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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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4 **Association between recovery/occurrence of metabolic syndrome and rapid**
5 **estimated glomerular filtration rate decline in middle-aged and older**
6 **populations: evidence from the China Health and Retirement Longitudinal**
7 **Study**
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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 \geq 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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4 status and rapid glomerular filtration rate decline in a nationwide cohort.

5 Metabolic syndrome scores were applied to evaluate the metabolic syndrome
6 severity.
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9 Blood tests related to metabolic syndrome and serum creatinine were performed
10 only once.
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12 13 **Introduction**

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15 Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to
16 abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood
17 pressure (BP) (1-3). As of 2017, there were approximately 1 billion individuals with
18 MetS around the world, of which China accounted for 21.7% (4). In China, MetS
19 prevalence has been undergoing a steady increase, concomitant with an increasingly
20 aged population, an obesity epidemic, and increased diabetes and hypertension levels,
21 which collectively pose a considerable threat to people's health and impose a heavy
22 burden on healthcare systems (4-6).
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31 While investigations of causality relationships between MetS and cardiovascular
32 events have gained considerable traction in recent years (7-9), MetS also impacts the
33 kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly
34 include insulin resistance, increased oxidative stress, and a chronic inflammatory
35 state, which may lead to kidney degeneration and chronic kidney disease (CKD)
36 development (5, 6). Previously, it was confirmed that MetS and associated
37 components (abdominal obesity, elevated BG, elevated BP, and lipid metabolic
38 disorder) are strongly related to CKD and a decreased estimated glomerular filtration
39 rate (eGFR) (10-14). Several longitudinal studies reported that MetS and its
40 components were associated with incremental rapid eGFR decline and CKD incidence
41 (15-18). However, these studies failed to articulate the relationship between MetS
42 alterations and renal function changes. This dearth of information on this subject
43 warrants further study, especially within a Chinese population context.
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56 The China Health and Retirement Longitudinal Study (CHARLS) is a prospective
57 cohort study conducted by the National School of Development, Peking University,
58 China (19). The nationwide sample assesses the social, behavioral, and health status
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4 of individuals aged 45 and older (19). The CHARLS baseline survey was
5 implemented in 2011 (Wave 1), and the samples were followed up every two years.
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7 Blood samples from populations were only collected in 2011 (Wave1) and 2015
8 (Wave 3). In the current study, we explored the relationship between MetS
9 recovery/occurrence and rapid eGFR decline in middle-aged and older populations in
10 the 4-year follow-up cohort.
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15 **Methods**

16 **Study population**

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18 CHARLS is a nationally representative longitudinal survey on the social,
19 economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the
20 community (19). In total, 17,708 participants were registered at baseline (Wave 1), of
21 which 11,847 had blood sample tests.
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27 In this study, our exclusion criteria excluded participants with the following: 1)
28 missing values; 2) without fasting blood values; 3) baseline eGFR < 60
29 ml/min/1.73m²; 4) clinician-reported malignant tumor, heart disease, stroke or kidney
30 disease; 5) < 45 years old; and 6) no follow-up records and related blood
31 examinations in Wave 3. After applying these criteria, 4142 participants were finally
32 included. The participant screening process is outlined (Fig. 1).
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39 The Medical Ethics Review Committee of Peking University approved this study.
40 All participants provided written informed consent before participating. This study is
41 a secondary analysis of a public dataset and does not require ethics approval again.
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45 **Blood examinations**

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47 At baseline (Wave 1), blood measurements and hemoglobin were assayed by the
48 Center for Disease Control and Prevention of the local county, whereas other
49 biochemical indicators were analyzed by Youanmen Center for Clinical Laboratory of
50 Capital Medical University, Beijing, China. Serum creatinine (Scr) was measured by
51 the picric acid method; blood urea nitrogen (BUN) was determined by an enzymatic
52 UV method with urease; blood glucose (BG), total cholesterol, high density
53 lipoprotein (HDL) cholesterol, and triglyceride (TG) were assayed by enzymatic
54 colorimetric 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 $\geq 6.5\%$, 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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4 scores were introduced to assess MetS severity (23, 24). These scores were calculated
5 using principal component (PC) analysis of WC, mean arterial pressure (MAP), FBG,
6 fasting TG, and the inverse HDL values. All MetS related variables were normalized
7 by 0–1. According to the PC analysis results, PC1 and PC2 explained 38.9% and
8 20.9% of the variance, respectively. MetS scores were calculated as follows:
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$$12 \quad PC1 = 0.369 \times WC + 0.378 \times FBG + 0.585 \times TG + 0.562 \times \left(\frac{1}{HDL}\right) + 0.252 \times MAP,$$

$$13 \quad PC2 = 0.503 \times WC - 0.171 \times FBG - 0.268 \times TG - 0.274 \times \left(\frac{1}{HDL}\right) + 0.755 \times MAP,$$

$$14 \quad MetS \text{ score} = 0.389 \times PC1 + 0.209 \times PC2$$

15 **Study outcomes**

16 We calculated eGFR values using the 2012 Chronic Kidney Disease
17 Epidemiology Collaboration equation based on creatinine levels (25). A rapid eGFR
18 decline was defined as an average annual eGFR decline of $> 3 \text{ ml/min/1.73m}^2$ (16,
19 26). In this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the
20 eGFR in Wave 1, $> 12 \text{ ml/min/1.73m}^2$.
21

22 **Covariate assessments**

23 Covariates included gender (male vs. female), age, marital status (married with
24 spouse vs. others), education (illiterate, middle school and below, or high school and
25 above), household per capita income, smoking (yes vs. no), drinking (yes vs. no),
26 eGFR, grip strength, height, weight, body mass index (BMI), WC, SBP, DBP, MAP,
27 depressive symptom (yes vs. no), episodic memory scores, self-reporting disease
28 (hypertension, diabetes, and dyslipidemia), and corresponding medication. We
29 categorized eGFR into two groups: 60–89 and ≥ 90 . Grip strength was divided into
30 three groups (T1, T2, and T3) according to the one-third percentile. BMI was
31 calculated by weight (kg)/height squared (m^2). The BP of each participant was
32 measured three times every 45–60 s with the Omron™ HEM-7112
33 sphygmomanometer (Omron Co. LTD, Dalian, China) at rest. Both SBP and DBP
34 were averaged from three measurements. MAP was defined as $MAP = 1/3 \times SBP +$
35 $2/3 \times DBP$. Previous study demonstrated that depressive symptom was association
36 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.

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

11 **Discussion**

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

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27 Longitudinal cohort studies in several Asian countries concluded that MetS
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29 increased the risk of CKD, although follow-up times varied from study to study
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31 (15-18, 33). However, the effect of MetS on the rapid decline of eGFR remains
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33 controversial. In a 3-year cohort, Cheng *et al.* found no significant correlations
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35 between MetS and eGFR rapid decline in the elderly (33). However, other studies
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37 reported that MetS was associated with a decline in eGFR and even acted as an
38
39 independent predictor of eGFR decline (16-18). We noted that none of the
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41 aforementioned studies accounted for the MetS status of participants during follow-up
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43 periods. Park *et al.* explored the relationship between MetS status change and CKD
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45 events and concluded that MetS recovery was associated with a decreased risk of
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47 CKD incidence, but the occurrence of MetS increased the risk of CKD incidence (34).
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49 Park *et al.* did not discuss the association with the rapid eGFR decline. In this study,
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51 we concluded that MetS recovery was associated with a reduced risk of rapid eGFR
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53 decline, while MetS occurrence was not related to rapid eGFR decline. Studies
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55 exploring the relationship between MetS dynamic changes and the rapid decline of
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57 eGFR in the Chinese population are rare. Our investigation of the relationship
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59 between MetS recovery/occurrence and eGFR rapid decline in a large nationwide
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61 cohort may support renal function management in individuals with MetS.

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

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

33 34 35 36 37 38 39 40 41 **Conclusions**

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

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54 Longitudinal Study (CHARLS) team for providing the data.

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60 **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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4 the manuscript. All authors have approved the final manuscript.
5

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10 **Competing interests** All authors declared no competing interests.
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12 **Data availability statement** CHARLS data of the study will be available to
13 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 (P25~P75)	(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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3	HDL cholesterol (mg/dl)	49.1 (41.0~59.5)	49.5 (41.0~59.9)	49.1 (41.0~59.5)	0.81
4	hs-CRP (mg/l)	1.0 (0.5~2.0)	1.0 (0.6~2)	1.0 (0.5~2.0)	0.43
5	GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.36
6	Uric acid (mg/dl)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	4.2 (3.5~5.0)	0.83
7	Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.0 (12.8~15.1)	14.3 (13.1~15.5)	<0.001
8	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
9	eGFR group				
10	60~89 ml/min/1.73m ² [<i>n</i> (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	0.02
11	90~ ml/min/1.73m ² [<i>n</i> (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
12	Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
13	Grip strength group				
14	T1 [<i>n</i> (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	0.01
15	T2 [<i>n</i> (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	
16	T3 [<i>n</i> (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	
17	Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
18	Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
19	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
20	Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
21	Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
22	Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
23	Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
24	Depression symptom [<i>n</i> (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
25	Self-report hypertension [<i>n</i> (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
26	Self-report dyslipidemia [<i>n</i> (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
27	Self-report diabetes or HbG [<i>n</i> (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
28	Antihypertensive therapy [<i>n</i> (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
29	Lipid-lowering therapy [<i>n</i> (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
30	Hypoglycemic therapy [<i>n</i> (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
31	Metabolic syndrome [<i>n</i> (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
32	MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
33	Metabolic syndrome components				
34	Central obesity [<i>n</i> (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
35	Elevated blood pressure [<i>n</i> (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
36	Dyslipidemia [<i>n</i> (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
37	Elevated blood glucose [<i>n</i> (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
38	Baseline non-MetS group				
39	MetS-free [<i>n</i> (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
40	MetS-developed [<i>n</i> (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
41	Baseline Mets group				
42	MetS-recovery [<i>n</i> (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
43	MetS-chronic [<i>n</i> (%)]	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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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

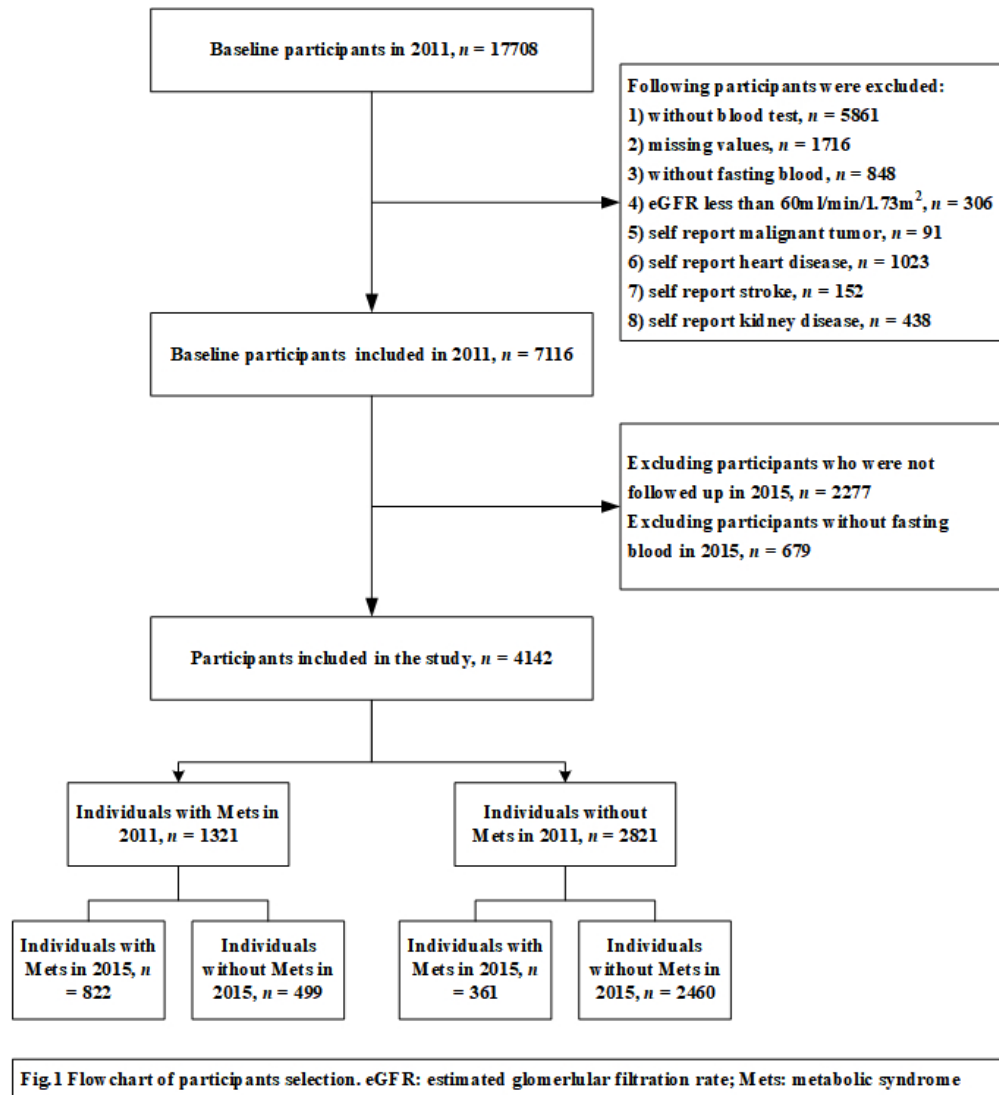
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Model 1: additional adjusted for age and sex.

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.

For peer review only



flowchart of participants selection

180x197mm (96 x 96 DPI)

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

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Secondary Subject Heading:	Urology, Diabetes and endocrinology, Public health
Keywords:	Chronic renal failure < NEPHROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

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4 1 **Association between recovery/occurrence of metabolic syndrome and rapid**
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6 2 **estimated glomerular filtration rate decline in middle-aged and older**
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8 3 **populations: evidence from the China Health and Retirement Longitudinal**
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10 4 **Study**

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4 25 **Abstract**

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6 26 **Objectives** We sought to address this knowledge gap by investigating associations
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8 27 between metabolic syndrome (MetS) recovery/development and rapid estimated
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10 28 glomerular filtration rate (eGFR) decline in the China Health and Retirement
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12 29 Longitudinal Study (CHARLS).

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14 30 **Design** Longitudinal cohort study.

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16 31 **Setting** This study is a secondary analysis of CHARLS.

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18 32 **Participants** After excluding individuals with age < 45 years old, eGFR < 60
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20 33 ml/min/1.73m² and clinician-reported malignant tumor, heart disease, stroke or kidney
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22 34 disease at baseline, 4142 participants with complete data were selected from the
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24 35 CHARLS during the 4-year follow-up.

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26 36 **Outcome measures** MetS were measured at both the beginning and the end of the
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28 37 4-year follow-up. A rapid eGFR decline was defined as an average annual eGFR
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30 38 decline of > 3 ml/min/1.73m². The associations between rapid eGFR decline and
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32 39 MetS recovery/development were analyzed using multivariable adjusted logistic
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34 40 models.

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36 41 **Results** According to MetS baseline status and follow-up, participants were divided
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38 42 into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the
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40 43 MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822
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42 44 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group,
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44 45 the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the
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46 46 MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, *P*
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48 47 = 0.01). In contrast, when compared with the MetS-free group, the multivariable
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50 48 adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00;
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52 49 95% CI: 0.73–1.38, *P* = 0.98).

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54 50 **Conclusions** Over a 4-year follow-up period, we found that MetS recovery was
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56 51 associated with a reduced risk of rapid eGFR decline in middle-aged and older adults,
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58 52 while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS
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4 53 appeared to protect against a rapid decline in eGFR.

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6 54 **Keywords:** chronic renal failure; lipid disorders; public health;

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10 56 **Strength and limitation of this study**

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12 57 This study investigated the association between altered metabolic syndrome
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14 58 status and rapid glomerular filtration rate decline in a nationwide cohort.

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16 59 Metabolic syndrome scores were applied to evaluate the metabolic syndrome
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18 60 severity.

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20 61 Blood tests related to metabolic syndrome and serum creatinine were performed
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22 62 only once.

63 Introduction

64 Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to
65 abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood
66 pressure (BP)¹⁻³. As of 2017, there were approximately 1 billion individuals with
67 MetS around the world, of which China accounted for 21.7%⁴. In China, MetS
68 prevalence has been undergoing a steady increase, concomitant with an increasingly
69 aged population, an obesity epidemic, and increased diabetes and hypertension levels,
70 which collectively pose a considerable threat to people's health and impose a heavy
71 burden on healthcare systems⁴⁻⁶.

72 While investigations of causality relationships between MetS and cardiovascular
73 events have gained considerable traction in recent years⁷⁻⁹, MetS also impacts the
74 kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly
75 include insulin resistance, increased oxidative stress, and a chronic inflammatory
76 state, which may lead to kidney degeneration and chronic kidney disease (CKD)
77 development^{5,6}. Previously, it was confirmed that MetS and associated components
78 (abdominal obesity, elevated BG, elevated BP, and lipid metabolic disorder) are
79 strongly related to CKD and a decreased estimated glomerular filtration rate (eGFR)
80¹⁰⁻¹⁴. Several longitudinal studies reported that MetS and its components were
81 associated with incremental rapid eGFR decline and CKD incidence¹⁵⁻¹⁸. However,
82 these studies failed to articulate the relationship between MetS alterations and renal
83 function changes. This dearth of information on this subject warrants further study,
84 especially within a Chinese population context.

85 The China Health and Retirement Longitudinal Study (CHARLS) is a prospective
86 cohort study conducted by the National School of Development, Peking University,
87 China¹⁹. The nationwide sample assesses the social, behavioral, and health status of
88 individuals aged 45 and older¹⁹. The CHARLS baseline survey was implemented in
89 2011 (Wave 1), and the samples were followed up every two years. Blood samples
90 from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the

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4 91 current study, we explored the relationship between MetS recovery/occurrence and
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6 92 rapid eGFR decline in middle-aged and older populations in the 4-year follow-up
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8 93 cohort.

94 **Methods**

95 **Study population**

96 CHARLS is a nationally representative longitudinal survey on the social,
97 economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the
98 community¹⁹. In total, 17,708 participants were registered at baseline (Wave 1), of
99 which 11,847 had blood sample tests.

100 In this study, our exclusion criteria excluded participants with the following: 1)
101 missing values; 2) without fasting blood values; 3) baseline eGFR < 60
102 ml/min/1.73m²; 4) clinician-reported malignant tumor, heart disease, stroke or kidney
103 disease; 5) < 45 years old; and 6) no follow-up records and related blood
104 examinations in Wave 3. After applying these criteria, 4142 participants were finally
105 included. The participant screening process is outlined (Fig. 1).

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

109 **Blood examinations**

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

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4 119 examined by immunoturbidimetric assay; and uric acid (UA) was determined by the
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6 120 UA plus method ²⁰. Blood specimen testing in 2015 (Wave 3) was completed by
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8 121 KingMed Diagnostics, the leading third-party institution in China, which has testing
9
10 122 laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG
11
12 123 were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were
13
14 124 determined by the same methods as Wave 1, while HDL was determined by a direct
15
16 125 method, TG by an oxidase method, and BG by a hexokinase method ²¹. The
17
18 126 collection, storage, transport, processing, and other blood sample details are described
19
20 127 elsewhere ^{20 21}. Of note, the models and manufacturer information of blood test
21
22 128 instruments in Wave 1 and Wave 3 were not available. All inspections and
23
24 129 calibrations were performed by trained personnel.

130 **Definition and grouping of MetS**

131 Currently, there was no unified definition for MetS. The World Health
132
133 Origination (WHO) diagnostic criteria proposed in 1999, the National Cholesterol
134
135 Education Program Adult Panel III (ATP III) diagnostic criteria proposed in 2005,
136
137 and International Diabetes Federation (IDF) diagnostic criteria proposed in 2006 were
138
139 commonly used for metabolic syndrome ²². These diagnostic criteria basically related
140
141 to abdominal obesity, dyslipidemia, glucose metabolism disorder, and elevated blood
142
143 pressure. However, these diagnostic criteria had different views and cut-off values for
144
145 some specific indicators. This study adopted the 2018 China Guidelines for the
146
147 Prevention and Treatment of Hypertension (CGPTH) definition for MetS, which was
148
149 similar to the ATP III diagnostic criteria ². Compared with ATP III diagnostic criteria,
150
151 the cut points of waist circumference defined by CGPTH were smaller and more
152
153 suitable for the Chinese population. According to the 2018 CGPTH definition, MetS
154
155 was diagnosed when three of the following four conditions were met: 1) Central
156
157 obesity: waist circumference (WC) ≥ 90 cm in men and ≥ 85 cm in women; 2)
158
159 Elevated BP: systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure
160
(DBP) ≥ 85 mmHg, or diagnosed as hypertension and treated; 3) Dyslipidemia:

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4 147 fasting TG \geq 150 mg/dL, or HDL \leq 40 mg/dL, or diagnosed as dyslipidemia and
5
6 148 treated; and 4) Elevated BG: Fasting BG (FBG) \geq 100 mg/dL, or 2 h postprandial BG
7
8 149 \geq 100 mg/dL, or diagnosed as diabetes and treated². Diabetes was defined as fasting
9
10 150 BG \geq 126 mg/dL, and/or HbA1c \geq 6.5%, and/or a self-reported history of diabetes²³.
11
12 151 Of note, we did not have 2 h postprandial BG data.

13
14 152 According to MetS baseline status and follow-up, participants were categorized
15
16 153 into 1) MetS-free, 2) MetS-developed, 3) MetS-recovery, and 4) MetS-chronic
17
18 154 groups.

19 20 155 **Study outcomes**

21
22 156 We calculated eGFR values using the 2012 Chronic Kidney Disease
23
24 157 Epidemiology Collaboration equation based on creatinine levels²⁴. A rapid eGFR
25
26 158 decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m²^{16 25}. In
27
28 159 this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR
29
30 160 in Wave 1, > 12 ml/min/1.73m².

31 32 161 **MetS scores**

33
34 162 MetS severity potentially affects the recovery or occurrence of MetS. For
35
36 163 instance, individuals with high MetS severity may be less liable to recover. Similarly,
37
38 164 for those without MetS, it is not straightforward to progress to severe MetS.
39
40 165 Therefore, MetS scores were introduced to assess MetS severity in the study, which
41
42 166 was thought to be more sufficient and accurate than other ways using the number of
43
44 167 symptoms and complications to reflect MetS severity^{26 27}. These scores were
45
46 168 calculated using principal component (PC) analysis of WC, mean arterial pressure
47
48 169 (MAP), FBG, fasting TG, and the inverse HDL values. All MetS related variables
49
50 170 were normalized by 0–1. According to the PC analysis results, PC1 and PC2
51
52 171 explained 38.9% and 20.9% of the variance, respectively. MetS scores were
53
54 172 calculated as follows:

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56
57 173
$$PC1 = 0.369 \times WC + 0.378 \times FBG + 0.585 \times TG + 0.562 \times \left(\frac{1}{HDL} \right) + 0.252 \times MAP,$$

$$174 \quad PC2 = 0.503 \times WC - 0.171 \times FBG - 0.268 \times TG - 0.274 \times \left(\frac{1}{HDL} \right) + 0.755 \times MAP,$$

$$175 \quad \text{MetS score} = 0.389 \times PC1 + 0.209 \times PC2$$

176 **Other covariates**

177 All potential covariates were all collected at baseline in Wave 1, including gender
178 (male vs. female), age, marital status (married with spouse vs. others), education
179 (illiterate, middle school and below, or high school and above), household per capita
180 income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height,
181 weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs.
182 no), self-reporting disease (hypertension, diabetes, dyslipidemia and), and
183 corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90 .
184 Grip strength was divided into three groups (T1, T2, and T3) according to the
185 one-third percentile. BMI was calculated by weight (kg)/height squared (m²). The BP
186 of each participant was measured three times every 45–60 s with the OmronTM
187 HEM-7112 sphygmomanometer (Omron Co. LTD, Dalian, China) at rest. Both SBP
188 and DBP were averaged from three measurements. MAP was defined as $MAP = 1/3 \times$
189 $SBP + 2/3 \times DBP$. Previous study demonstrated that depressive symptom was
190 association with baseline eGFR²⁸. Thus, we should not overlook this variable. The
191 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was applied
192 in the study²⁹. A CESD-10 score ≥ 10 was grouped into the depressive symptom
193 group, and < 10 into the non-depressive symptom group. Self-reporting disease was
194 disease diagnosed by a doctor. Medical interventions included taking Chinese
195 traditional and Western modern medicines.

196 **Statistical methods**

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

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4 202 preliminary analyses, variables with P values < 0.15 were used to calibrate the logistic
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6 203 model. Continuous variables not presenting a linear relationship with the logit
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8 204 conversion value of the dependent variable were converted to categorical variables.
9
10 205 Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This
11
12 206 existed if the tolerance was < 0.1 or the VIF was > 10. Eventually, age, sex, BMI, Scr,
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14 207 hemoglobin, eGFR classification, grip strength classification and MetS scores were
15
16 208 selected as confounding variables for model adjustments in this study. Most selected
17
18 209 covariates have been reported to be related to renal events^{26 30-33}. Univariate analysis
19
20 210 of variables between eGFR decline group and non-rapid eGFR decline group were
21
22 211 carried out. Logistic models were used to test the association between MetS
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24 212 recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding
25
26 213 factors. Furthermore, alterations in MetS status were accompanied by changes of
27
28 214 diagnostic conditions (elevated blood glucose, elevated blood pressure, central obesity
29
30 215 and dyslipidemia). As a result, logistic models were used to explore the relationship
31
32 216 between the recovery/occurrence of Mets components and the rapid decline of eGFR
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34 217 using different adjustments of confounding factors, respectively. $P < 0.05$ was
35
36 218 considered statistically significant (two-sided test). Statistics were generated in IBM
37
38 219 SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software
39
40 220 (StataCorp, Texas, USA).

41 42 221 **Patient and public involvement**

43
44 222 There were no participants involved in the development. The results of the
45
46 223 survey are disseminated to the public through websites.

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48 224

49 50 225 **Results**

51 52 226 **Participant characteristics**

53
54 227 As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the
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56 228 MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS
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58 229 recovery-group, and 822 (19.8%) in the MetS-chronic group. Comparison of the basic
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4 230 characteristics between the 4142 enrolled participants and 2974 ones that excluded
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6 231 during follow-up were shown in Supplemental Table 1.

7
8 232 Participant characteristics were grouped by the eGFR decline rate (Table 1). A
9
10 233 rapid decline in eGFR developed in 711 (17.2%) participants during the 4-year
11
12 234 follow-up. The median age was 58 (52~64) years and males accounted for 42.5% at
13
14 235 baseline. In contrast to rapid eGFR decline group, the non-rapid eGFR decline group
15
16 236 was significantly higher with respect to FBG, Scr, hemoglobin, eGFR, weight, BMI,
17
18 237 WC, MetS scores, central obesity, and elevated BG (all $P < 0.05$). Those in non-rapid
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20 238 eGFR decline group were more likely to be female and younger when compared with
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22 239 the eGFR decline group (both $P < 0.05$).

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24 240

25 26 241 **Rapid eGFR decline odds based on Mets recovery or occurrence**

27
28 242 Univariate analysis was conducted to select covariates for correction
29
30 243 (Supplemental Table 2). As shown (Table 2), after adjustment for age, sex, BMI, Scr,
31
32 244 hemoglobin, eGFR classification, grip strength classification, and MetS scores, the
33
34 245 odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR:
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36 246 0.64; 95% CI: 0.45–0.90, $P = 0.01$) when compared with the MetS-chronic group. In
37
38 247 contrast, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR
39
40 248 classification, grip strength classification, and MetS score, the OR of rapid eGFR
41
42 249 decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, $P =$
43
44 250 0.98) when compared with the MetS-free group.

45 46 251 **MetS components and rapid eGFR decline odds**

47
48 252 The association of changes in the composition of MetS groups with rapid eGFR
49
50 253 decline is shown (Table 3). In the baseline MetS population, after adjustment for age,
51
52 254 sex, BMI, serum creatinine, hemoglobin, eGFR classification, grip strength
53
54 255 classification, and MetS score, the OR of rapid eGFR decline in the population
55
56 256 recovered from central obesity was 0.31 (OR: 0.31; 95% CI: 0.15–0.65, $P < 0.01$)
57
58 257 when compared with chronic central obesity, whereas recovery from elevated BP,
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4 258 dyslipidemia, and elevated BG did not show statistically significant differences when
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6 259 compared with the corresponding population (all $P > 0.05$). In the baseline population
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8 260 without MetS, we observed no statistical difference in the rapid decline of eGFR
9
10 261 between the occurrence of all MetS component groups and corresponding contrast
11
12 262 groups (all $P > 0.05$). This was consistent with the overall trend.

13 14 263 **Discussion**

15
16 264 We examined the relationship between MetS changes and rapid eGFR decline in
17
18 265 a large nationwide cohort. At the 4-year follow-up, MetS recovery was significantly
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20 266 associated with a reduced risk of rapid eGFR decline in the middle-aged and elderly,
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22 267 with only WC recovery consistent with the overall trend. The occurrence of MetS and
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24 268 its components did not significantly increase the risk of rapid eGFR decline. Further
25
26 269 follow-up is required to elucidate the relationship between MetS dynamics and the
27
28 270 rapid decline in eGFR.

29
30 271 Longitudinal cohort studies in several Asian countries concluded that MetS
31
32 272 increased the risk of CKD, although follow-up times varied from study to study¹⁵⁻¹⁸
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34 273³⁴. However, the effect of MetS on the rapid decline of eGFR remains controversial.
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36 274 In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and
37
38 275 eGFR rapid decline in the elderly³⁴. However, other studies reported that baseline
39
40 276 MetS was associated with a decline in eGFR and even acted as an independent
41
42 277 predictor of eGFR decline¹⁶⁻¹⁸. Wu *et al.* investigated the association between the
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44 278 MetS severity score and kidney function, and found that the MetS severity score was
45
46 279 an independent risk factor for the CKD development and progressive eGFR decline,
47
48 280 although the definition of rapid eGFR decline was different from this study²⁶. Here,
49
50 281 the MetS severity score was a continuous variable that was primarily used to calibrate
51
52 282 the MetS (yes vs. no). We noted that none of the aforementioned studies accounted
53
54 283 for the MetS status of participants during follow-up periods. In a 4-year follow-up
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56 284 cohort, Park *et al.* explored the relationship between MetS status change and CKD
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58 285 events and concluded that MetS recovery was associated with a decreased risk of
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4 286 CKD incidence, but the occurrence of MetS increased the risk of CKD incidence ³⁵.
5
6 287 One of the highlights of the article was to observe the status of MetS three times over
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8 288 a 4-year period, thereby making the MetS diagnosis more robust. However, Park *et al.*
9
10 289 did not discuss the association with the rapid eGFR decline. In this study, we
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12 290 concluded that MetS recovery was associated with a reduced risk of rapid eGFR
13
14 291 decline, while MetS occurrence was not related to rapid eGFR decline. It should be
15
16 292 emphasized that we need to be cautious about the conclusion between the MetS
17
18 293 occurrence and the rapid eGFR decline in this study. Because the follow-up time was
19
20 294 short and the timing of MetS onset was unknown, the impairment of renal function
21
22 295 caused by MetS may not have occurred in some populations. To sum up, studies
23
24 296 exploring the relationship between MetS dynamic changes and the rapid decline of
25
26 297 eGFR in the Chinese population are rare. Our investigation of the relationship
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28 298 between MetS recovery/occurrence and eGFR rapid decline in a large nationwide
29
30 299 cohort may support renal function management in individuals with MetS.

31
32 300 The effect of MetS on renal function is complex, thus, no definitive mechanisms
33
34 301 can explain our study observations. The evidence suggests that every component of
35
36 302 MetS is associated with adverse renal events (10-14). It is accepted that hypertension
37
38 303 and diabetes play pivotal roles in CKD development and progression ³⁶⁻³⁸. Also, lipid
39
40 304 metabolism dysregulation and abnormal lipid distribution can lead to
41
42 305 lipotoxicity-related renal damage ^{39 40}. Thus, MetS may result from the combined
43
44 306 effects of central obesity, increased BP, insulin resistance, and blood lipid disorder,
45
46 307 leading to physiopathological lipotoxicity, oxidative stress increments, endothelial
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48 308 dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney
49
50 309 dysfunction ^{5 39}. However, the relationship between MetS components and the weight
51
52 310 of each factor on kidney injury remain unclear.

53
54 311 Our study had some limitations. Firstly, MetS diagnoses were not
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56 312 comprehensively checked (using multiple tests), and the exact timing of the MetS
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58 313 alteration is unknown. Secondly, renal stone disease, epiculopathy, epiculoepicardial
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4 314 disease or acute urinary tract infection are related to the occurrence and development
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6 315 of renal disease. Unfortunately, urine or kidney ultrasound results were unavailable in
7
8 316 CHARLS cohort. Thirdly, CKD occurrence was not included as a study outcome
9
10 317 because of the lack of urine test results, which would underestimate the CKD
11
12 318 incidence. Fourthly, blood analyses from Wave 1 and Wave 3 were performed at a
13
14 319 different testing center, with inconsistent HDL, TG, and BG measurement methods,
15
16 320 therefore, measurement errors may have occurred. Fifthly, a large proportion of
17
18 321 individuals were excluded due to exclusion criteria or missing values and this may
19
20 322 have biased some of our results. Sixthly, we did not establish a model with all 4 MetS
21
22 323 change groups included in the study.

23 24 324 **Conclusions**

25
26 325 Over a 4-year follow-up, we observed that MetS recovery, including recovery of
27
28 326 central obesity, was associated with a reduced risk of rapid eGFR decline in
29
30 327 middle-aged and older adults, while MetS occurrence was not related to rapid eGFR
31
32 328 decline. Reversing MetS, especially central obesity, might benefit the kidney function
33
34 329 in MetS population. But, further follow-up studies are required to observe the
35
36 330 relationship between MetS alterations and adverse renal events.

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38
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40
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43
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45
46 334 and interpretation of data and preparation of the manuscript. XL—study concept and
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48 335 design, and preparation and critical review of the manuscript. CC—critical review and
49
50 336 statistical guidance of the revised manuscript. All authors have approved the final
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52 337 manuscript.

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55
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59 340 **Competing interests** All authors declared no competing interests.

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4 341 **Data availability statement** CHARLS data of the study will be available to
5
6 342 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 (2336.7~13487.5)	6000.0 (1866.7~13490.0)	6560.0 (2450.0~13486.7)	0.20
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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3	Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
4	Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
5	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
6	Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
7	Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
8	Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
9	Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
10	Depression symptom [<i>n</i> (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
11	Self-report hypertension [<i>n</i> (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
12	Self-report dyslipidemia [<i>n</i> (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
13	Self-report diabetes or HBG [<i>n</i> (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
14	Self-report arthritis or rheumatism [<i>n</i> (%)]	1345 (32.5)	235 (33.1)	1110 (32.4)	0.71
15	Antihypertensive therapy [<i>n</i> (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
16	Lipid-lowering therapy [<i>n</i> (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
17	Hypoglycemic therapy [<i>n</i> (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
18	Therapy for arthritis or rheumatism [<i>n</i> (%)]	643 (15.5)	116 (16.3)	527 (15.4)	0.52
19	Metabolic syndrome [<i>n</i> (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
20	MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
21	Metabolic syndrome components				
22	Central obesity [<i>n</i> (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
23	Elevated blood pressure [<i>n</i> (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
24	Dyslipidemia [<i>n</i> (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
25	Elevated blood glucose [<i>n</i> (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
26	Baseline non-MetS group				
27	MetS-free [<i>n</i> (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
28	MetS-developed [<i>n</i> (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
29	Baseline MetS group				
30	MetS-recovery [<i>n</i> (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
31	MetS-chronic [<i>n</i> (%)]	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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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
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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 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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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

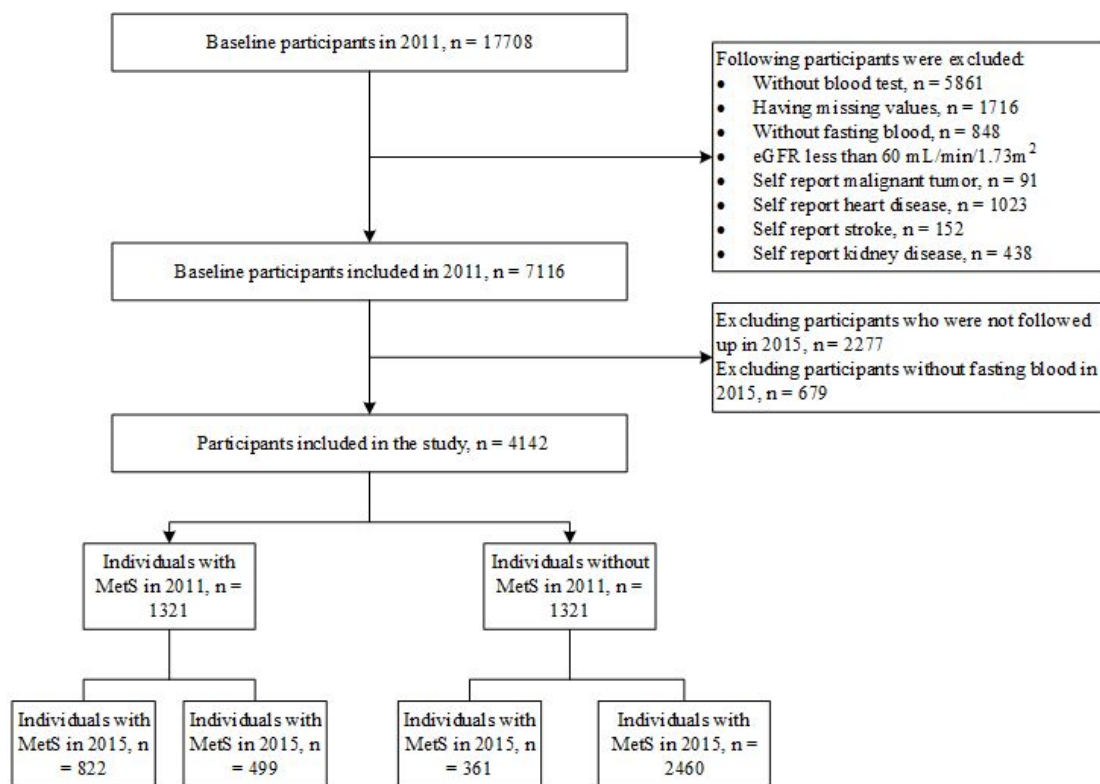
eGFR: estimated glomerular filtration rate; CI: confidence interval; OR: odds ratio; MetS: metabolic syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL: high density lipoprotein.

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

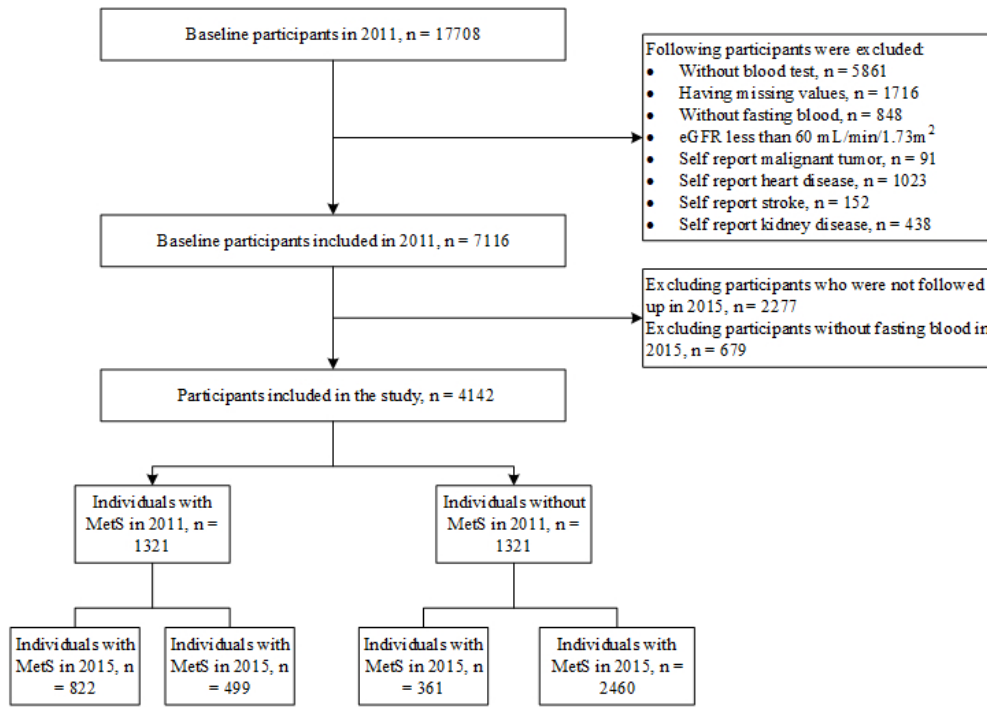


Fig 1. Flow chart of of participants selection. eGFR: estimated glomerular filtration rate; MetS: metabolic syndrome

Flow chart of of participants selection

193x148mm (96 x 96 DPI)

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4 **Association between recovery/occurrence of metabolic syndrome and rapid estimated**
5 **glomerular filtration rate decline in middle-aged and older populations: evidence from**
6
7 **the China Health and Retirement Longitudinal Study**

8
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Supplemental Table 1. Baseline characteristics of participants included and excluded in the study

Characteristics	participants included			P-value
	in baseline (n=7116)	group 1 (n=2974)	group 2 (n=4142)	
Age (years)	58 (52~65)	58 (52~64)	58 (51~66)	0.98
Male [<i>n</i> (%)]	3332 (46.8)	1458 (49.0)	1874 (45.2)	0.002
Married with spouse [<i>n</i> (%)]	5977 (84.0)	2974 (81.7)	3548 (87.5)	<0.001
Education				0.07
Illiterate [<i>n</i> (%)]	2106 (29.6)	900 (30.3)	1206 (29.1)	
Middle school and below [<i>n</i> (%)]	2853 (40.1)	1146 (38.5)	1770 (41.2)	
High school and above [<i>n</i> (%)]	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 [<i>n</i> (%)]	2461 (34.6)	1054 (35.4)	1470 (32.2)	0.20
Smoke [<i>n</i> (%)]	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 [<i>n</i> (%)]	3172 (44.6)	1268 (42.6)	1904 (46.0)	0.005
Metabolic syndrome [<i>n</i> (%)]	2228 (31.3)	907 (30.5)	1321 (31.9)	0.21
Metabolic syndrome components				
Elevated blood pressure [<i>n</i> (%)]	3622 (50.9)	1523 (51.2)	2099 (50.7)	0.66
Elevated blood glucose [<i>n</i> (%)]	4179 (58.7)	1723 (57.9)	2456 (59.3)	0.25
Dyslipidemia [<i>n</i> (%)]	2673 (37.6)	1078 (36.2)	1595 (38.5)	0.052
Central obesity [<i>n</i> (%)]	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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3 syndrome. Group 1: participants included in the baseline and excluded after follow-up; Group 2:
4 participants included in the study.
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8 **Supplemental Table 2. Univariate analysis of variables between eGFR decline group and non-**
9 **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 [<i>n</i> (%)]			
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 [<i>n</i> (%)]			
Smoke [<i>n</i> (%)]	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 [<i>n</i> (%)]	ref	ref	
90~ ml/min/1.73m ² [<i>n</i> (%)]	0.203	0.026~0.379	0.02
Grip strength (kg)	0.004	-0.005~0.012	0.38
Grip strength group			
T1 [<i>n</i> (%)]	ref	ref	
T2 [<i>n</i> (%)]	0.311	0.112~0.511	<0.01
T3 [<i>n</i> (%)]	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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3	Waist circumference (cm)	-0.012	-0.018~-0.005	<0.001
4	Systolic blood pressure (mmHg)	0.002	-0.002~-0.006	0.33
5	Diastolic blood pressure (mmHg)	-0.001	-0.008~-0.005	0.76
6	Mean arterial pressure (mmHg)	0.001	-0.005~-0.007	0.75
7	Depression symptom [<i>n</i> (%)]	-0.054	-0.216~-0.109	0.52
8	Self-report hypertension [<i>n</i> (%)]	0.047	-0.148~-0.243	0.63
9	Self-report dyslipidemia [<i>n</i> (%)]	0.019	-0.276~-0.315	0.90
10	Self-report diabetes or HBG [<i>n</i> (%)]	-0.196	-0.065~-0.213	0.35
11	Self-report arthritis or rheumatism [<i>n</i> (%)]	-0.032	-0.204~-0.140	0.71
12	Antihypertensive therapy [<i>n</i> (%)]	0.062	-0.155~-0.280	0.57
13	Lipid-lowering therapy [<i>n</i> (%)]	0.183	-0.186~-0.552	0.33
14	Hypoglycemic therapy [<i>n</i> (%)]	-0.169	-0.663~-0.326	0.50
15	Therapy for arthritis or rheumatism [<i>n</i> (%)]	0.072	-0.148~-0.291	0.52
16	Metabolic syndrome [<i>n</i> (%)]	-0.158	-0.334~-0.019	0.08
17	MetS scores	-0.138	-0.279~-0.003	0.055
18	Metabolic syndrome components			
19	Central obesity [<i>n</i> (%)]	-0.229	-0.395~-0.062	0.01
20	Elevated blood pressure [<i>n</i> (%)]	0.052	-0.109~-0.214	0.53
21	Dyslipidemia [<i>n</i> (%)]	0.030	-0.135~-0.196	0.72
22	Elevated blood glucose [<i>n</i> (%)]	-0.268	-0.431~-0.105	0.001

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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.

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) <i>Cohort study</i> —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) <i>Cohort study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	10*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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

(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.

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

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Keywords:	Chronic renal failure < NEPHROLOGY, Lipid disorders < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

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4 1 **Association between recovery/occurrence of metabolic syndrome and rapid**
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6 2 **estimated glomerular filtration rate decline in middle-aged and older**
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8 3 **populations: evidence from the China Health and Retirement Longitudinal**
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10 4 **Study**

11
12 5 **Peijia Liu,^{1,2} Leile Tang,³ Jia fang,¹ Chaojin Chen,^{4*} Xun Liu^{1*}**

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4 27 **Abstract**

5
6 28 **Objectives** Few studies have explored correlations between metabolic syndrome
7
8 29 (MetS) alterations and renal deterioration in longitudinal cohorts. We aim to
9
10 30 investigate associations between MetS recovery/development and rapid estimated
11
12 31 glomerular filtration rate (eGFR) decline in the China Health and Retirement
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14 32 Longitudinal Study (CHARLS).

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16 33 **Design** Longitudinal cohort study.

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18 34 **Setting** This study is a secondary analysis of CHARLS.

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20 35 **Participants** After excluding individuals with age < 45 years old, eGFR < 60
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22 36 ml/min/1.73m² and clinician-reported malignant tumor, heart disease, stroke or kidney
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24 37 disease at baseline, 4142 participants with complete data were selected from the
25
26 38 CHARLS during the 4-year follow-up period (2011-2015).

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28 39 **Outcome measures** MetS were measured at 2011 and 2015 in CHARLS. A rapid
29
30 40 eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m².
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32 41 The associations between rapid eGFR decline and MetS recovery/development were
33
34 42 analyzed using multivariable adjusted logistic models.

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36 43 **Results** According to MetS baseline status and follow-up, participants were divided
37
38 44 into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the
39
40 45 MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822
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42 46 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group,
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44 47 the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the
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46 48 MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, *P*
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48 49 = 0.01). In contrast, when compared with the MetS-free group, the multivariable
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50 50 adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00;
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52 51 95% CI: 0.73–1.38, *P* = 0.98).

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54 52 **Conclusions** Over the 4-year follow-up period, we found that MetS recovery was
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56 53 associated with a reduced risk of rapid eGFR decline in middle-aged and older adults,
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58 54 while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS
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4 55 appeared to protect against a rapid decline in eGFR.

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6 56 **Keywords:** chronic renal failure; lipid disorders; public health;

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10 58 **Strength and limitation of this study**

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12 59 This study investigated the association between altered metabolic syndrome
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14 60 status and rapid glomerular filtration rate decline in a nationwide cohort.

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16 61 Metabolic syndrome scores were applied to evaluate the metabolic syndrome
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18 62 severity.

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20 63 Blood tests related to metabolic syndrome and serum creatinine were performed
21
22 64 only once.

65 Introduction

66 Metabolic Syndrome (MetS) is a cluster of clinical characteristics related to
67 abdominal obesity, dyslipidemia, elevated blood glucose (BG), and elevated blood
68 pressure (BP)¹⁻³. As of 2017, there were approximately 1 billion individuals with
69 MetS around the world, of which China accounted for 21.7%⁴. In China, MetS
70 prevalence has been undergoing a steady increase, concomitant with an increasingly
71 aged population, an obesity epidemic, and increased diabetes and hypertension levels,
72 which collectively pose a considerable threat to people's health and impose a heavy
73 burden on healthcare systems⁴⁻⁶.

74 While investigations of causality relationships between MetS and cardiovascular
75 events have gained considerable traction in recent years⁷⁻⁹, MetS also impacts the
76 kidneys. It is accepted that the pathological mechanisms underpinning MetS mainly
77 include insulin resistance, increased oxidative stress, and a chronic inflammatory
78 state, which may lead to kidney degeneration and chronic kidney disease (CKD)
79 development^{5,6}. Previously, it was confirmed that MetS and associated components
80 (abdominal obesity, elevated BG, elevated BP, and lipid metabolic disorder) are
81 strongly related to CKD and a decreased estimated glomerular filtration rate (eGFR)
82¹⁰⁻¹⁴. Several longitudinal studies reported that MetS and its components were
83 associated with incremental rapid eGFR decline and CKD incidence¹⁵⁻¹⁸. However,
84 these studies failed to articulate the relationship between MetS alterations and renal
85 function changes. This dearth of information on this subject warrants further study,
86 especially within a Chinese population context.

87 The China Health and Retirement Longitudinal Study (CHARLS) is a prospective
88 cohort study conducted by the National School of Development, Peking University,
89 China¹⁹. The nationwide sample assesses the social, behavioral, and health status of
90 individuals aged 45 and older¹⁹. The CHARLS baseline survey was implemented in
91 2011 (Wave 1), and the samples were followed up every two years. Blood samples
92 from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the

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4 93 current study, we explored the relationship between MetS recovery/occurrence and
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6 94 rapid eGFR decline in middle-aged and older populations in the 4-year follow-up
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8 95 cohort.

96 **Methods**

97 **Study population**

98 CHARLS is a nationally representative longitudinal survey on the social,
99 economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the
100 community¹⁹. In total, 17,708 participants were registered at baseline (Wave 1 at
101 2011), of which 11,847 had blood sample tests.

102 In this study, our exclusion criteria excluded participants with the following: 1)
103 missing values; 2) without fasting blood values; 3) baseline eGFR < 60
104 ml/min/1.73m²; 4) clinician-reported malignant tumor, heart disease, stroke or kidney
105 disease; 5) < 45 years old; and 6) no follow-up records and related blood
106 examinations in Wave 3 at 2015. After applying these criteria, 4142 participants were
107 finally included. The participant screening process is outlined (Fig. 1).

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

111 **Blood examinations**

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

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4 121 examined by immunoturbidimetric assay; and uric acid (UA) was determined by the
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6 122 UA plus method ²⁰. Blood specimen testing in 2015 (Wave 3) was completed by
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8 123 KingMed Diagnostics, the leading third-party institution in China, which has testing
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10 124 laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG
11
12 125 were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were
13
14 126 determined by the same methods as Wave 1, while HDL was determined by a direct
15
16 127 method, TG by an oxidase method, and BG by a hexokinase method ²¹. The
17
18 128 collection, storage, transport, processing, and other blood sample details are described
19
20 129 elsewhere ^{20 21}. Of note, the models and manufacturer information of blood test
21
22 130 instruments in Wave 1 and Wave 3 were not available. All inspections and
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24 131 calibrations were performed by trained personnel.

132 **Definition and grouping of MetS**

133 Currently, there was no unified definition for MetS. The World Health
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4 149 fasting TG \geq 150 mg/dL, or HDL \leq 40 mg/dL, or diagnosed as dyslipidemia and
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6 150 treated; and 4) Elevated BG: Fasting BG (FBG) \geq 100 mg/dL, or 2 h postprandial BG
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8 151 \geq 100 mg/dL, or diagnosed as diabetes and treated². Diabetes was defined as fasting
9
10 152 BG \geq 126 mg/dL, and/or HbA1c \geq 6.5%, and/or a self-reported history of diabetes²³.
11
12 153 Of note, we did not have 2 h postprandial BG data.

13
14 154 According to MetS baseline status and follow-up, participants were categorized
15
16 155 into 1) MetS-free, 2) MetS-developed, 3) MetS-recovery, and 4) MetS-chronic
17
18 156 groups.

19 20 157 **Study outcomes**

21
22 158 We calculated eGFR values using the 2012 Chronic Kidney Disease
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24 159 Epidemiology Collaboration equation based on creatinine levels²⁴. A rapid eGFR
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26 160 decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m²^{16 25}. In
27
28 161 this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR
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30 162 in Wave 1, > 12 ml/min/1.73m².

31 32 163 **MetS scores**

33
34 164 MetS severity potentially affects the recovery or occurrence of MetS. For
35
36 165 instance, individuals with high MetS severity may be less liable to recover. Similarly,
37
38 166 for those without MetS, it is not straightforward to progress to severe MetS.
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40 167 Therefore, MetS scores were introduced to assess MetS severity in the study, which
41
42 168 was thought to be more sufficient and accurate than other ways using the number of
43
44 169 symptoms and complications to reflect MetS severity^{26 27}. These scores were
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46 170 calculated using principal component (PC) analysis of WC, mean arterial pressure
47
48 171 (MAP), FBG, fasting TG, and the inverse HDL values. All MetS related variables
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50 172 were normalized by 0–1. According to the PC analysis results, PC1 and PC2
51
52 173 explained 38.9% and 20.9% of the variance, respectively. MetS scores were
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54 174 calculated as follows:

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57 175
$$PC1 = 0.369 \times WC + 0.378 \times FBG + 0.585 \times TG + 0.562 \times \left(\frac{1}{HDL} \right) + 0.252 \times MAP,$$

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

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

178 **Other covariates**

179 All potential covariates were all collected at baseline in Wave 1, including gender
180 (male vs. female), age, marital status (married with spouse vs. others), education
181 (illiterate, middle school and below, or high school and above), household per capita
182 income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height,
183 weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs.
184 no), self-reporting disease (hypertension, diabetes, dyslipidemia and), and
185 corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90 .
186 Grip strength was divided into three groups (T1, T2, and T3) according to the
187 one-third percentile. BMI was calculated by weight (kg)/height squared (m²). The BP
188 of each participant was measured three times every 45–60 s with the OmronTM
189 HEM-7112 sphygmomanometer (Omron Co. LTD, Dalian, China) at rest. Both SBP
190 and DBP were averaged from three measurements. MAP was defined as $MAP = 1/3 \times$
191 $SBP + 2/3 \times DBP$. Previous study demonstrated that depressive symptom was
192 association with baseline eGFR²⁸. Thus, we should not overlook this variable. The
193 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was applied
194 in the study²⁹. A CESD-10 score ≥ 10 was grouped into the depressive symptom
195 group, and < 10 into the non-depressive symptom group. Self-reporting disease was
196 disease diagnosed by a doctor. Medical interventions included taking Chinese
197 traditional and Western modern medicines.

198 **Statistical methods**

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

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4 204 preliminary analyses, variables with P values < 0.15 were used to calibrate the logistic
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6 205 model. Continuous variables not presenting a linear relationship with the logit
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8 206 conversion value of the dependent variable were converted to categorical variables.
9
10 207 Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This
11
12 208 existed if the tolerance was < 0.1 or the VIF was > 10. Eventually, age, sex, BMI, Scr,
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14 209 hemoglobin, eGFR classification, grip strength classification and MetS scores were
15
16 210 selected as confounding variables for model adjustments in this study. Most selected
17
18 211 covariates have been reported to be related to renal events^{26 30-33}. Univariate analysis
19
20 212 of variables between eGFR decline group and non-rapid eGFR decline group were
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22 213 carried out. Logistic models were used to test the association between MetS
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24 214 recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding
25
26 215 factors. Furthermore, alterations in MetS status were accompanied by changes of
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28 216 diagnostic conditions (elevated blood glucose, elevated blood pressure, central obesity
29
30 217 and dyslipidemia). As a result, logistic models were used to explore the relationship
31
32 218 between the recovery/occurrence of Mets components and the rapid decline of eGFR
33
34 219 using different adjustments of confounding factors, respectively. $P < 0.05$ was
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36 220 considered statistically significant (two-sided test). Statistics were generated in IBM
37
38 221 SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software
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40 222 (StataCorp, Texas, USA).

41 42 223 **Patient and public involvement**

43
44 224 There were no participants involved in the development. The results of the
45
46 225 survey are disseminated to the public through websites.

47 48 226 49 50 227 **Results**

51 52 228 **Participant characteristics**

53
54 229 As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the
55
56 230 MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS
57
58 231 recovery-group, and 822 (19.8%) in the MetS-chronic group. Comparison of the basic

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

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

242

243 **Rapid eGFR decline odds based on Mets recovery or occurrence**

244 Univariate analysis was conducted to select covariates for correction
245 (Supplemental Table 2). As shown (Table 2), after adjustment for age, sex, BMI, Scr,
246 hemoglobin, eGFR classification, grip strength classification, and MetS scores, the
247 odds ratio (OR) of rapid eGFR decline in the MetS-recovery group was 0.64 (OR:
248 0.64; 95% CI: 0.45–0.90, $P = 0.01$) when compared with the MetS-chronic group. In
249 contrast, after adjustment for age, sex, BMI, serum creatinine, hemoglobin, eGFR
250 classification, grip strength classification, and MetS score, the OR of rapid eGFR
251 decline in the MetS-developed group was 1.00 (OR: 1.00; 95% CI: 0.73–1.38, $P =$
252 0.98) when compared with the MetS-free group.

253 **MetS components and rapid eGFR decline odds**

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

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4 260 dyslipidemia, and elevated BG did not show statistically significant differences when
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6 261 compared with the corresponding population (all $P > 0.05$). In the baseline population
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8 262 without MetS, we observed no statistical difference in the rapid decline of eGFR
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10 263 between the occurrence of all MetS component groups and corresponding contrast
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12 264 groups (all $P > 0.05$). This was consistent with the overall trend.

13 14 265 **Discussion**

15
16 266 We examined the relationship between MetS changes and rapid eGFR decline in
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18 267 a large nationwide cohort. At the 4-year follow-up, MetS recovery was significantly
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20 268 associated with a reduced risk of rapid eGFR decline in the middle-aged and elderly,
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22 269 with only WC recovery consistent with the overall trend. The occurrence of MetS and
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24 270 its components did not significantly increase the risk of rapid eGFR decline. Further
25
26 271 follow-up is required to elucidate the relationship between MetS dynamics and the
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28 272 rapid decline in eGFR.

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30 273 Longitudinal cohort studies in several Asian countries concluded that MetS
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32 274 increased the risk of CKD, although follow-up times varied from study to study¹⁵⁻¹⁸
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34 275³⁴. However, the effect of MetS on the rapid decline of eGFR remains controversial.
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36 276 In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and
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38 277 eGFR rapid decline in the elderly³⁴. However, other studies reported that baseline
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40 278 MetS was associated with a decline in eGFR and even acted as an independent
41
42 279 predictor of eGFR decline¹⁶⁻¹⁸. Wu *et al.* investigated the association between the
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44 280 MetS severity score and kidney function, and found that the MetS severity score was
45
46 281 an independent risk factor for the CKD development and progressive eGFR decline,
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48 282 although the definition of rapid eGFR decline was different from this study²⁶. Here,
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50 283 the MetS severity score was a continuous variable that was primarily used to calibrate
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52 284 the MetS (yes vs. no). We noted that none of the aforementioned studies accounted
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54 285 for the MetS status of participants during follow-up periods. In a 4-year follow-up
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56 286 cohort, Park *et al.* explored the relationship between MetS status change and CKD
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58 287 events and concluded that MetS recovery was associated with a decreased risk of
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4 288 CKD incidence, but the occurrence of MetS increased the risk of CKD incidence ³⁵.
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6 289 One of the highlights of the article was to observe the status of MetS three times over
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8 290 a 4-year period, thereby making the MetS diagnosis more robust. However, Park *et al.*
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10 291 did not discuss the association with the rapid eGFR decline. In this study, we
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12 292 concluded that MetS recovery was associated with a reduced risk of rapid eGFR
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14 293 decline, while MetS occurrence was not related to rapid eGFR decline. It should be
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16 294 emphasized that we need to be cautious about the conclusion between the MetS
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18 295 occurrence and the rapid eGFR decline in this study. Because the follow-up time was
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20 296 short and the timing of MetS onset was unknown, the impairment of renal function
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22 297 caused by MetS may not have occurred in some populations. To sum up, studies
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24 298 exploring the relationship between MetS dynamic changes and the rapid decline of
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26 299 eGFR in the Chinese population are rare. Our investigation of the relationship
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28 300 between MetS recovery/occurrence and eGFR rapid decline in a large nationwide
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30 301 cohort may support renal function management in individuals with MetS.

31
32 302 The effect of MetS on renal function is complex, thus, no definitive mechanisms
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34 303 can explain our study observations. The evidence suggests that every component of
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36 304 MetS is associated with adverse renal events (10-14). It is accepted that hypertension
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38 305 and diabetes play pivotal roles in CKD development and progression ³⁶⁻³⁸. Also, lipid
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40 306 metabolism dysregulation and abnormal lipid distribution can lead to
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42 307 lipotoxicity-related renal damage ^{39 40}. Thus, MetS may result from the combined
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44 308 effects of central obesity, increased BP, insulin resistance, and blood lipid disorder,
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46 309 leading to physiopathological lipotoxicity, oxidative stress increments, endothelial
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48 310 dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney
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50 311 dysfunction ^{5 39}. However, the relationship between MetS components and the weight
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52 312 of each factor on kidney injury remain unclear.

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54 313 Our study had some limitations. Firstly, MetS diagnoses were not
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56 314 comprehensively checked (using multiple tests), and the exact timing of the MetS
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58 315 alteration is unknown. Secondly, renal stone disease, epiculopathy, epiculoepicardial
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4 316 disease or acute urinary tract infection are related to the occurrence and development
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6 317 of renal disease. Unfortunately, urine or kidney ultrasound results were unavailable in
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8 318 CHARLS cohort. Thirdly, CKD occurrence was not included as a study outcome
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10 319 because of the lack of urine test results, which would underestimate the CKD
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12 320 incidence. Fourthly, blood analyses from Wave 1 and Wave 3 were performed at a
13
14 321 different testing center, with inconsistent HDL, TG, and BG measurement methods,
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16 322 therefore, measurement errors may have occurred. Fifthly, a large proportion of
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18 323 individuals were excluded due to exclusion criteria or missing values, and the basic
19
20 324 characteristics between the 4142 enrolled participants and 2974 ones that excluded
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22 325 during follow-up might have biased some of our results. Sixthly, we did not establish
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24 326 a model with all 4 MetS change groups included in the study.

26 327 **Conclusions**

28 328 Over a 4-year follow-up, we observed that MetS recovery, including recovery of
29
30 329 central obesity, was associated with a reduced risk of rapid eGFR decline in
31
32 330 middle-aged and older adults, while MetS occurrence was not related to rapid eGFR
33
34 331 decline. Reversing MetS, especially central obesity, might benefit the kidney function
35
36 332 in MetS population. But, further follow-up studies are required to observe the
37
38 333 relationship between MetS alterations and adverse renal events.

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41
42 335 and interpretation of data and preparation of the manuscript. XL—study concept and
43
44 336 design, and preparation and critical review of the manuscript. CC—critical review and
45
46 337 statistical guidance of the revised manuscript. All authors have approved the final
47
48 338 manuscript.

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53
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56 342 Clinical Research on Major Chronic Diseases Based on Data Security
57
58 343 (2018YFC1315403).

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4 344 **Data availability statement** CHARLS data of the study will be available to
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6 345 investigators at the CHARLS website (<http://charls.pku.edu.cn/en>).

7
8 346 **Ethics statement** The Medical Ethics Review Committee of Peking University
9
10 347 approved this study and all participants provided written informed consent before
11
12 348 participating. This study is a secondary analysis of a public dataset and does not
13
14 349 require ethics approval again.

15
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17
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29 **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
<i>M</i> (P25~P75)	(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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3	Hemoglobin (mg/dl)	14.2 (13.1~15.5)	14.0 (12.8~15.1)	14.3 (13.1~15.5)	<0.001
4	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
5	eGFR group				
6					
7	60~89 ml/min/1.73m ² [<i>n</i> (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	0.02
8	90~ ml/min/1.73m ² [<i>n</i> (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
9	Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
10	Grip strength group				
11					
12	T1 [<i>n</i> (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	0.01
13	T2 [<i>n</i> (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	
14	T3 [<i>n</i> (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	
15	Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
16	Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
17	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
18	Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
19	Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
20	Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
21	Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
22	Depression symptom [<i>n</i> (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
23	Self-report hypertension [<i>n</i> (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
24	Self-report dyslipidemia [<i>n</i> (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
25	Self-report diabetes or HBG [<i>n</i> (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
26	Self-report arthritis or rheumatism [<i>n</i> (%)]	1345 (32.5)	235 (33.1)	1110 (32.4)	0.71
27	Antihypertensive therapy [<i>n</i> (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
28	Lipid-lowering therapy [<i>n</i> (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
29	Hypoglycemic therapy [<i>n</i> (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
30	Therapy for arthritis or rheumatism [<i>n</i> (%)]	643 (15.5)	116 (16.3)	527 (15.4)	0.52
31	Metabolic syndrome [<i>n</i> (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
32	MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
33	Metabolic syndrome components				
34	Central obesity [<i>n</i> (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
35	Elevated blood pressure [<i>n</i> (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
36	Dyslipidemia [<i>n</i> (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
37	Elevated blood glucose [<i>n</i> (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
38	Baseline non-MetS group				
39	MetS-free [<i>n</i> (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
40	MetS-developed [<i>n</i> (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
41	Baseline Mets group				
42	MetS-recovery [<i>n</i> (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
43	MetS-chronic [<i>n</i> (%)]	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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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.

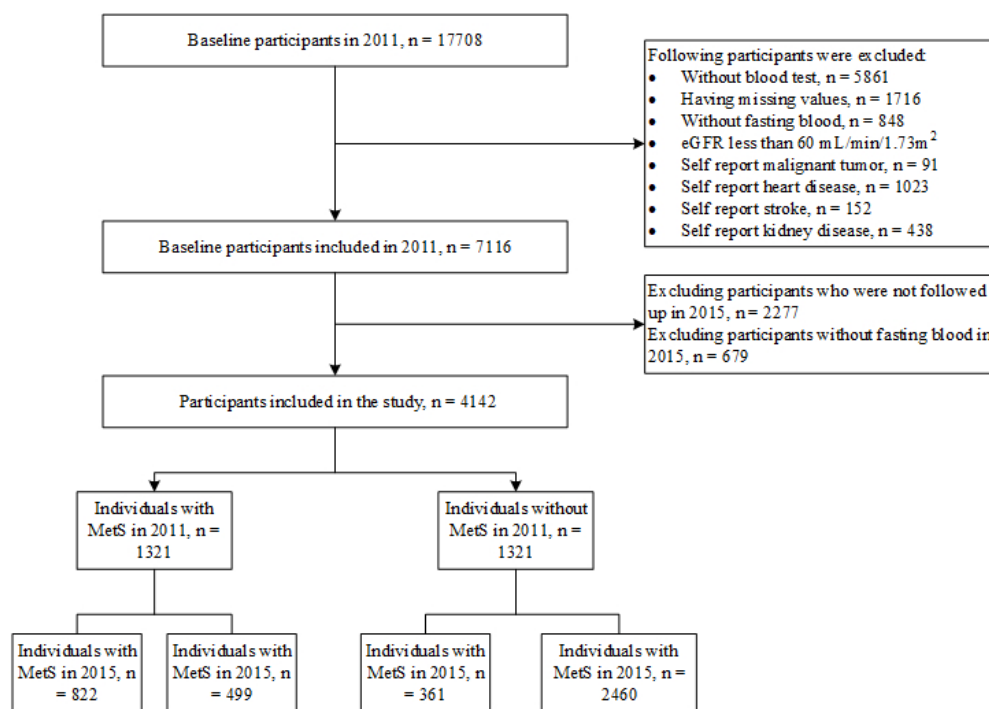
Each Mets components run in their own model to predict rapid eGFR decline

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

488 Supplementary file

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

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



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

193x135mm (96 x 96 DPI)

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4 **Association between recovery/occurrence of metabolic syndrome and rapid estimated**
5 **glomerular filtration rate decline in middle-aged and older populations: evidence from**
6
7 **the China Health and Retirement Longitudinal Study**

8
9 **Peijia Liu,^{1,2} Leile Tang,³ Jia fang,¹ Chaojin Chen,^{4*} Xun Liu^{1*}**

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

Characteristics	participants included			P-value
	in baseline (n=7116)	group 1 (n=2974)	group 2 (n=4142)	
Age (years)	58 (52~65)	58 (52~64)	58 (51~66)	0.98
Male [<i>n</i> (%)]	3332 (46.8)	1458 (49.0)	1874 (45.2)	0.002
Married with spouse [<i>n</i> (%)]	5977 (84.0)	2974 (81.7)	3548 (87.5)	<0.001
Education				0.07
Illiterate [<i>n</i> (%)]	2106 (29.6)	900 (30.3)	1206 (29.1)	
Middle school and below [<i>n</i> (%)]	2853 (40.1)	1146 (38.5)	1770 (41.2)	
High school and above [<i>n</i> (%)]	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 [<i>n</i> (%)]	2461 (34.6)	1054 (35.4)	1470 (32.2)	0.20
Smoke [<i>n</i> (%)]	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 [<i>n</i> (%)]	3172 (44.6)	1268 (42.6)	1904 (46.0)	0.005
Metabolic syndrome [<i>n</i> (%)]	2228 (31.3)	907 (30.5)	1321 (31.9)	0.21
Metabolic syndrome components				
Elevated blood pressure [<i>n</i> (%)]	3622 (50.9)	1523 (51.2)	2099 (50.7)	0.66
Elevated blood glucose [<i>n</i> (%)]	4179 (58.7)	1723 (57.9)	2456 (59.3)	0.25
Dyslipidemia [<i>n</i> (%)]	2673 (37.6)	1078 (36.2)	1595 (38.5)	0.052
Central obesity [<i>n</i> (%)]	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.

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 [<i>n</i> (%)]			
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 [<i>n</i> (%)]			
Smoke [<i>n</i> (%)]	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 [<i>n</i> (%)]	ref	ref	
90~ ml/min/1.73m ² [<i>n</i> (%)]	0.203	0.026~0.379	0.02
Grip strength (kg)	0.004	-0.005~0.012	0.38
Grip strength group			
T1 [<i>n</i> (%)]	ref	ref	
T2 [<i>n</i> (%)]	0.311	0.112~0.511	<0.01
T3 [<i>n</i> (%)]	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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3	Diastolic blood pressure (mmHg)	-0.001	-0.008~0.005	0.76
4	Mean arterial pressure (mmHg)	0.001	-0.005~0.007	0.75
5	Depression symptom [<i>n</i> (%)]	-0.054	-0.216~0.109	0.52
6	Self-report hypertension [<i>n</i> (%)]	0.047	-0.148~0.243	0.63
7	Self-report dyslipidemia [<i>n</i> (%)]	0.019	-0.276~0.315	0.90
8	Self-report diabetes or HBG [<i>n</i> (%)]	-0.196	-0.065~0.213	0.35
9	Self-report arthritis or rheumatism [<i>n</i> (%)]	-0.032	-0.204~0.140	0.71
10	Antihypertensive therapy [<i>n</i> (%)]	0.062	-0.155~0.280	0.57
11	Lipid-lowering therapy [<i>n</i> (%)]	0.183	-0.186~0.552	0.33
12	Hypoglycemic therapy [<i>n</i> (%)]	-0.169	-0.663~0.326	0.50
13	Therapy for arthritis or rheumatism [<i>n</i> (%)]	0.072	-0.148~0.291	0.52
14	Metabolic syndrome [<i>n</i> (%)]	-0.158	-0.334~0.019	0.08
15	MetS scores	-0.138	-0.279~0.003	0.055
16	Metabolic syndrome components			
17	Central obesity [<i>n</i> (%)]	-0.229	-0.395~-0.062	0.01
18	Elevated blood pressure [<i>n</i> (%)]	0.052	-0.109~0.214	0.53
19	Dyslipidemia [<i>n</i> (%)]	0.030	-0.135~0.196	0.72
20	Elevated blood glucose [<i>n</i> (%)]	-0.268	-0.431~0.105	0.001

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

23 estimated glomerular filtration rate; MetS: metabolic syndrome.

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

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) <i>Cohort study</i> —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) <i>Cohort study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	10*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —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
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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
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23 *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.

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26 **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

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

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4 27 **Abstract**

5
6 28 **Objectives** Few studies have explored correlations between metabolic syndrome
7
8 29 (MetS) alterations and renal deterioration in longitudinal cohorts. We aim to
9
10 30 investigate associations between MetS recovery/development and rapid estimated
11
12 31 glomerular filtration rate (eGFR) decline in the China Health and Retirement
13
14 32 Longitudinal Study (CHARLS).

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16 33 **Design** Longitudinal cohort study.

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18 34 **Setting** This study is a secondary analysis of CHARLS.

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20 35 **Participants** After excluding individuals with age < 45 years old, eGFR < 60
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22 36 ml/min/1.73m² and clinician-reported malignant tumor, heart disease, stroke or kidney
23
24 37 disease at baseline, 4142 participants with complete data were selected from the
25
26 38 CHARLS during the 4-year follow-up period (2011-2015).

27
28 39 **Outcome measures** MetS were measured at 2011 and 2015 in CHARLS. A rapid
29
30 40 eGFR decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m².
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32 41 The associations between rapid eGFR decline and MetS recovery/development were
33
34 42 analyzed using multivariable adjusted logistic models.

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36 43 **Results** According to MetS baseline status and follow-up, participants were divided
37
38 44 into four groups: (1) 2460 (59.4%) in the MetS-free group, (2) 361 (8.7%) in the
39
40 45 MetS-developed group, (3) 499 (12.0%) in the MetS recovery-group, and (4) 822
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42 46 (19.8%) in the MetS-chronic group. When compared with the MetS-chronic group,
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44 47 the multivariable adjusted odds ratio (OR) of rapid eGFR decline in the
45
46 48 MetS-recovery group was 0.64 (OR: 0.64; 95% confidence interval (CI): 0.45–0.90, *P*
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48 49 = 0.01). In contrast, when compared with the MetS-free group, the multivariable
49
50 50 adjusted OR of rapid eGFR decline in the MetS-developed group was 1.00 (OR: 1.00;
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52 51 95% CI: 0.73–1.38, *P* = 0.98).

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54 52 **Conclusions** Over the 4-year follow-up period, we found that MetS recovery was
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56 53 associated with a reduced risk of rapid eGFR decline in middle-aged and older adults,
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58 54 while MetS occurrence was not related to rapid eGFR decline. Recovery from MetS
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4 55 appeared to protect against a rapid decline in eGFR.

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6 56 **Keywords:** chronic renal failure; lipid disorders; public health;

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10 58 **Strength**

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12 59 A high-quality data from a nationally representative longitudinal cohort was applied
13
14 60 to confirm the association between altered metabolic syndrome status and rapid
15
16 61 glomerular filtration rate decline.

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18 62 The metabolic syndrome scores calculated by principal component analysis was
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20 63 applied for model calibration in the study.

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22 64 **Limitation**

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24 65 Some participants were missing during the follow-up, which biased the results of the
25
26 66 study.

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28 67 Blood tests related to metabolic syndrome and serum creatinine were performed only
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30 68 once, resulting in data inaccuracy.

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32 69 The unavailability of urine tests and kidney imaging prevented the analysis of the
33
34 70 association between metabolic syndrome status and chronic kidney disease.
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71 **Introduction**

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

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

93 The China Health and Retirement Longitudinal Study (CHARLS) is a prospective
94 cohort study conducted by the National School of Development, Peking University,
95 China ¹⁹. The nationwide sample assesses the social, behavioral, and health status of
96 individuals aged 45 and older ¹⁹. The CHARLS baseline survey was implemented in
97 2011 (Wave 1), and the samples were followed up every two years. Blood samples
98 from populations were only collected in 2011 (Wave1) and 2015 (Wave 3). In the
99 current study, we explored the relationship between MetS recovery/occurrence and

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

102 **Methods**

103 **Study population**

104 CHARLS is a nationally representative longitudinal survey on the social,
105 economic, and health status of Chinese citizens aged ≥ 45 and their spouses in the
106 community¹⁹. In total, 17,708 participants were registered at baseline (Wave 1 at
107 2011), of which 11,847 had blood sample tests.

108 In this study, our exclusion criteria excluded participants with the following: 1)
109 missing values; 2) without fasting blood values; 3) baseline eGFR < 60
110 ml/min/1.73m²; 4) clinician-reported malignant tumor, heart disease, stroke or kidney
111 disease; 5) < 45 years old; and 6) no follow-up records and related blood
112 examinations in Wave 3 at 2015. After applying these criteria, 4142 participants were
113 finally included. The participant screening process is outlined (Fig. 1).

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

117 **Blood examinations**

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

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4 128 UA plus method ²⁰. Blood specimen testing in 2015 (Wave 3) was completed by
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6 129 KingMed Diagnostics, the leading third-party institution in China, which has testing
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8 130 laboratories in 27 provincial-level cities nationwide. GHbA1c, Scr, HDL, TG and BG
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10 131 were the required blood biomarkers from Wave 3. GHbA1c and Scr levels were
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12 132 determined by the same methods as Wave 1, while HDL was determined by a direct
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14 133 method, TG by an oxidase method, and BG by a hexokinase method ²¹. The
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16 134 collection, storage, transport, processing, and other blood sample details are described
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18 135 elsewhere ^{20 21}. Of note, the models and manufacturer information of blood test
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20 136 instruments in Wave 1 and Wave 3 were not available. All inspections and
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22 137 calibrations were performed by trained personnel.

138 **Definition and grouping of MetS**

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

156 treated; and 4) Elevated BG: Fasting BG (FBG) \geq 100 mg/dL, or 2 h postprandial BG
 157 \geq 100 mg/dL, or diagnosed as diabetes and treated². Diabetes was defined as fasting
 158 BG \geq 126 mg/dL, and/or HbA1c \geq 6.5%, and/or a self-reported history of diabetes²³.
 159 Of note, we did not have 2 h postprandial BG data.

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

163 **Study outcomes**

164 We calculated eGFR values using the 2012 Chronic Kidney Disease
 165 Epidemiology Collaboration equation based on creatinine levels²⁴. A rapid eGFR
 166 decline was defined as an average annual eGFR decline of > 3 ml/min/1.73m²^{16 25}. In
 167 this study, we defined a rapid eGFR decline as the eGFR in Wave 3 minus the eGFR
 168 in Wave 1, > 12 ml/min/1.73m².

169 **MetS scores**

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

$$181 \quad PC1 = 0.369 \times WC + 0.378 \times FBG + 0.585 \times TG + 0.562 \times \left(\frac{1}{HDL}\right) + 0.252 \times MAP,$$

$$182 \quad PC2 = 0.503 \times WC - 0.171 \times FBG - 0.268 \times TG - 0.274 \times \left(\frac{1}{HDL}\right) + 0.755 \times MAP,$$

$$183 \quad \text{MetS score} = 0.389 \times PC1 + 0.209 \times PC2$$

184 **Other covariates**

185 All potential covariates were all collected at baseline in Wave 1, including gender
186 (male vs. female), age, marital status (married with spouse vs. others), education
187 (illiterate, middle school and below, or high school and above), household per capita
188 income, smoking (yes vs. no), drinking (yes vs. no), eGFR, grip strength, height,
189 weight, body mass index (BMI), WC, SBP, DBP, MAP, depressive symptom (yes vs.
190 no), self-reporting disease (hypertension, diabetes, dyslipidemia and), and
191 corresponding medication. We categorized eGFR into two groups: 60–89 and ≥ 90 .
192 Grip strength was divided into three groups (T1, T2, and T3) according to the
193 one-third percentile. BMI was calculated by weight (kg)/height squared (m^2). The BP
194 of each participant was measured three times every 45–60 s with the OmronTM
195 HEM-7112 sphygmomanometer (Omron Co. LTD, Dalian, China) at rest. Both SBP
196 and DBP were averaged from three measurements. MAP was defined as $MAP = 1/3 \times$
197 $SBP + 2/3 \times DBP$. Previous study demonstrated that depressive symptom was
198 association with baseline eGFR²⁸. Thus, we should not overlook this variable. The
199 10-item Center for Epidemiological Studies Depression Scale (CESD-10) was applied
200 in the study²⁹. A CESD-10 score ≥ 10 was grouped into the depressive symptom
201 group, and < 10 into the non-depressive symptom group. Self-reporting disease was
202 disease diagnosed by a doctor. Medical interventions included taking Chinese
203 traditional and Western modern medicines.

204 **Statistical methods**

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

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4 212 conversion value of the dependent variable were converted to categorical variables.
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6 213 Tolerance and variance inflation factors (VIFs) were used to test for collinearity. This
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8 214 existed if the tolerance was < 0.1 or the VIF was > 10 . Eventually, age, sex, BMI, Scr,
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10 215 hemoglobin, eGFR classification, grip strength classification and MetS scores were
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12 216 selected as confounding variables for model adjustments in this study. Most selected
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14 217 covariates have been reported to be related to renal events^{26 30-33}. Univariate analysis
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16 218 of variables between eGFR decline group and non-rapid eGFR decline group were
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18 219 carried out. Logistic models were used to test the association between MetS
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20 220 recovery/occurrence and eGFR rapid decline after adjusting for multiple confounding
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22 221 factors. Furthermore, alterations in MetS status were accompanied by changes of
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24 222 diagnostic conditions (elevated blood glucose, elevated blood pressure, central obesity
25
26 223 and dyslipidemia). As a result, logistic models were used to explore the relationship
27
28 224 between the recovery/occurrence of MetS components and the rapid decline of eGFR
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30 225 using different adjustments of confounding factors, respectively. $P < 0.05$ was
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32 226 considered statistically significant (two-sided test). Statistics were generated in IBM
33
34 227 SPSS 20.0 software (IBM Corp, Armonk, NY, USA) and StataMP 16 software
35
36 228 (StataCorp, Texas, USA).

38 229 **Patient and public involvement**

40 230 There were no participants involved in the development. The results of the
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42 231 survey are disseminated to the public through websites.
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46 233 **Results**

48 234 **Participant characteristics**

50 235 As shown (Fig. 1), 4142 participants were selected, including 2460 (59.4%) in the
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52 236 MetS-free group, 361 (8.7%) in the MetS-developed group, 499 (12.0%) in the MetS
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54 237 recovery-group, and 822 (19.8%) in the MetS-chronic group. Comparison of the basic
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56 238 characteristics between the 4142 enrolled participants and 2974 ones that excluded
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58 239 during follow-up were shown in Supplemental Table 1.
60

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

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

270 **Discussion**

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

278 Longitudinal cohort studies in several Asian countries concluded that MetS
279 increased the risk of CKD, although follow-up times varied from study to study¹⁵⁻¹⁸
280³⁴. However, the effect of MetS on the rapid decline of eGFR remains controversial.
281 In a 3-year cohort, Cheng *et al.* found no significant correlations between MetS and
282 eGFR rapid decline in the elderly³⁴. However, other studies reported that baseline
283 MetS was associated with a decline in eGFR and even acted as an independent
284 predictor of eGFR decline¹⁶⁻¹⁸. Wu *et al.* investigated the association between the
285 MetS severity score and kidney function, and found that the MetS severity score was
286 an independent risk factor for the CKD development and progressive eGFR decline,
287 although the definition of rapid eGFR decline was different from this study²⁶. Here,
288 the MetS severity score was a continuous variable that was primarily used to calibrate
289 the MetS (yes vs. no). We noted that none of the aforementioned studies accounted
290 for the MetS status of participants during follow-up periods. In a 4-year follow-up
291 cohort, Park *et al.* explored the relationship between MetS status change and CKD
292 events and concluded that MetS recovery was associated with a decreased risk of
293 CKD incidence, but the occurrence of MetS increased the risk of CKD incidence³⁵.
294 One of the highlights of the article was to observe the status of MetS three times over
295 a 4-year period, thereby making the MetS diagnosis more robust. However, Park *et al.*

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4 296 did not discuss the association with the rapid eGFR decline. In this study, we
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6 297 concluded that MetS recovery was associated with a reduced risk of rapid eGFR
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8 298 decline, while MetS occurrence was not related to rapid eGFR decline. It should be
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10 299 emphasized that we need to be cautious about the conclusion between the MetS
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12 300 occurrence and the rapid eGFR decline in this study. Because the follow-up time was
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14 301 short and the timing of MetS onset was unknown, the impairment of renal function
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16 302 caused by MetS may not have occurred in some populations. To sum up, studies
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18 303 exploring the relationship between MetS dynamic changes and the rapid decline of
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20 304 eGFR in the Chinese population are rare. Our investigation of the relationship
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22 305 between MetS recovery/occurrence and eGFR rapid decline in a large nationwide
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24 306 cohort may support renal function management in individuals with MetS.

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26 307 The effect of MetS on renal function is complex, thus, no definitive mechanisms
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28 308 can explain our study observations. The evidence suggests that every component of
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30 309 MetS is associated with adverse renal events (10-14). It is accepted that hypertension
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32 310 and diabetes play pivotal roles in CKD development and progression³⁶⁻³⁸. Also, lipid
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34 311 metabolism dysregulation and abnormal lipid distribution can lead to
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36 312 lipotoxicity-related renal damage^{39 40}. Thus, MetS may result from the combined
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38 313 effects of central obesity, increased BP, insulin resistance, and blood lipid disorder,
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40 314 leading to physiopathological lipotoxicity, oxidative stress increments, endothelial
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42 315 dysfunction, elevated inflammation, and apoptosis, which would contribute to kidney
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44 316 dysfunction^{5 39}. However, the relationship between MetS components and the weight
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46 317 of each factor on kidney injury remain unclear.

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48 318 Our study had some limitations. Firstly, MetS diagnoses were not
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50 319 comprehensively checked (using multiple tests), and the exact timing of the MetS
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52 320 alteration is unknown. Secondly, renal stone disease, epiculopathy, epiculoepicardial
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54 321 disease or acute urinary tract infection are related to the occurrence and development
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56 322 of renal disease. Unfortunately, urine or kidney ultrasound results were unavailable in
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58 323 CHARLS cohort. Thirdly, CKD occurrence was not included as a study outcome
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4 324 because of the lack of urine test results, which would underestimate the CKD
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6 325 incidence. Fourthly, blood analyses from Wave 1 and Wave 3 were performed at a
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8 326 different testing center, with inconsistent HDL, TG, and BG measurement methods,
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10 327 therefore, measurement errors may have occurred. Fifthly, a large proportion of
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12 328 individuals were excluded due to exclusion criteria or missing values, and the basic
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14 329 characteristics between the 4142 enrolled participants and 2974 ones that excluded
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16 330 during follow-up might have biased some of our results. Sixthly, we did not establish
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18 331 a model with all 4 MetS change groups included in the study.

332 **Conclusions**

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

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340 and interpretation of data and preparation of the manuscript. XL—study concept and
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349 **Data availability statement** CHARLS data of the study will be available to
350 investigators at the CHARLS website (<http://charls.pku.edu.cn/en>).

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4 351 **Ethics statement** The Medical Ethics Review Committee of Peking University
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6 352 approved this study and all participants provided written informed consent before
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8 353 participating. This study is a secondary analysis of a public dataset and does not
9
10 354 require ethics approval again.

11
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25 **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 (P25~P75)	(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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3	60~89 ml/min/1.73m ² [<i>n</i> (%)]	1368 (33.0)	209 (29.4)	1158 (33.8)	
4	90~ ml/min/1.73m ² [<i>n</i> (%)]	2774 (67.0)	502 (70.6)	2272 (66.2)	
5	Grip strength (kg)	29.3 (23.8~36.5)	29.5 (24.9~36.2)	29.3 (23.5~36.7)	0.13
6	Grip strength group				
7					
8	T1 [<i>n</i> (%)]	1386 (33.5)	209 (29.4)	1177 (34.3)	
9	T2 [<i>n</i> (%)]	1387 (33.5)	268 (37.7)	1199 (32.6)	0.01
10	T3 [<i>n</i> (%)]	1369 (33.1)	234 (32.9)	1135 (33.1)	
11					
12	Height (cm)	157.7 (152.0~163.8)	157.9 (152.0~163.7)	157.6 (152.0~163.9)	0.64
13	Weight (kg)	58 (51.3~65.5)	57.1 (50.8~65.1)	58.2 (51.4~65.7)	0.08
14	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
15	Waist circumference (cm)	84.4 (78.0~92.0)	83.6 (77.0~90.2)	84.8 (78.1~92.0)	<0.01
16	Systolic blood pressure (mmHg)	127 (114~141)	128 (114~142)	127 (114~141)	0.72
17	Diastolic blood pressure (mmHg)	75 (67~83)	74 (66~83)	75 (67~83)	0.41
18	Mean arterial pressure (mmHg)	92 (83~102)	92 (83~103)	92 (84~102)	0.76
19	Depression symptom [<i>n</i> (%)]	1904 (46.0)	319 (44.9)	1585 (46.2)	0.52
20	Self-report hypertension [<i>n</i> (%)]	887 (21.4)	157 (22.1)	730 (21.3)	0.63
21	Self-report dyslipidemia [<i>n</i> (%)]	333 (8.0)	58 (8.2)	275 (8.0)	0.90
22	Self-report diabetes or HBG [<i>n</i> (%)]	191 (4.6)	28 (3.9)	163 (4.8)	0.35
23	Self-report arthritis or rheumatism [<i>n</i> (%)]	1345 (32.5)	235 (33.1)	1110 (32.4)	0.71
24	Antihypertensive therapy [<i>n</i> (%)]	664 (16.0)	119 (16.7)	545 (19.5)	0.57
25	Lipid-lowering therapy [<i>n</i> (%)]	187 (4.5)	37 (5.2)	150 (4.4)	0.33
26	Hypoglycemic therapy [<i>n</i> (%)]	127 (3.1)	19 (2.7)	108 (3.1)	0.50
27	Therapy for arthritis or rheumatism [<i>n</i> (%)]	643 (15.5)	116 (16.3)	527 (15.4)	0.52
28	Metabolic syndrome [<i>n</i> (%)]	1321 (31.9)	207 (29.1)	1114 (32.5)	0.08
29	MetS scores	-0.1 (-0.4~0.3)	-0.1 (-0.5~0.3)	0 (-0.4~0.3)	0.02
30	Metabolic syndrome components				
31	Central obesity [<i>n</i> (%)]	1726 (41.7)	264 (37.1)	1462 (42.6)	<0.01
32	Elevated blood pressure [<i>n</i> (%)]	2099 (50.7)	368 (51.8)	1731 (50.5)	0.52
33	Dyslipidemia [<i>n</i> (%)]	1595 (38.5)	278 (39.1)	1317 (38.4)	0.72
34	Elevated blood glucose [<i>n</i> (%)]	2456 (59.3)	383 (53.9)	2073 (60.4)	<0.01
35	Baseline non-MetS group				
36	MetS-free [<i>n</i> (%)]	2460 (59.4)	444 (62.4)	2016 (58.8)	
37	MetS-developed [<i>n</i> (%)]	361 (8.7)	60 (8.4)	301 (8.8)	
38	Baseline MetS group				
39	MetS-recovery [<i>n</i> (%)]	499 (12.0)	64 (9.0)	435 (12.7)	
40	MetS-chronic [<i>n</i> (%)]	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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> 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

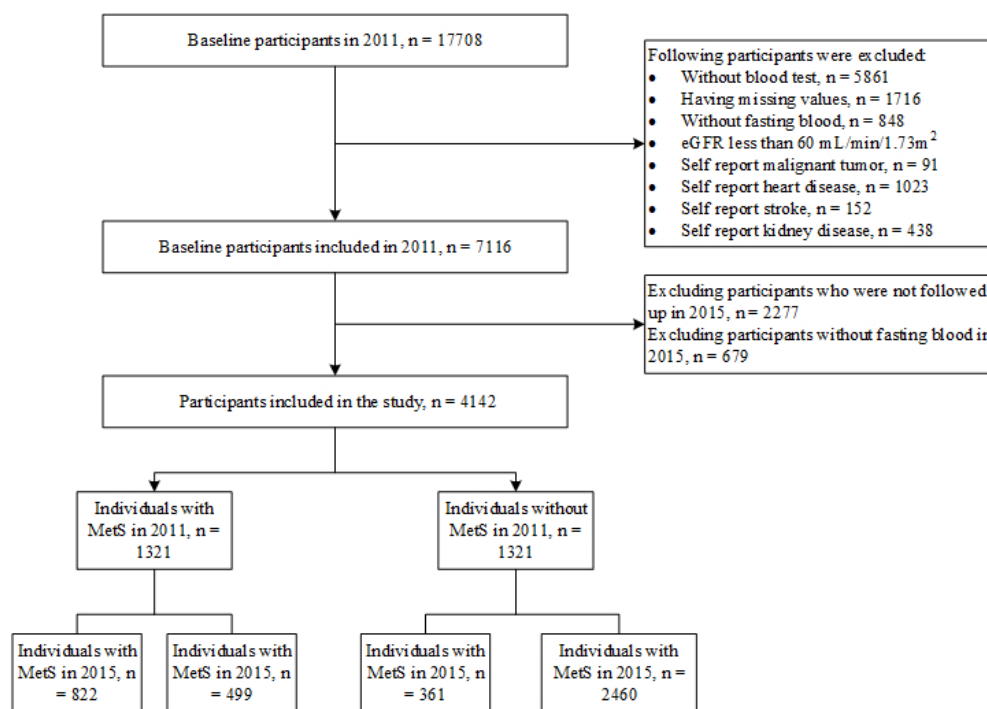
491 Figure 1. Flowchart of participants selection. eGFR: estimated glomerular filtration
492 rate; MetS: metabolic syndrome

493 Supplementary file

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

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

For peer review only



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

193x135mm (96 x 96 DPI)

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4 **Association between recovery/occurrence of metabolic syndrome and rapid estimated**
5 **glomerular filtration rate decline in middle-aged and older populations: evidence from**
6
7 **the China Health and Retirement Longitudinal Study**

8
9 **Peijia Liu,^{1,2} Leile Tang,³ Jia fang,¹ Chaojin Chen,^{4*} Xun Liu^{1*}**

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

Characteristics	participants included			P-value
	in baseline (n=7116)	group 1 (n=2974)	group 2 (n=4142)	
Age (years)	58 (52~65)	58 (52~64)	58 (51~66)	0.98
Male [<i>n</i> (%)]	3332 (46.8)	1458 (49.0)	1874 (45.2)	0.002
Married with spouse [<i>n</i> (%)]	5977 (84.0)	2974 (81.7)	3548 (87.5)	<0.001
Education				0.07
Illiterate [<i>n</i> (%)]	2106 (29.6)	900 (30.3)	1206 (29.1)	
Middle school and below [<i>n</i> (%)]	2853 (40.1)	1146 (38.5)	1770 (41.2)	
High school and above [<i>n</i> (%)]	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 [<i>n</i> (%)]	2461 (34.6)	1054 (35.4)	1470 (32.2)	0.20
Smoke [<i>n</i> (%)]	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 [<i>n</i> (%)]	3172 (44.6)	1268 (42.6)	1904 (46.0)	0.005
Metabolic syndrome [<i>n</i> (%)]	2228 (31.3)	907 (30.5)	1321 (31.9)	0.21
Metabolic syndrome components				
Elevated blood pressure [<i>n</i> (%)]	3622 (50.9)	1523 (51.2)	2099 (50.7)	0.66
Elevated blood glucose [<i>n</i> (%)]	4179 (58.7)	1723 (57.9)	2456 (59.3)	0.25
Dyslipidemia [<i>n</i> (%)]	2673 (37.6)	1078 (36.2)	1595 (38.5)	0.052
Central obesity [<i>n</i> (%)]	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.

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 [<i>n</i> (%)]			
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 [<i>n</i> (%)]			
Smoke [<i>n</i> (%)]	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 [<i>n</i> (%)]	ref	ref	
90~ ml/min/1.73m ² [<i>n</i> (%)]	0.203	0.026~0.379	0.02
Grip strength (kg)	0.004	-0.005~0.012	0.38
Grip strength group			
T1 [<i>n</i> (%)]	ref	ref	
T2 [<i>n</i> (%)]	0.311	0.112~0.511	<0.01
T3 [<i>n</i> (%)]	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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3	Diastolic blood pressure (mmHg)	-0.001	-0.008~0.005	0.76
4	Mean arterial pressure (mmHg)	0.001	-0.005~0.007	0.75
5	Depression symptom [<i>n</i> (%)]	-0.054	-0.216~0.109	0.52
6	Self-report hypertension [<i>n</i> (%)]	0.047	-0.148~0.243	0.63
7	Self-report dyslipidemia [<i>n</i> (%)]	0.019	-0.276~0.315	0.90
8	Self-report diabetes or HbG [<i>n</i> (%)]	-0.196	-0.065~0.213	0.35
9	Self-report arthritis or rheumatism [<i>n</i> (%)]	-0.032	-0.204~0.140	0.71
10	Antihypertensive therapy [<i>n</i> (%)]	0.062	-0.155~0.280	0.57
11	Lipid-lowering therapy [<i>n</i> (%)]	0.183	-0.186~0.552	0.33
12	Hypoglycemic therapy [<i>n</i> (%)]	-0.169	-0.663~0.326	0.50
13	Therapy for arthritis or rheumatism [<i>n</i> (%)]	0.072	-0.148~0.291	0.52
14	Metabolic syndrome [<i>n</i> (%)]	-0.158	-0.334~0.019	0.08
15	MetS scores	-0.138	-0.279~0.003	0.055
16	Metabolic syndrome components			
17	Central obesity [<i>n</i> (%)]	-0.229	-0.395~0.062	0.01
18	Elevated blood pressure [<i>n</i> (%)]	0.052	-0.109~0.214	0.53
19	Dyslipidemia [<i>n</i> (%)]	0.030	-0.135~0.196	0.72
20	Elevated blood glucose [<i>n</i> (%)]	-0.268	-0.431~0.105	0.001

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

23 estimated glomerular filtration rate; MetS: metabolic syndrome.

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

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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P5L107-112
		<i>Case-control study</i> —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	
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	-
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-8L138-201
Bias	9	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
Study size	10	Describe any efforts to address potential sources of bias	-
Quantitative variables	11	Explain how the study size was arrived at	P5L112
Statistical methods	12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-
		(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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	-
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	-
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	-
		(e) Describe any sensitivity analyses	-

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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	P9-10L238-240
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	P9-10L238-240
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	-
		<i>Cross-sectional study</i> —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.