
Antihypertensive therapy [*n* (%)]	0.062	-0.155~0.280	0.57
Lipid-lowering therapy [*n* (%)]	0.183	-0.186~0.552	0.33
Hypoglycemic therapy [*n* (%)]	-0.169	-0.663~0.326	0.50
Therapy for arthritis or rheumatism [*n* (%)]	0.072	-0.148~0.291	0.52
Metabolic syndrome [*n* (%)]	-0.158	-0.334~0.019	0.08
MetS scores	-0.138	-0.279~0.003	0.055
Metabolic syndrome components			
Central obesity [*n* (%)]	-0.229	-0.395~-0.062	0.01
Elevated blood pressure [*n* (%)]	0.052	-0.109~0.214	0.53
Dyslipidemia [*n* (%)]	0.030	-0.135~0.196	0.72
Elevated blood glucose [*n* (%)]	-0.268	-0.431~0.105	0.001

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR:

estimated glomerular filtration rate; MetS: metabolic syndrome.

grip strength is divided into T1, T2 and T3 groups by one-third percentile.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1-3	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4	Explain the scientific background and rationale for the investigation being reported
Objectives	4-5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	4-5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	5	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants.
Data sources/ measurement	5-6*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Variables	6-8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Bias	5	Describe any efforts to address potential sources of bias
Study size	5	Explain how the study size was arrived at
Quantitative variables	8-9	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	8-9	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	9*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	10*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	10*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	10	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

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		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	10-11	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	11	Summarise key results with reference to study objectives
Limitations	12-13	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	11-13	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	13	Discuss the generalisability (external validity) of the study results
Other information		
Funding	13	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059504.R3
Article Type:	Original research
Date Submitted by the Author:	07-Sep-2022
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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Urology, Diabetes and endocrinology, Public health
Keywords:	Chronic renal failure < NEPHROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

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Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Abstract

Objectives Few studies have explored correlations between metabolic syndrome (MetS) alterations and renal deterioration in longitudinal cohorts. We aim to investigate associations between MetS recovery/development and rapid estimated glomerular filtration rate (eGFR) decline in the China Health and Retirement Longitudinal Study (CHARLS).

Design Longitudinal cohort study.

Setting This study is a secondary analysis of CHARLS.

Participants After excluding individuals with age < 45 years old, eGFR < 60 ml/min/1.73m^2 and clinician-reported malignant tumor, heart disease, stroke or kidney disease at baseline, 4142 participants with complete data were selected from the CHARLS during the 4-year follow-up period (2011-2015).

Outcome measures MetS were measured at 2011 and 2015 in CHARLS. A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2. The associations between rapid eGFR decline and MetS recovery/development were analyzed using multivariable adjusted logistic models.

Results According to MetS baseline status and follow-up, participants were divided into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group, the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, P = 0.01). In contrast, when compared with the MetS-free group, the multivariable adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, P = 0.98).

Conclusions Over the 4-year follow-up period, we found that MetS recovery was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS

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appeared to protect against a rapid decline in eGFR.

Keywords: chronic renal failure; lipid disorders; public health;

Strength

A high-quality data from a nationally representative longitudinal cohort was applied to confirm the association between altered metabolic syndrome status and rapid glomerular filtration rate decline.

The metabolic syndrome scores calculated by principal component analysis was applied for model calibration in the study.

Limitation

Some participants were missing during the follow-up, which biased the results of the study.

Blood tests related to metabolic syndrome and serum creatinine were performed only once, resulting in data inaccuracy.

The unavailability of urine tests and kidney imaging prevented the analysis of the association between metabolic syndrome status and chronic kidney disease.

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Introduction

Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood pressure (BP) [1-3]. As of 2017, there were approximately 1 billion individuals with MetS around the world, of which China accounted for 21.7% [4]. In China, MetS prevalence has been undergoing a steady increase, concomitant with an increasingly aged population, an obesity epidemic, and increased diabetes and hypertension levels, which collectively pose a considerable threat to people's health and impose a heavy burden on healthcare systems [4-6].

While investigations of causality relationships between MetS and cardiovascular events have gained considerable traction in recent years [7-9], MetS also impacts the kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly include insulin resistance, increased oxidative stress, and a chronic inflammatory state, which may lead to kidney degeneration and chronic kidney disease (CKD) development [5 6]. Previously, it was confirmed that MetS and associated components (abdominal obesity, elevated BG, elevated BP, and lipid metabolic disorder) are strongly related to CKD and a decreased estimated glomerular filtration rate (eGFR) [10-14]. Several longitudinal studies reported that MetS and its components were associated with incremental rapid eGFR decline and CKD incidence [15-18]. However, these studies failed to articulate the relationship between MetS alterations and renal function changes. This dearth of information on this subject warrants further study, especially within a Chinese population context.

The China Health and Retirement Longitudinal Study (CHARLS) is a prospective cohort study conducted by the National School of Development, Peking University, China [19]. The nationwide sample assesses the social, behavioral, and health status of individuals aged 45 and older [19]. The CHARLS baseline survey was implemented in 2011 (Wave 1), and the samples were followed up every two years. Blood samples from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the current study, we explored the relationship between MetS recovery/occurrence and

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rapid eGFR decline in middle-aged and older populations in the 4-year follow-up cohort.

Methods

Study population

CHARLS is a nationally representative longitudinal survey on the social, economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the community [19]. In total, 17,708 participants were registered at baseline (Wave 1 at 2011), of which 11,847 had blood sample tests.

In this study, our exclusion criteria excluded participants with the following: 1) missing values; 2) without fasting blood values; 3) baseline eGFR < 60 ml/min/1.73m^2; 4) clinician-reported malignant tumor, heart disease, stroke or kidney disease; 5) < 45 years old; and 6) no follow-up records and related blood examinations in Wave 3 at 2015. After applying these criteria, 4142 participants were finally included. The participant screening process is outlined (Fig. 1).

The Medical Ethics Review Committee of Peking University approved this study. All participants provided written informed consent before participating. This study is a secondary analysis of a public dataset and does not require ethics approval again.

Blood examinations

At baseline (Wave 1), blood measurements and hemoglobin were assayed by the Center for Disease Control and Prevention of the local county, whereas other biochemical indicators were analyzed by Youanmen Center for Clinical Laboratory of Capital Medical University, Beijing, China. Serum creatinine (Scr) was measured by the picric acid method; blood urea nitrogen (BUN) was determined by an enzymatic UV method with urease; blood glucose (BG), total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride (TG) were assayed by enzymatic colormetric tests; glycosylated hemoglobin (GHbA1c) was determined by high performance liquid chromatography; high-sensitivity C-reactive protein (hs-CRP) was examined by immunoturbidimetric assay; and uric acid (UA) was determined by the

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UA plus method [20]. Blood specimen testing in 2015 (Wave 3) was completed by KingMed Diagnostics, the leading third-party institution in China, which has testing laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were determined by the same methods as Wave 1, while HDL was determined by a direct method, TG by an oxidase method, and BG by a hexokinase method [21]. The collection, storage, transport, processing, and other blood sample details are described elsewhere [20 21]. Of note, the models and manufacturer information of blood test instruments in Wave 1 and Wave 3 were not available. All inspections and calibrations were performed by trained personnel.

Definition and grouping of MetS

Currently, there was no unified definition for MetS. The World Health Origination (WHO) diagnostic criteria proposed in 1999, the National Cholesterol Education Program Adult Panel Ⅲ (ATP Ⅲ) diagnostic criteria proposed in 2005, and International Diabetes Federation (IDF) diagnostic criteria proposed in 2006 were commonly used for metabolic syndrome [22]. These diagnostic criteria basically related to abdominal obesity, dyslipidemia, glucose metabolism disorder, and elevated blood pressure. However, these diagnostic criteria had different views and cut-off values for some specific indicators. This study adopted the 2018 China Guidelines for the Prevention and Treatment of Hypertension (CGPTH) definition for MetS, which was similar to the ATP Ⅲ diagnostic criteria [2]. Compared with ATP Ⅲ diagnostic criteria, the cut points of waist circumference defined by CGPTH were smaller and more suitable for the Chinese population. According to the 2018 CGPTH definition, MetS was diagnosed when three of the following four conditions were met: 1) Central obesity: waist circumference (WC) ≥ 90 cm in men and ≥ 85 cm in women; 2) Elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg, or diagnosed as hypertension and treated; 3) Dyslipidemia: fasting TG ≥ 150 mg/dL, or HDL ≤ 40 mg/dL, or diagnosed as dyslipidemia and

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treated; and 4) Elevated BG: Fasting BG (FBG) ≥ 100 mg/dL, or 2 h postprandial BG ≥ 100 mg/dL, or diagnosed as diabetes and treated [2]. Diabetes was defined as fasting BG ≥ 126 mg/dL, and/or HbA1c ≥ 6.5%, and/or a self-reported history of diabetes [23]. Of note, we did not have 2 h postprandial BG data.

According to MetS baseline status and follow-up, participants were categorized into 1) MetS-free, 2) MetS-developed, 3) MetS-recovery, and 4) MetS-chronic groups.

Study outcomes

We calculated eGFR values using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine levels [24]. A rapid eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m^2 [16 25]. In this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR in Wave 1, > 12 ml/min/1.73m^2.

MetS scores

MetS severity potentially affects the recovery or occurrence of MetS. For instance, individuals with high MetS severity may be less liable to recover. Similarly, for those without MetS, it is not straightforward to progress to severe MetS. Therefore, MetS scores were introduced to assess MetS severity in the study, which was thought to be more sufficient and accurate than other ways using the number of symptoms and complications to reflect MetS severity [26 27]. These scores were calculated using principal component (PC) analysis of WC, mean arterial pressure (MAP), FBG, fasting TG, and the inverse HDL values. All MetS related variables were normalized by 0–1. According to the PC analysis results, PC1 and PC2 explained 38.9% and 20.9% of the variance, respectively. MetS scores were calculated as follows:

$$\mathrm{PC1} = 0.369 \times \mathrm{WC} + 0.378 \times \mathrm{FBG} + 0.585 \times \mathrm{TG} + 0.562 \times \left(\frac{1}{\mathrm{HDL}}\right) + 0.252 \times \mathrm{MAP},$$

$$\mathrm{PC2} = 0.503 \times \mathrm{WC} - 0.171 \times \mathrm{FBG} - 0.268 \times \mathrm{TG} - 0.274 \times \left(\frac{1}{\mathrm{HDL}}\right) + 0.755 \times \mathrm{MAP},$$

$$\mathrm{MetS\ score} = 0.389 \times \mathrm{PC1} + 0.209 \times \mathrm{PC2}$$

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Other covariates

All potential covariates were all collected at baseline in Wave 1, including gender (male vs. female), age, marital status (married with spouse vs. others), education (illiterate, middle school and below, or high school and above), household per capita income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height, weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs. no), self-reporting disease (hypertension, diabetes, dyslipidemia and), and corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90. Grip strength was divided into three groups (T1, T2, and T3) according to the one-third percentile. BMI was calculated by weight (kg)/height squared (m^2). The BP of each participant was measured three times every 45–60 s with the OmronTM HEM-7112 sphygmomanometer (Omron Co. LTD， Dalian, China) at rest. Both SBP and DBP were averaged from three measurements. MAP was defined as MAP = 1/3 × SBP + 2/3 × DBP. Previous study demonstrated that depressive symptom was association with baseline eGFR [28]. Thus, we should not overlook this variable. The 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was applied in the study [29]. A CESD-10 score ≥ 10 was grouped into the depressive symptom group, and < 10 into the non-depressive symptom group. Self-reporting disease was disease diagnosed by a doctor. Medical interventions included taking Chinese traditional and Western modern medicines.

Statistical methods

The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Continuous variables were expressed by the median (interquartile range) and categorical variables by frequency (%). The Mann-Whitney U test was performed on continuous variables, and categorical variables between the rapid eGFR decline group and the non-rapid eGFR decline group were tested by the Chi-square test. In preliminary analyses, variables with P values < 0.15 were used to calibrate the logistic model. Continuous variables not presenting a linear relationship with the logit

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conversion value of the dependent variable were converted to categorical variables. Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This existed if the tolerance was < 0.1 or the VIF was > 10. Eventually, age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification and MetS scores were selected as confounding variables for model adjustments in this study. Most selected covariates have been reported to be related to renal events [26 30-33]. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group were carried out. Logistic models were used to test the association between MetS recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding factors. Furthermore, alterations in MetS status were accompanied by changes of diagnostic conditions (elevated blood glucose, elevated blood pressure, central obesity and dyslipidemia). As a result, logistic models were used to explore the relationship between the recovery/occurrence of Mets components and the rapid decline of eGFR using different adjustments of confounding factors, respectively. $P < 0.05$ was considered statistically significant (two-sided test). Statistics were generated in IBM SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software (StataCorp, Texas, USA).

Patient and public involvement

There were no participants involved in the development. The results of the survey are disseminated to the public through websites.

Results

Participant characteristics

As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS recovery-group, and 822 (19.8%) in the MetS-chronic group. Comparison of the basic characteristics between the 4142 enrolled participants and 2974 ones that excluded during follow-up were shown in Supplemental Table 1.

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Participant characteristics were grouped by the eGFR decline rate (Table 1). A rapid decline in eGFR developed in 711 (17.2%) participants during the 4-year follow-up. The median age was 58 (52~64) years and males accounted for 42.5% at baseline. In contrast to rapid eGFR decline group, the non-rapid eGFR decline group was significantly higher with respect to FBG, Scr, hemoglobin, eGFR, weight, BMI, WC, MetS scores, central obesity, and elevated BG (all $P < 0.05$). Those in non-rapid eGFR decline group were more likely to be female and younger when compared with the eGFR decline group (both $P < 0.05$).

Rapid eGFR decline odds based on Mets recovery or occurrence

Univariate analysis was conducted to select covariates for correction (Supplemental Table 2). As shown (Table 2), after adjustment for age, sex, BMI, Scr, hemoglobin, eGFR classification, grip strength classification, and MetS scores, the odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR: 0.64; 95% CI: 0.45–0.90, $P = 0.01$) when compared with the MetS-chronic group. In contrast, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, $P = 0.98$) when compared with the MetS-free group.

MetS components and rapid eGFR decline odds

The association of changes in the composition of MetS groups with rapid eGFR decline is shown (Table 3). In the baseline MetS population, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength classification, and MetS score, the OR of rapid eGFR decline in the population recovered from central obesity was 0.31 (OR: 0.31; 95% CI: 0.15–0.65, $P < 0.01$) when compared with chronic central obesity, whereas recovery from elevated BP, dyslipidemia, and elevated BG did not show statistically significant differences when compared with the corresponding population (all $P > 0.05$). In the baseline population without MetS, we observed no statistical difference in the rapid decline of eGFR

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between the occurrence of all MetS component groups and corresponding contrast groups (all $P > 0.05$). This was consistent with the overall trend.

Discussion

We examined the relationship between MetS changes and rapid eGFR decline in a large nationwide cohort. At the 4-year follow-up, MetS recovery was significantly associated with a reduced risk of rapid eGFR decline in the middle-aged and elderly, with only WC recovery consistent with the overall trend. The occurrence of MetS and its components did not significantly increase the risk of rapid eGFR decline. Further follow-up is required to elucidate the relationship between MetS dynamics and the rapid decline in eGFR.

Longitudinal cohort studies in several Asian countries concluded that MetS increased the risk of CKD, although follow-up times varied from study to study [15-18] [34]. However, the effect of MetS on the rapid decline of eGFR remains controversial. In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and eGFR rapid decline in the elderly [34]. However, other studies reported that baseline MetS was associated with a decline in eGFR and even acted as an independent predictor of eGFR decline [16-18]. *Wu et al.* investigated the association between the MetS severity score and kidney function, and found that the MetS severity score was an independent risk factor for the CKD development and progressive eGFR decline, although the definition of rapid eGFR decline was different from this study [26]. Here, the Mets severity score was a continuous variable that was primarily used to calibrate the MetS (yes vs. no). We noted that none of the aforementioned studies accounted for the MetS status of participants during follow-up periods. In a 4-year follow-up cohort, Park *et al.* explored the relationship between MetS status change and CKD events and concluded that MetS recovery was associated with a decreased risk of CKD incidence, but the occurrence of MetS increased the risk of CKD incidence [35]. One of the highlights of the article was to observe the status of MetS three times over a 4-year period, thereby making the MetS diagnosis more robust. However, Park *et al.*

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did not discuss the association with the rapid eGFR decline. In this study, we concluded that MetS recovery was associated with a reduced risk of rapid eGFR decline, while MetS occurrence was not related to rapid eGFR decline. It should be emphasized that we need to be cautious about the conclusion between the MetS occurrence and the rapid eGFR decline in this study. Because the follow-up time was short and the timing of MetS onset was unknown, the impairment of renal function caused by MetS may not have occurred in some populations. To sum up, studies exploring the relationship between MetS dynamic changes and the rapid decline of eGFR in the Chinese population are rare. Our investigation of the relationship between MetS recovery/occurrence and eGFR rapid decline in a large nationwide cohort may support renal function management in individuals with MetS.

The effect of MetS on renal function is complex, thus, no definitive mechanisms can explain our study observations. The evidence suggests that every component of MetS is associated with adverse renal events (10-14). It is accepted that hypertension and diabetes play pivotal roles in CKD development and progression [36-38]. Also, lipid metabolism dysregulation and abnormal lipid distribution can lead to lipotoxicity-related renal damage [39 40]. Thus, MetS may result from the combined effects of central obesity, increased BP, insulin resistance, and blood lipid disorder, leading to physiopathological lipotoxicity, oxidative stress increments, endothelial dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney dysfunction [5 39]. However, the relationship between MetS components and the weight of each factor on kidney injury remain unclear.

Our study had some limitations. Firstly, MetS diagnoses were not comprehensively checked (using multiple tests), and the exact timing of the MetS alteration is unknown. Secondly, renal stone disease, epiculopathy, epiculoepicardial disease or acute urinary tract infection are related to the occurrence and development of renal disease. Unfortunately, urine or kidney ultrasound results were unavailable in CHARLS cohort. Thirdly, CKD occurrence was not included as a study outcome

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because of the lack of urine test results, which would underestimate the CKD incidence. Fourthly, blood analyses from Wave 1 and Wave 3 were performed at a different testing center, with inconsistent HDL, TG, and BG measurement methods, therefore, measurement errors may have occurred. Fifthly, a large proportion of individuals were excluded due to exclusion criteria or missing values, and the basic characteristics between the 4142 enrolled participants and 2974 ones that excluded during follow-up might have biased some of our results. Sixthly, we did not establish a model with all 4 MetS change groups included in the study.

Conclusions

Over a 4-year follow-up, we observed that MetS recovery, including recovery of central obesity, was associated with a reduced risk of rapid eGFR decline in middle-aged and older adults, while MetS occurrence was not related to rapid eGFR decline. Reversing MetS, especially central obesity, might benefit the kidney function in MetS population. But, further follow-up studies are required to observe the relationship between MetS alterations and adverse renal events.

Contributors PL and LT contributed equally to this paper. PL, LT and JF—analysis and interpretation of data and preparation of the manuscript. XL—study concept and design, and preparation and critical review of the manuscript. CC—critical review and statistical guidance of the revised manuscript. All authors have approved the final manuscript.

Competing interests All authors declared no competing interests.

Funding This work was supported by Guangzhou Municipal Science and Technology Bureau (202002020047) and Legal and Ethical Compliance Standards for Data Use in Clinical Research on Major Chronic Diseases Based on Data Security (2018YFC1315403).

Data availability statement CHARLS data of the study will be available to investigators at the CHARLS website (http://charls.pku.edu.cn/en).

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Ethics statement The Medical Ethics Review Committee of Peking University approved this study and all participants provided written informed consent before participating. This study is a secondary analysis of a public dataset and does not require ethics approval again.

Acknowledgements The authors are grateful to the China Health and Retirement Longitudinal Study (CHARLS) team for providing the data.

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Table 1. Baseline characteristics of participants between rapid eGFR decline group and non-rapid eGFR decline group

Characteristics	Overall (*n* = 4142)	Rapid eGFR decline (*n* = 711)	Non-rapid eGFR decline (*n* = 3431)	*P* value
Male [*n* (%)]	1874 (45.2)	351 (49.4)	1523 (44.4)	0.02
Age (years)	58 (52~64)	59 (52~66)	58 (52~64)	0.02
Married with spouse [*n* (%)]	3548 (87.5)	610 (85.8)	2938 (85.6)	0.91
Education				
Illiterate [*n* (%)]	1206 (29.1)	191 (26.9)	1015 (29.6)	
Middle school and below [*n* (%)]	1770 (41.2)	309 (43.5)	1398 (40.7)	0.28
High school and above [*n* (%)]	1229 (29.7)	211 (29.7)	1018 (29.7)	
Household per capita income (yuan)	6461.0	6000.0	6560.0	0.20
M (*P*25~*P*75)	(2336.7~13487.5)	(1866.7~13490.0)	(2450.0~13486.7)	
Drink [*n* (%)]	1470 (32.2)	234 (32.9)	1173 (34.2)	0.51
Smoke [*n* (%)]	1567 (37.8)	272 (38.3)	1295 (37.7)	0.80
Blood urea nitrogen (mg/dl)	15.0 (12.5~17.8)	15.1 (12.6~18.2)	15.0 (12.5~17.7)	0.18
Fasting glucose (mg/dl)	102.4 (94.9~111.2)	100.6 (93.4~109.8)	102.4 (95.2~111.4)	0.001
Creatinine (mg/dl)	0.75 (0.64~0.84)	0.71 (0.60~0.84)	0.76 (0.64~0.86)	<0.001
Total cholesterol (mg/dl)	190.6 (168.6~215.8)	189.8 (164.7~215.3)	190.6 (169.3~216.1)	0.20
Triglyceride (mg/dl)	105.3 (74.3~148.7)	101.8 (71.7~146)	106.2 (74.3~148.7)	0.23
HDL cholesterol (mg/dl)	49.1 (41.0~59.5)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	0.81
hs-CRP (mg/l)	1.0 (0.5~2.0)	1.0 (0.6~2)	1.0 (0.5~2.0)	0.43
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.36
Uric acid (mg/dl)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	0.83
Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.0 (12.8~15.1)	14.3 (13.1~15.5)	<0.001
eGFR (ml/min/1.73m^2)	95.9 (86.4~102.9)	97.0 (88.3~106.1)	95.6 (85.9~102.4)	<0.001
eGFR group				0.02

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60~89 ml/min/1.73m^2 [*n* (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	
90~ ml/min/1.73m^2 [*n* (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
Grip strength group				
T1 [*n* (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	0.01
T2 [*n* (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	
T3 [*n* (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	
Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
Body mass index (kg/m^2)	23.2 (21~25.7)	22.9 (20.8~25.4)	23.3 (21.1~25.8)	0.01
Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
Depression symptom [*n* (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
Self-report hypertension [*n* (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
Self-report dyslipidemia [*n* (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
Self-report diabetes or HBG [*n* (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
Self-report arthritis or rheumatism [*n* (%)]	1345 (32.5)	235 (33.1)	1110 (32.4)	0.71
Antihypertensive therapy [*n* (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
Lipid-lowering therapy [*n* (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
Hypoglycemic therapy [*n* (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
Therapy for arthritis or rheumatism [*n* (%)]	643 (15.5)	116 (16.3)	527 (15.4)	0.52
Metabolic syndrome [*n* (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
Metabolic syndrome components				
Central obesity [*n* (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
Elevated blood pressure [*n* (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
Dyslipidemia [*n* (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
Elevated blood glucose [*n* (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
Baseline non-MetS group				
MetS-free [*n* (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
MetS-developed [*n* (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
Baseline Mets group				
MetS-recovery [*n* (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
MetS-chronic [*n* (%)]	822 (19.8)	143 (20.1)	679 (19.8)	

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome.

grip strength is divided into T1, T2 and T3 groups by one-third percentile.

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Table 2. Multivariate logistic regression of rapid eGFR decline between study groups

	Model 1	Model 2

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	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Baseline MetS groups				
MetS-chronic	ref		ref	
MetS-recovery	0.68 (0.50-0.95)	0.02	0.64 (0.45-0.90)	0.01
Baseline non-MetS groups				
MetS-free	ref		ref	
MetS-developed	0.93 (0.69-1.25)	0.64	1.00 (0.73-1.38)	0.98

Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification; hemoglobin; MetS scores and body mass index.

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome.

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Table 3. Multivariate logistic regression of rapid eGFR decline between study groups according the changes of MetS components

	Model 1		Model 2	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Recovered components in baseline MetS groups (chronic MetS components as reference)				
Central obesity	0.29 (0.15-0.59)	0.01	0.31 (0.15-0.65)	<0.01
Elevated blood pressure	0.80 (0.50-1.26)	0.33	0.79 (0.49-1.27)	0.33
Elevated SBP	0.89 (0.61-1.31)	0.56	0.88 (0.59-1.30)	0.51
Elevated DBP	0.75 (0.46-1.23)	0.26	0.68 (0.41-1.15)	0.15
Dyslipidemia	1.09 (0.82-1.44)	0.57	1.05 (0.78-1.40)	0.77
Elevated TG	1.22 (0.87-1.72)	0.26	1.14 (0.79-1.36)	0.50
Decreased HDL	0.84 (0.59-1.12)	0.32	0.85 (0.59-1.22)	0.38
Elevated blood glucose	1.08 (0.87-1.34)	0.49	1.08 (0.86-1.36)	0.52
Elevated fasting glucose	1.14 (0.91-1.43)	0.25	1.13 (0.89-1.43)	0.32
Developed components in baseline non-MetS groups (free MetS components as reference)				
Central obesity	1.21 (0.92-1.59)	0.16	1.32 (0.97-1.77)	0.74
Elevated blood pressure	0.84 (0.63-1.13)	0.26	0.87 (0.64-1.18)	0.37
Elevated SBP	0.88 (0.66-1.17)	0.37	0.92 (0.68-1.23)	0.56
Elevated DBP	0.88 (0.62-1.24)	0.46	0.91 (0.63-1.30)	0.59
Dyslipidemia	0.92 (0.69-1.22)	0.54	0.96 (0.72-1.30)	0.81
Elevated TG	0.93 (0.70-1.25)	0.64	1.02 (0.75-1.37)	0.91
Decreased HDL	1.02 (0.65-1.59)	0.95	0.97 (0.61-1.55)	0.91
Elevated blood glucose	1.07 (0.76-1.50)	0.71	1.07 (0.75-1.52)	0.71
Elevated fasting glucose	1.06 (0.74-1.51)	0.76	1.09 (0.76-1.57)	0.64

eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high density lipoprotein.

Model 1: additional adjusted for age and sex.

Model 2: additional adjusted for age, sex, serum creatinine, eGFR classification, grip strength classification,

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hemoglobin, MetS score and body mass index.

Each Mets components run in their own model to predict rapid eGFR decline

Figure 1. Flowchart of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

Supplementary file

Table S1. Baseline characteristics of participants included and excluded in the study

Table S2. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group

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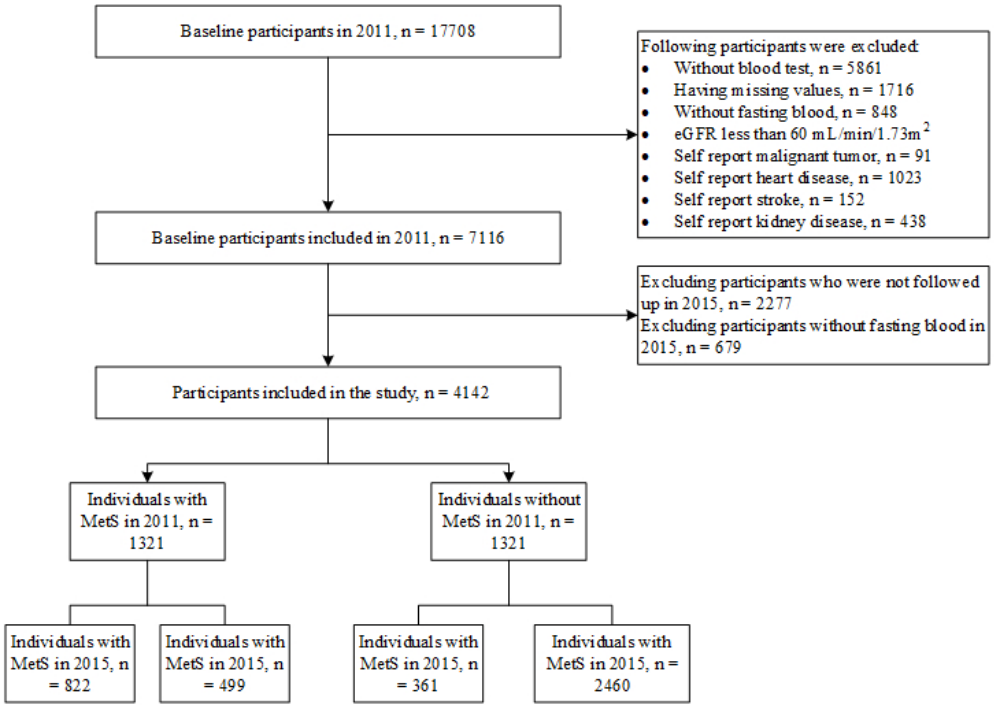

Flowchart of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

193x135mm (96 x 96 DPI)

Association between recovery/occurrence of metabolic syndrome and rapid estimated glomerular filtration rate decline in middle-aged and older populations: evidence from the China Health and Retirement Longitudinal Study

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Table S1. Baseline characteristics of participants included and excluded in the study

Characteristics	participants included in baseline (n=7116)	group 1 (n=2974)	group 2 (n=4142)	*P*-value
Age (years)	58 (52~65)	58 (52~64)	58 (51~66)	0.98
Male [*n* (%)]	3332 (46.8)	1458 (49.0)	1874 (45.2)	0.002
Married with spouse [*n* (%)]	5977 (84.0)	2974 (81.7)	3548 (87.5)	<0.001
Education				0.07
Illiterate [*n* (%)]	2106 (29.6)	900 (30.3)	1206 (29.1)	
Middle school and below [*n* (%)]	2853 (40.1)	1146 (38.5)	1770 (41.2)	
High school and above [*n* (%)]	2157 (30.3)	928 (31.2)	1229 (29.7)	
Household per capita income (yuan)	6748 (2417~14298)	6461 (2337~13487)	7276 (2500~15600)	0.02
Drink [*n* (%)]	2461 (34.6)	1054 (35.4)	1470 (32.2)	0.20
Smoke [*n* (%)]	2775 (39.0)	1208 (40.6)	1567 (37.8)	0.02
Blood urea nitrogen (mg/dl)	15.1 (12.52~17.90)	15.0 (12.5~17.8)	15.1 (12.8~18.0)	0.16
Fasting glucose (mg/dl)	102.4 (94.5~111.6)	102.4 (94.9~111.2)	102.1 (94.1~112.5)	0.72
Creatinine (mg/dl)	0.76 (0.64~0.86)	0.75 (0.64~0.85)	0.76 (0.66~0.88)	<0.001
Total cholesterol (mg/dl)	190.2 (168.2~215.3)	190.6 (168.6~215.7)	189.8 (167.4~214.9)	0.36
Triglyceride (mg/dl)	104.4 (74.34~147.8)	105.3 (74.34~148.7)	104.4 (73.46~147.8)	0.77
HDL cholesterol (mg/dl)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	49.9 (41.4~60.3)	0.02
hs-CRP (mg/l)	1.03 (0.54~2.04)	1.02 (0.54~1.97)	1.04 (0.55~2.17)	0.62
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.65
Uric acid (mg/dl)	4.3 (3.6~5.1)	4.2 (3.5~5.0)	4.4 (3.6~5.1)	<0.001
Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.2 (13.1~15.5)	14.2 (13.1~15.5)	0.75
Height (cm)	157.9 (152.0~164.1)	157.7 (152.0~163.8)	157.9 (152~164.5)	0.74
Weight (kg)	57.7 (51.0~65.4)	58.0 (51.3~65.5)	57.5 (50.3~65.2)	0.01
Waist (cm)	84.3 (77.6~91.4)	84.4 (78.0~92.0)	84.0 (77.0~91.0)	0.08
Body mass index (kg/m^2)	23.1 (20.8~25.6)	23.2 (21.0~25.7)	22.9 (20.6~25.5)	0.01
Hand grip strength (kg)	29.3 (23.5~36.5)	29.1 (23.0~36.5)	29.3 (23.8~36.5)	0.59
Systolic blood pressure (mmHg)	127.3 (114.7~141.3)	127.0 (114.3~141.0)	127.7 (115.3~142.0)	0.32
Diastolic blood pressure (mmHg)	74.7 (67.3~83.0)	74.7 (67.0~82.7)	75.0 (67.3~83.0)	0.34
Mean arterial pressure (mmHg)	92.6 (83.7~102.0)	92.2 (83.4~101.7)	92.6 (84.0~102.6)	0.28
eGFR (ml/min/1.73m^2)	95.2 (85.5~102.7)	95.9 (86.4~102.9)	94.0 (84.3~102.3)	<0.001
Depression symptom [*n* (%)]	3172 (44.6)	1268 (42.6)	1904 (46.0)	0.005
Metabolic syndrome [*n* (%)]	2228 (31.3)	907 (30.5)	1321 (31.9)	0.21
Metabolic syndrome components				
Elevated blood pressure [*n* (%)]	3622 (50.9)	1523 (51.2)	2099 (50.7)	0.66
Elevated blood glucose [*n* (%)]	4179 (58.7)	1723 (57.9)	2456 (59.3)	0.25
Dyslipidemia [*n* (%)]	2673 (37.6)	1078 (36.2)	1595 (38.5)	0.052
Central obesity [*n* (%)]	2862 (40.2)	1136 (38.2)	1726 (41.7)	0.003

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR:estimated glomerular filtration rate; MetS: metabolic syndrome. Group 1: participants included in the baseline and excluded after follow-up; Group 2: participants included in the study.

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Table S2. Univariate analysis of variables between eGFR decline group and non-rapid eGFR decline group

Characteristics	Coef.	95% Conf.	*P*-value
Sex (female as ref)	0.200	0.038~0.362	0.02
Age (years)	0.011	0.002~0.021	0.02
Married status [*n* (%)]			
Other married status	ref	ref	
Married with spouse	0.013	-0.218~0.245	0.91
Education			
Illiterate	ref	ref	
Middle school and below	0.160	--0.037~0.359	0.11
High school and above	0.097	-0.118~0.311	0.34
Household per capita income (per 10000 yuan)	0.005	-0.053~0.062	0.88
Drink [*n* (%)]			
Smoke [*n* (%)]	0.022	-0.145~0.188	0.80
Blood urea nitrogen (mg/dl)	0.019	-0.001~0.038	0.06
Fasting glucose (mg/dl)	-0.002	-0.005~0.001	0.28
Creatinine (mg/dl))	-1.818	-2.368~-1.268	<0.001
Total cholesterol (mg/dl)	-0.001	-0.004~0.001	0.21
Triglyceride (mg/dl)	-0.0004	-0.0014~0.0050	0.39
HDL cholesterol (mg/dl)	0.007	-0.005~0.006	0.80
hs-CRP (mg/l)	0.004	-0.013~0.020	0.66
GHbA1c (%)	-0.051	-0.167~0.066	0.40
Uric acid (mg/dl)	0.003	-0.066~0.072	0.93
Hemoglobin (mg/dl)	-0.102	-0.144~-0.060	<0.001
eGFR (ml/min/1.73m^2)	0.023	0.017~0.030	<0.001
eGFR group			
60~89 ml/min/1.73m^2 [*n* (%)]	ref	ref	
90~ ml/min/1.73m^2 [*n* (%)]	0.203	0.026~0.379	0.02
Grip strength (kg)	0.004	-0.005~0.012	0.38
Grip strength group			
T1 [*n* (%)]	ref	ref	
T2 [*n* (%)]	0.311	0.112~0.511	<0.01
T3 [*n* (%)]	0.148	-0.056~0.353	0.16
Height (cm)	0.003	-0.007~0.013	0.58
Weight (kg)	-0.008	-0.015~0.000	0.048
Body mass index (kg/m^2)	-0.032	-0.056~-0.009	0.01
Waist circumference (cm)	-0.012	-0.018~-0.005	<0.001
Systolic blood pressure (mmHg)	0.002	-0.002~0.006	0.33

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Diastolic blood pressure (mmHg)	-0.001	-0.008~0.005	0.76
Mean arterial pressure (mmHg)	0.001	-0.005~0.007	0.75
Depression symptom [*n* (%)]	-0.054	-0.216~0.109	0.52
Self-report hypertension [*n* (%)]	0.047	-0.148~0.243	0.63
Self-report dyslipidemia [*n* (%)]	0.019	-0.276~0.315	0.90
Self-report diabetes or HBG [*n* (%)]	-0.196	-0.065~0.213	0.35
Self-report arthritis or rheumatism [*n* (%)]	-0.032	-0.204~0.140	0.71
Antihypertensive therapy [*n* (%)]	0.062	-0.155~0.280	0.57
Lipid-lowering therapy [*n* (%)]	0.183	-0.186~0.552	0.33
Hypoglycemic therapy [*n* (%)]	-0.169	-0.663~0.326	0.50
Therapy for arthritis or rheumatism [*n* (%)]	0.072	-0.148~0.291	0.52
Metabolic syndrome [*n* (%)]	-0.158	-0.334~0.019	0.08
MetS scores	-0.138	-0.279~0.003	0.055
Metabolic syndrome components			
Central obesity [*n* (%)]	-0.229	-0.395~-0.062	0.01
Elevated blood pressure [*n* (%)]	0.052	-0.109~0.214	0.53
Dyslipidemia [*n* (%)]	0.030	-0.135~0.196	0.72
Elevated blood glucose [*n* (%)]	-0.268	-0.431~0.105	0.001

Data are *n* (%) or median (interquartile range); HDL: high density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR:

estimated glomerular filtration rate; MetS: metabolic syndrome.

grip strength is divided into T1, T2 and T3 groups by one-third percentile.

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1L1-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2-3L27-54
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4L71-91
Objectives	3	State specific objectives, including any prespecified hypotheses	P4-5L97-100
Methods			
Study design	4	Present key elements of study design early in the paper	-
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5L103-106
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P5L107-112
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-8L138-201
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P5-6L117-136
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	P5L112
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P8-9L203-219
		(*b*) Describe any methods used to examine subgroups and interactions	P9L219-223
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	

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Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P9L233-237
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	P9L233
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P10L240-245
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	P9-10L238-240
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	P9-10L238-240
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P10L247-255
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P10-11L257-267
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11L269-275
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12-13L316-329
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11-12L276-315
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12L331-336
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P13L343-346

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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