Doctoral Dissertation

Usefulness of Handgrip Strength as a Predictor of Incident Chronic Kidney Disease According to Gender: A Cohort Study in Koreans

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Directed by Jong-Koo Kim

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ABSTRACT

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Handgrip strength (HGS) can indicate a number of diseases including cancer, cardiovascular disease, and pneumonia. In patients with chronic kidney disease (CKD), HGS can also predict renal function; however, it is unclear how useful HGS is as an indicator of incident CKD.

A cohort of 173,195 participants was recruited nationwide and monitored for 4.1 years. Following exclusions, 35,637 subjects were still left in the final trial, and 1062 of them occurred CKD throughout the follow-up period. Laboratory, anthropometric, and lifestyle data were assessed to the risk of CKD.

Relative handgrip strength (RGS) was used to divide the subjects into quartiles. The results of cox regression showed a negative relationship between RGS and new-onset CKD. After controlling for variables, the hazard ratios (HRs) [95% confidence intervals (CIs)] for new-onset CKD for the highest quartile (Q4) were 0.62 (0.45 – 0.86) in men compared with the lowest quartile, 1.03 (0.69 – 1.56) in pre-menopause women, and 0.92 (0.69 – 1.24) in post-menopause women. The incidence of CKD decreased as RGS increased. The baseline RGS provided predictive power for incident CKD according to the receiver operating characteristic (ROC) curve. Area under the curve (AUC) (95% CIs) for men, pre-menopausal women, and post-menopausal women were 0.597 (0.571 – 0.623), 0.506 (0.468 – 0.545) and 0.541 (0.513 – 0.568). Kaplan Meier curve found that

trends in the difference for cumulative incidence of CKD according to baseline RSG quartiles remained unchanged in men and post-menopause women during follow-up time.

This is the first study to show a link between RGS and CKD incidence in both genders. In men compared to women, RGS and CKD incidence are strongly correlated. RGS can be utilized to assess renal prognosis in clinical settings. It is crucial to assess handgrip strength on a regular basis, particularly in men, in order to detect CKD.

Keywords: Handgrip strength, Sarcopenia, Renal function, Chronic Kidney Disease, Gender difference

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I. INTRODUCTION

1. Background

The number of cases of CKD has increased in recent decades. 13.4% is the global all-stage mean prevalence of CKD (1). Additionally, diabetes, metabolic syndrome, and hypertension, all of which increase the risk of cardiovascular diseases (CVDs), can be made worse by chronic kidney disease (CKD) (2, 3). Moreover, several studies have discovered links between various comorbidities with CKD including end-stage renal disease (ESRD) (4).

To stop CKD from progressing to ESRD, which can cause a number of problems such as malnourishment, anemia, acidosis, and bone metabolism disorders, prediction and early identification of CKD are crucial (5). However, there is frequently little personal willingness to prevent the onset and progression of CKD. Moreover, early CKD is frequently misdiagnosed as there aren't any clinical indications or symptoms. Just 8% of CKD patients in the Third National Health and Nutrition Survey (NHANES III) knew what their CKD diagnosis meant (6).

Sarcopenia is a generalized disease that is defined by a loss of muscle mass and strength. It is a major global public health concern. Estimates put the prevalence of

sarcopenia worldwide at 10% (7). Various comorbidities including pneumonia, falls, cardiovascular disease, and cancer, are linked to sarcopenia (8-10). This makes it crucial to diagnose sarcopenia as soon as possible. One practical and affordable way to assess muscle strength and identify sarcopenia is by measuring handgrip strength (11). In the past, handgrip strength has been used to predict non-alcoholic fatty liver disease (12, 13). According to recent research, body mass index (BMI)-adjusted RGS is a more meaningful measure than handgrip strength alone (14). As a result, the final index in this investigation was RGS, absolute HGS divided by BMI (14).

2. Research purpose

Handgrip strength and CKD have previously been linked in a number of research; however, these investigations are cross-sectional, which shows there are no studies to date on whether handgrip strength can be utilized as an indicator of chronic kidney disease (15, 16). Using nationwide cohort data, we examined the relationship between RGS and CKD in Korean adults and evaluated the usefulness of RGS as an indicator of incident CKD by excluding baseline CKD from the data. We also analysed the group by subdividing the total group with and without diabetes respectively because diabetes is an essential risk factor for CKD. Furthermore, we investigated whether handgrip strength could be used as a tool to assess renal

function in patients with chronic kidney disease.

II. METHODS AND MATERIALS

1. Study population

Data from the Korean Genome and Epidemiology Study (KoGES) of the general Korean population was used in the cohort study. The KoGES data contain three studies: the KoGES_cardiovascular disease association study (CAVAS), the KoGES_health examinee (HEXA) study, and the KoGES_Ansan-Ansung study. We utilized the KoGES HEXA study, which included individuals recruited from various clinics with a baseline age of at least 40 years. In order to assess lifestyle and environmental factors for the prevalence and incidence of chronic diseases (such as CKD, osteoporosis, hypertension, diabetes mellitus, metabolic syndrome, and obesity), a population-based prospective cohort study was carried out. The KoGES study design and data have been thoroughly detailed (17).

173,195 men and women between the ages of 40 and 80 took part in the baseline HEXA study, which was carried out between 2004 and 2013 at 38 health centers around the country. A 2007 – 2016 follow-up study was performed. The following individuals were not included in the baseline study: (1) lost to follow-up, (2) absent from HGS data, (3) missing laboratory data, or (4) diagnosed with CKD at the time

of the baseline study (Figure 1).

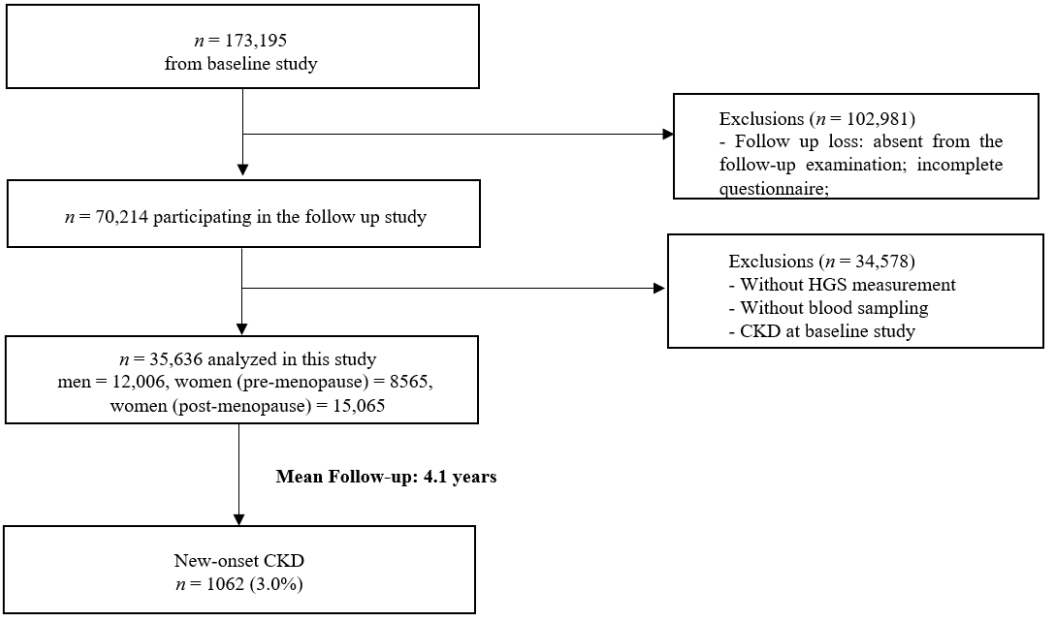


Figure 1. Diagram showing the research that fulfills the inclusion and exclusion criteria

The Institutional Review Board (IRB) of Yonsei University Wonju College of Medicine authorized the study protocol (IRB No. CR322322). This research was carried out in accordance with the Helsinki Declaration. Every participant gave their informed consent, and all data were anonymized.

2. Measurement of handgrip strength

A digital grip strength dynamometer (T.K.K.5401, TAKEI Scientific Instruments Co., Ltd., Nigata, Japan) was used to measure handgrip strength twice, with a one-minute rest interval in between (18). The dynamometer was to be squeezed by the participants as hard as they could. Once the grip was held at 15º from hip flexion, each HGS was evaluated. The maximum value from both hands was the definition of absolute HGS, which was expressed in kilograms (14). Relative handgrip strength (RGS) was applied to normalize the effect of body size on HGS. The absolute HGS divided by the BMI was the definition of RGS, which formally served as a muscular strength measure (14). The RGS data were split into quartiles according to gender.

3. General information, laboratory and anthropometric measurements

All of the subjects had their anthropometric, demographic, lifestyle, and laboratory data collected. Gender, age, waist circumference (WC), BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were among the anthropometric data. During expiration, WC was measured with a flexible tape (Seca 220; Seca) at the midpoint between the uppermost border of the iliac crest and the lowest margin

of the ribs (19). Weight divided by height squared (kg/m^2) was used to compute the BMI. A mercury sphygmomanometer was used to measure the subjects' blood pressure (BP) following a five-minute rest period while seated (Baumanometer Wall Unit 33 (0850)). The identical device was used to perform each blood pressure check twice on the right arm at intervals of 30 seconds (20). SBP > 140 mmHg, DBP ≥ 90 mmHg, or using antihypertensive medication were considered hypertension (21). Based on the criteria established by the American Diabetes Association (ADA), diabetes mellitus was defined as the fulfillment of one of the following conditions: HbA1c > 6.5%, plasma glucose level 2 hours after 75 g OGTT ≥ 200 mg/dL, or fasting plasma glucose ≥ 126 mg/dL (22). Individuals who said that they used diabetic medication were also considered to have the disease. Questionnaires were used to get the history of medications used. The participants completed questionnaires about their demographics, lifestyle, and medical problems including their age, gender, alcohol consumption, smoking history, history of regular exercise, and previous and present medical history of illnesses, in addition to providing information on their medication history. Utilizing questionnaires covering the kind (beer, hard liquor, and soju), quantity, and frequency of drinks, information about past alcohol consumption was identified. Drinking at least once a week was considered alcohol intake, with a weekly threshold of > 140 g for males and > 70 g for women (23). There were three groups

based on smoking history: never smokers, ex-smokers, and current smokers. Those who said "yes" to the question, "I still smoke and have smoked more than five packs of cigarettes in my lifetime," were considered current smokers. Those who said "yes" to the question, "I used to smoke more than five packs of cigarettes, but I no longer do," were considered to be ex-smokers. Those who said "yes" to the question, "In my entire life, I have smoked fewer than five packs of cigarettes," were considered never smokers (24). Participating in intense physical activity more than three times a week was considered regular exercise. Individuals who answered "yes" to the question, "A doctor has diagnosed me with cardiovascular disease," were categorized as having the disease. The degree of physical activity was evaluated using the Global Physical Activity Questionnaire (GPAQ) (25). Using an automated HGLC-723G7 analyzer (Tosoh Corporation, Tokyo, Japan), high-performance liquid chromatography was used to detect the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglyceride, and c-reactive protein (CRP).

4. Definition of chronic kidney disease, TyG index, and TG/HDL ratio

Kidney Disease Outcomes Quality Initiative (KDOQI) CKD categorization

defined CKD as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or albuminuria ≥ 30 mg/g (26). eGFR was calculated using the equation from the chronic kidney disease epidemiology collaboration, CKD-EPI 2021. This equation is (27):

$$eGFR = 142 \times min\left(\frac{S_{cr}}{K}, 1\right)^{\alpha} \times max\left(\frac{S_{Cr}}{K}, 1\right)^{-1.200} \times 0.9938^{Age} \times 1.012\ [if\ female]$$

Abbreviations: S_{cr} (serum creatinine) = mg/dL,

K = 0.9 (males) or 0.7 (females),

α = -0.302 (males) or -0.241 (females),

min = denotes the lowest value of S_{cr} or 1,

max = denotes the lowest value of S_{cr} or 1

Participants were considered to have CKD if they reported receiving a medical diagnosis by physicians. The TyG index was determined using ln (fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2) (28).

TG/HDL ratio was defined as triglyceride divided by HDL-cholesterol (29).

5. Statistical analysis

For categorical variables, the chi-square test was used to analyze all covariates; for continuous variables, the independent t-test and analysis of variance (ANOVA) tests were used. The continuous variable was represented as mean ± standard deviation and the categorical variable as *n* (%), respectively (Table 1). The study performed cox regression analysis to assess the relationship between RGS (per 0.01 kg) and CKD incidence after controlling for age, alcohol consumption, smoking status, regular exercise, SBP, DBP, AST, ALT, serum albumin, TC, HDL-cholesterol, triglyceride, and CRP levels (Table 2). RGS data were subdivided into quartiles for men and women, respectively. The reference group was determined to be the weakest RGS group (Q1). After correcting for confounding variables, cox regression was used to determine the HRs and 95% CIs of new-onset CKD according to RGS quartiles (Table 3). Both baseline and follow-up eGFR in CKD patients according to the baseline handgrip strength quartile were analyzed to show changes of eGFR according to relative handgrip strength (Table 4) and absolute handgrip strength (Table 5).

AUC was computed, and ROC curves were used to analyse the prediction power for incident CKD based on baseline RGS. Kaplan-Meier curves with a concordance index were constructed to assess survival probability and predictivity for incident

CKD according to baseline RGS quartiles. Maximally selected log-rank tests were performed to set the cutpoints of relative handgrip strength for new-onset CKD. Scatter plots with least squares lines and Pearson correlation coefficients were illustrated to find the relationship between handgrip strength and inflammatory markers and insulin resistance markers. p-value < 0.05 was considered statistically significant. R version 4.4.0 and SPSS version 27.0 (IBM Corp., Armonk, NY, USA) were used for the statistical analyses.

III. RESULTS

1. Baseline characteristics of study population

Table 1 describes the baseline characteristics of the study population based on the baseline RGS quartile. A total of 35,636 participants (12,006 men, 23630 women, 8565 pre-menopause women, and 15,065 post-menopause women) were included in our study. As the RGS quartile increased, the mean values of a few variables reduced. These variables were age, WC, BMI, triglyceride, AST, ALT, WBC, CRP, SBP, DBP, and the existence of hypertension and diabetes in men, pre-menopause women, and post-menopause women. On the other hand, serum albumin, eGFR, and HDL-cholesterol were significantly increased with increasing RGS quartile. In pre-menopause women, these variables which were age, WC, BMI, TC, triglyceride, ALT, WBC, SBP, DBP, existence of hypertension and diabetes were significantly decreased with increasing RGS quartile. However, serum albumin, eGFR, and HDL-cholesterol were significantly increased with increasing RGS quartile.

Table 1-1. Study population's baseline characteristics based on the baseline RGS quartile in male

	Men	$Q_1 \leq 1.38$	$1.38 < Q_2 \leq 1.59$	$1.59 < Q_3 \leq 1.82$	$1.82 < Q_4$	*p*-value
N	12006	3001	3001	3002	3002	
HGS (kg)	38.9 ± 8.4	30.0 ± 6.0	37.1 ± 3.8	41.1 ± 4.3	47.3 ± 7.6	< 0.001
RGS (m^2)	1.61 ± 0.37	1.16 ± 0.20	1.49 ± 0.06	1.70 ± 0.07	2.06 ± 0.26	< 0.001
Age (years)	55.2 ± 8.4	58.3 ± 8.0	56.4 ± 8.1	54.7 ± 8.1	51.3 ± 7.9	< 0.001
Waist circumference	85.4 ± 7.5	88.5 ± 7.5	86.5 ± 6.8	84.9 ± 6.9	81.8 ± 7.0	< 0.001
BMI (kg/m^2)	24.4 ± 2.7	25.7 ± 2.8	24.9 ± 2.4	24.2 ± 2.4	23.0 ± 2.4	< 0.001
eGFR ($mL/min/1.73m^2$)	94.5 ± 11.8	92.6 ± 11.7	93.7 ± 11.7	94.7 ± 11.9	96.9 ± 11.7	< 0.001
Total cholesterol (mg/dl)	191.9 ± 34.8	191.2 ± 36.1	192.6 ± 35.5	192.8 ± 34.4	191.1 ± 33.0	0.104
HDL-cholesterol (mg/dl)	49.7 ± 11.9	48.1 ± 11.2	49.0 ± 11.9	49.9 ± 11.8	51.7 ± 12.5	< 0.001
TG (mg/dl)	148.5 ± 102.7	154.5 ± 101.2	152.7 ± 102.2	150.4 ± 105.9	136.6 ± 100.5	< 0.001
Albumin (mg/dl)	4.69 ± 0.25	4.67 ± 0.26	4.69 ± 0.26	4.70 ± 0.25	4.72 ± 0.25	< 0.001
AST (IU/L)	25.0 ± 12.9	25.5 ± 11.8	25.5 ± 14.4	25.1 ± 13.8	24.0 ± 11.5	< 0.001
ALT (IU/L)	25.9 ± 16.9	27.5 ± 17.0	26.8 ± 17.2	25.8 ± 17.4	23.4 ± 15.4	< 0.001
WBC ($10^3/\mu L$)	6.07 ± 1.60	6.24 ± 1.62	6.09 ± 1.57	6.04 ± 1.60	5.91 ± 1.58	< 0.001
CRP (mg/dL)	0.159 ± 0.389	0.185 ± 0.429	0.162 ± 0.358	0.144 ± 0.311	0.140 ± 0.442	< 0.001
Systolic BP (mmHg)	125.5 ± 13.9	127.2 ± 14.2	125.9 ± 13.7	125.4 ± 13.7	123.7 ± 13.7	< 0.001
Diastolic BP (mmHg)	78.1 ± 9.4	78.9 ± 9.4	78.2 ± 9.2	77.8 ± 9.3	77.2 ± 9.5	< 0.001
Alcohol intake, *n* (%)	4112 (34.3)	910 (30.3)	981 (32.7)	1096 (36.5)	1125 (37.5)	< 0.001
Smoking status, *n* (%)						< 0.001
Never smoker	3191 (26.7)	870 (29.1)	775 (25.9)	791 (26.5)	755 (25.2)	
Ex-smoker	5452 (45.6)	1435 (48.0)	1392 (46.5)	1376 (46.1)	1249 (41.7)	
Current smoker	3319 (27.7)	683 (22.9)	826 (27.6)	821 (27.5)	989 (33.0)	
Regular exercise, *n* (%)	5083 (42.3)	1293 (43.1)	1325 (44.2)	1289 (42.9)	1176 (39.2)	0.001
Hypertension, *n* (%)	2953 (24.6)	1031 (34.4)	834 (27.8)	674 (22.5)	414 (13.8)	< 0.001
Diabetes, *n* (%)	1138 (9.5)	406 (13.5)	333 (11.1)	253 (8.4)	146 (4.9)	< 0.001

HGS, handgrip strength; RGS, relative handgrip strength; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; CRP, c-reactive protein; TyG index, triglyceride-glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 1-2. Study population's baseline characteristics based on the baseline RGS quartile in female

	Women	$Q_1 \leq 0.84$	$0.84 < Q_2 \leq 1.00$	$1.00 < Q_3 \leq 1.16$	$1.16 < Q_4$	*p*-value
N	23630	5912	5912	5899	5907	
HGS (kg)	23.4 ± 5.3	17.8 ± 3.7	22.3 ± 2.5	24.9 ± 2.6	28.7 ± 4.6	< 0.001
RGS (m^2)	1.01 ± 0.25	0.70 ± 0.13	0.93 ± 0.04	1.08 ± 0.05	1.32 ± 0.18	< 0.001
Age (years)	53.3 ± 7.7	56.9 ± 7.5	54.4 ± 7.4	52.3 ± 7.2	49.5 ± 6.9	< 0.001
Waist circumference	77.9 ± 8.1	82.2 ± 8.4	79.2 ± 7.5	76.7 ± 7.1	73.4 ± 6.7	< 0.001
BMI (kg/m^2)	23.6 ± 2.9	25.4 ± 3.2	24.1 ± 2.6	23.1 ± 2.3	21.7 ± 2.2	< 0.001
eGFR ($mL/min/1.73m^2$)	99.2 ± 11.2	97.4 ± 11.1	99.0 ± 11.0	99.8 ± 11.1	100.7 ± 11.2	< 0.001
Total cholesterol (mg/dl)	199.8 ± 35.6	202.4 ± 36.9	202.0 ± 35.9	199.9 ± 35.2	195.0 ± 33.7	0.104
HDL-cholesterol (mg/dl)	56.3 ± 13.0	53.8 ± 12.2	55.2 ± 12.6	56.8 ± 12.9	59.5 ± 13.5	< 0.001
TG (mg/dl)	113.6 ± 72.6	127.1 ± 76.1	120.4 ± 79.8	110.4 ± 68.8	96.4 ± 60.7	< 0.001
Albumin (mg/dl)	4.61 ± 0.24	4.58 ± 0.25	4.61 ± 0.24	4.62 ± 0.24	4.64 ± 0.24	< 0.001
AST (IU/L)	22.2 ± 10.3	23.4 ± 11.1	22.7 ± 12.9	21.8 ± 9.0	20.9 ± 7.2	< 0.001
ALT (IU/L)	19.6 ± 15.1	22.0 ± 18.1	20.4 ± 17.7	18.8 ± 11.8	17.1 ± 10.8	< 0.001
WBC ($10^3/\mu L$)	5.43 ± 1.43	5.61 ± 1.49	5.47 ± 1.44	5.38 ± 1.39	5.28 ± 1.39	< 0.001
CRP (mg/dL)	0.131 ± 0.397	0.165 ± 0.407	0.146 ± 0.521	0.121 ± 0.333	0.091 ± 0.271	< 0.001
Systolic BP (mmHg)	120.9 ± 14.7	123.2 ± 14.7	121.9 ± 14.8	120.6 ± 14.8	118.0 ± 14.1	< 0.001
Diastolic BP (mmHg)	74.2 ± 9.4	75.4 ± 9.3	74.7 ± 9.3	74.1 ± 9.4	72.7 ± 9.3	< 0.001
Alcohol intake, *n* (%)	1112 (4.7)	206 (3.5)	262 (4.4)	300 (5.1)	344 (5.8)	< 0.001
Smoking status, *n* (%)						0.011
Never smoker	22860 (96.9)	5733 (97.2)	5720 (97.0)	5729 (97.2)	5678 (96.2)	
Ex-smoker	294 (1.2)	74 (1.3)	63 (1.1)	74 (1.3)	83 (1.4)	
Current smoker	437 (1.9)	94 (1.6)	113 (1.9)	91 (1.5)	139 (2.4)	
Regular exercise, *n* (%)	9939 (42.1)	2309 (39.1)	2460 (41.6)	2613 (44.3)	2557 (43.3)	< 0.001
Hypertension, *n* (%)	4192 (17.7)	1576 (26.7)	1167 (19.7)	898 (15.2)	551 (9.3)	< 0.001
Diabetes, *n* (%)	1217 (5.2)	528 (8.9)	327 (5.5)	225 (3.8)	137 (2.3)	< 0.001

HGS, handgrip strength; RGS, relative handgrip strength; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; CRP, c-reactive protein; TyG index, triglyceride-glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 1-3. Study population's baseline characteristics based on the baseline RGS quartile in pre-menopause women

	Women (pre-menopause)	$Q_1 \leq 0.96$	$0.96 < Q_2 \leq 1.09$	$1.09 < Q_3 \leq 1.24$	$1.24 < Q_4$	*p*-value
N	8565	2140	2143	2141	2141	
HGS (kg)	25 ± 5.2	19.8 ± 3.9	23.9 ± 2.7	26.4 ± 2.8	29.9 ± 4.7	< 0.001
RGS (m^2)	1.10 ± 0.25	0.79 ± 0.13	1.02 ± 0.04	1.17 ± 0.04	1.41 ± 0.19	< 0.001
Age (years)	45.8 ± 4.3	46.7 ± 4.5	46.1 ± 4.3	45.6 ± 4.1	44.9 ± 4.0	< 0.001
Waist circumference	75.7 ± 7.9	79.5 ± 8.6	76.5 ± 7.2	74.7 ± 7.2	72.0 ± 6.5	< 0.001
BMI (kg/m^2)	23.1 ± 2.9	24.9 ± 3.2	23.5 ± 2.6	22.6 ± 2.3	21.3 ± 2.1	< 0.001
eGFR ($mL/min/1.73m^2$)	104.7 ± 9.8	105.2 ± 9.6	104.9 ± 9.8	105.0 ± 9.7	103.8 ± 10.2	< 0.001
Total cholesterol (mg/dl)	191.5 ± 32.9	195.1 ± 35.0	192.4 ± 32.7	191.6 ± 32.1	187.1 ± 31.2	< 0.001
HDL-cholesterol (mg/dl)	58.1 ± 13.1	55.5 ± 12.4	57.3 ± 12.7	58.7 ± 13.3	60.7 ± 13.6	< 0.001
Triglyceride (mg/dl)	98.3 ± 64.0	110.0 ± 68.9	100.2 ± 66.4	96.8 ± 64.6	86.1 ± 52.5	< 0.001
Albumin (mg/dl)	4.59 ± 0.24	4.55 ± 0.25	4.58 ± 0.24	4.60 ± 0.24	4.63 ± 0.24	< 0.001
AST (IU/L)	20.0 ± 8.4	20.8 ± 9.0	19.8 ± 7.7	20.0 ± 9.4	19.4 ± 7.3	< 0.001
ALT (IU/L)	16.9 ± 11.9	19.2 ± 14.0	16.8 ± 10.3	16.5 ± 11.1	15.3 ± 11.4	< 0.001
WBC ($10^3/\mu L$)	5.51 ± 1.44	5.67 ± 1.48	5.56 ± 1.43	5.53 ± 1.45	5.28 ± 1.39	< 0.001
CRP (mg/dL)	0.102 ± 0.248	0.130 ± 0.244	0.101 ± 0.288	0.102 ± 0.276	0.074 ± 0.157	< 0.001
Systolic BP (mmHg)	117.1 ± 14.1	118.7 ± 14.8	117.3 ± 14.0	117.0 ± 14.0	115.4 ± 13.5	< 0.001
Diastolic BP (mmHg)	72.5 ± 9.5	73.7 ± 9.7	72.5 ± 9.4	72.3 ± 9.3	71.3 ± 9.2	< 0.001
Alcohol intake, *n* (%)	647 (7.6)	164 (7.7)	155 (7.2)	168 (7.8)	160 (7.5)	0.888
Smoking status, *n* (%)						0.296
Never smoker	8222 (96.2)	2054 (96.2)	2057 (96.2)	2054 (96.1)	2057 (96.2)	
Ex-smoker	139 (1.6)	34 (1.6)	43 (2.0)	36 (1.7)	26 (1.2)	
Current smoker	189 (2.2)	47 (2.2)	39 (1.8)	47 (2.2)	56 (2.6)	
Regular exercise, *n* (%)	3211 (37.5)	747 (34.9)	783 (36.5)	850 (39.7)	831 (38.8)	0.005
Hypertension, *n* (%)	561 (6.6)	195 (9.1)	152 (7.1)	126 (5.9)	88 (4.1)	< 0.001
Diabetes, *n* (%)	164 (1.9)	67 (3.1)	40 (1.9)	32 (1.5)	25 (1.2)	< 0.001

HGS, handgrip strength; RGS, relative handgrip strength; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; CRP, c-reactive protein; TyG index, triglyceride-glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 1-4. Study population's baseline characteristics based on the baseline RGS quartile in post-menopause women

	Women (post-menopause)	$Q_1 \leq 0.80$	$0.80 < Q_2 \leq 0.95$	$0.95 < Q_3 \leq 1.10$	$1.10 < Q_4$	*p*-value
N	15065	3766	3768	3766	3765	
HGS (kg)	22.5 ± 5.1	17.1 ± 3.6	21.5 ± 2.4	24.0 ± 2.5	27.6 ± 4.5	< 0.001
RGS (m^2)	0.96 ± 0.24	0.67 ± 0.12	0.88 ± 0.04	1.02 ± 0.04	1.26 ± 0.18	< 0.001
Age (years)	57.5 ± 5.8	59.6 ± 5.7	58.1 ± 5.7	56.9 ± 5.6	55.4 ± 5.5	< 0.001
Waist circumference	79.2 ± 8.0	83.1 ± 8.3	80.4 ± 7.5	78.3 ± 7.1	74.9 ± 6.8	< 0.001
BMI (kg/m^2)	23.9 ± 2.9	25.6 ± 3.2	24.5 ± 2.6	23.5 ± 2.3	22.0 ± 2.2	< 0.001
eGFR ($mL/min/1.73m^2$)	96.1 ± 10.6	95.3 ± 10.6	96.3 ± 10.6	96.4 ± 10.5	96.4 ± 10.9	< 0.001
Total cholesterol (mg/dl)	204.5 ± 36.1	203.8 ± 37.0	205.8 ± 36.7	204.8 ± 36.1	203.7 ± 34.7	0.038
HDL-cholesterol (mg/dl)	55.4 ± 12.8	53.4 ± 12.0	54.4 ± 12.6	55.7 ± 12.7	57.9 ± 13.4	< 0.001
Triglyceride (mg/dl)	122.3 ± 75.7	131.2 ± 78.2	128.0 ± 76.7	120.8 ± 77.3	109.2 ± 68.4	< 0.001
Albumin (mg/dl)	4.63 ± 0.24	4.59 ± 0.25	4.62 ± 0.24	4.64 ± 0.24	4.66 ± 0.24	< 0.001
AST (IU/L)	23.5 ± 11.1	24.1 ± 11.6	23.7 ± 13.6	23.4 ± 11.0	22.6 ± 7.0	< 0.001
ALT (IU/L)	21.1 ± 16.5	22.6 ± 19.8	21.7 ± 18.7	20.9 ± 15.2	19.1 ± 10.3	< 0.001
WBC ($10^3/\mu L$)	75.2 ± 9.2	75.8 ± 9.0	75.5 ± 9.2	75.3 ± 9.3	74.2 ± 9.2	< 0.001
CRP (mg/dL)	0.148 ± 0.458	0.177 ± 0.467	0.165 ± 0.607	0.138 ± 0.373	0.108 ± 0.323	< 0.001
SBP (mmHg)	123.1 ± 14.6	124.4 ± 14.6	123.6 ± 14.5	123.2 ± 14.8	121.0 ± 14.4	< 0.001
DBP (mmHg)	75.2 ± 9.2	75.8 ± 9.0	75.5 ± 9.2	75.3 ± 9.3	74.2 ± 9.2	< 0.001
Alcohol intake, *n* (%)	465 (3.1)	87 (2.3)	94 (2.5)	143 (3.8)	141 (3.7)	< 0.001
Smoking status, *n* (%)						0.258
Never smoker	14638 (97.3)	3660 (97.3)	3671 (97.8)	3657 (97.2)	3650 (97.0)	
Ex-smoker	155 (1.0)	43 (1.1)	33 (0.9)	34 (0.9)	45 (1.2)	
Current smoker	248 (1.6)	58 (1.5)	50 (1.3)	72 (1.9)	68 (1.8)	
Regular exercise, *n* (%)	6728 (44.7)	1504 (39.9)	1637 (43.4)	1771 (47.0)	1816 (48.2)	< 0.001
Hypertension, *n* (%)	3631 (24.1)	1180 (31.3)	985 (26.1)	845 (22.4)	621 (16.5)	< 0.001
Diabetes, *n* (%)	1053 (7.0)	402 (10.7)	274 (7.3)	228 (6.1)	149 (4.0)	< 0.001

HGS, handgrip strength; RGS, relative handgrip strength; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; TG, triglyceride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; CRP, c-reactive protein; TyG index, triglyceride-glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure

2. Incidence of CKD according to baseline RGS quartiles

The new-onset CKD is figured according to baseline RGS quartile. The incidence of CKD decreased with increasing baseline RGS quartiles in men, women, pre-menopause women, and post-menopause women (Figure 2). The correlations between baseline RGS and incident CKD were significantly negative for men, women, and post-menopausal women. However, it was not statistically significant for pre-menopausal women.

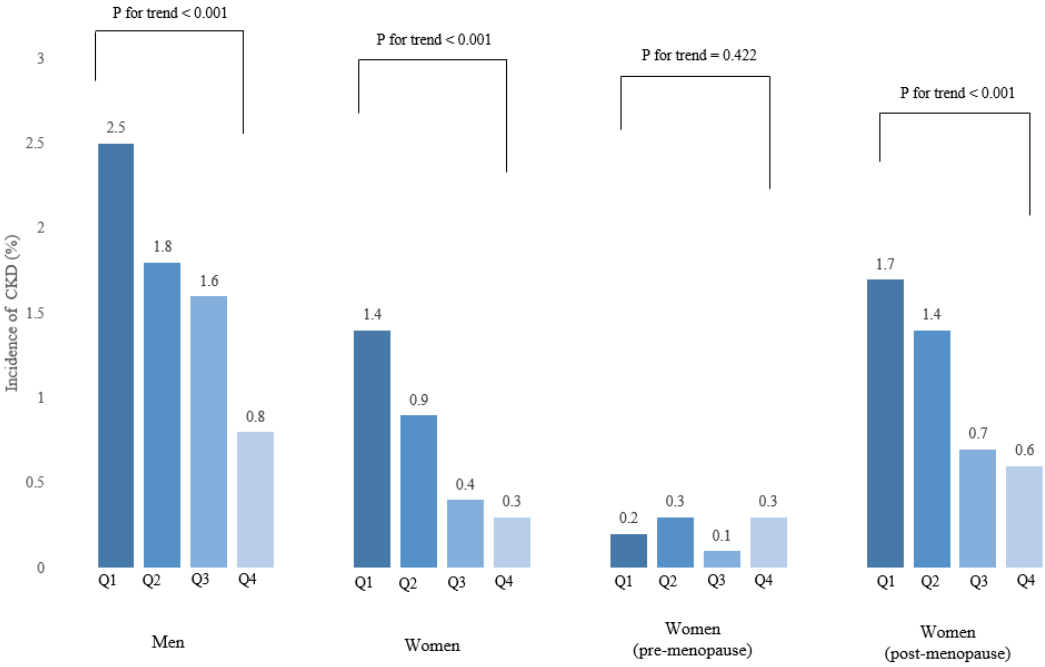


Figure 2. CKD incidence based on baseline RGS quartiles

3. Association of baseline RGS (per 0.01kg) and incidence of CKD

These findings imply that there is a dose-response association between CKD and RGS. Table 2 presents the findings of the correlation between the baseline RGS (per 0.01 kg) and the incidence of CKD. RGS was significantly associated with the incidence of CKD in all models of Table 2 for men. On the other hand, pre-menopause and post-menopause women were not statistically significant in any of the adjusted models.

Table 2-1. Association between baseline RGS (per 0.01kg) and incidence of CKD in men and women using cox-regression

Men			Women		
	HR	*p*-value		HR	*p*-value
Unadjusted	0.46 (0.35 – 0.60)	< 0.001	Unadjusted	0.68 (0.49 – 0.93)	0.017
Model 1	0.67 (0.50 – 0.90)	0.008	Model 1	0.81 (0.58 – 1.14)	0.226
Model 2	0.67 (0.50 – 0.90)	0.008	Model 2	0.79 (0.56 – 1.11)	0.173
Model 3	0.72 (0.53 – 0.97)	0.033	Model 3	0.86 (0.60 – 1.21)	0.376

CKD, chronic kidney disease; HR, hazard ratio; Model 1: adjusted for age; Model 2: adjusted for age, regular exercise, alcohol intake, and smoking status; Model 3: adjusted for age, regular exercise, alcohol intake, smoking status, SBP, DBP, AST, ALT, total cholesterol, HDL-cholesterol, and triglyceride

Table 2-2. Association between baseline RGS (per 0.01kg) and incidence of CKD in pre-menopause women and post-menopause women using cox-regression

Women (pre-menopause)			Women (post-menopause)		
	HR	*p*-value		HR	*p*-value
Unadjusted	0.88 (0.52 – 1.51)	0.650	Unadjusted	0.62 (0.41 – 0.95)	0.026
Model 1	0.78 (0.45 – 1.35)	0.381	Model 1	0.82 (0.53 – 1.27)	0.375
Model 2	0.77 (0.44 – 1.32)	0.338	Model 2	0.80 (0.52 – 1.23)	0.311
Model 3	0.79 (0.45 – 1.40)	0.424	Model 3	0.89 (0.57 – 1.38)	0.594

CKD, chronic kidney disease; HR, hazard ratio; Model 1: adjusted for age; Model 2: adjusted for age, regular exercise, alcohol intake, and smoking status; Model 3: adjusted for age, regular exercise, alcohol intake, smoking status, SBP, DBP, AST, ALT, total cholesterol, HDL-cholesterol, and triglyceride

4. Hazard ratio for new-onset CKD according to baseline RGS quartile

The HRs and 95% CIs for the incidence of CKD based on the baseline RGS quartile are displayed in Table 3-1. The reference group was determined to be the RGS's weakest quartile (Q1) (14). Compared with the reference group and after adjusting model 3, the statistically significant HRs (95% CI) for CKD of the participants were 0.62 (0.45 – 0.86) for the Q4 group of men, which are statistically significant. However, the results conducted in women, pre-menopause women, and post-menopause women by using cox-regression analysis are statistically insignificant in model 1, 2, and 3.

Table 3-1. Hazard ratio and 95% confidence intervals for incident CKD based on baseline RGS quartile

	Men				Women			
	$Q_1 \leq$ 1.38	1.38 < Q2 ≤ 1.59	1.59 < Q_3 ≤ 1.82	1.82 < Q_4	$Q_1 \leq$ 0.84	0.84 < Q_2 ≤ 1.00	1.00 < Q_3 ≤ 1.16	1.16 < Q_4
N	3001	3001	3002	3002	5906	5911	5907	5906
Unadjusted	1.00	0.67 (0.53 – 0.86)	0.67 (0.53 – 0.86)	0.39 (0.29 – 0.53)	1.00	0.93 (0.75 – 1.15)	0.84 (0.67 – 1.04)	0.78 (0.62 – 0.98)
Model 1	1.00	0.76 (0.59 – 0.97)	0.83 (0.65 – 1.07)	0.58 (0.42 – 0.79)	1.00	0.96 (0.78 – 1.19)	0.90 (0.72 – 1.13)	0.88 (0.70 – 1.12)
Model 2	1.00	0.75 (0.59 – 0.96)	0.83 (0.64 – 1.06)	0.58 (0.42 – 0.79)	1.00	0.96 (0.78 – 1.19)	0.89 (0.71 – 1.12)	0.87 (0.68 – 1.10)
Model 3	1.00	0.77 (0.60 – 0.99)	0.86 (0.67 – 1.11)	0.62 (0.45 – 0.86)	1.00	0.96 (0.78 – 1.19)	0.91 (0.73 – 1.13)	0.92 (0.72 – 1.17)

Model 1: adjusted for age; Model 2: adjusted for age, regular exercise, alcohol intake, and smoking status; Model 3: adjusted for age, regular exercise, alcohol intake, smoking status, SBP, DBP, AST, ALT, total cholesterol, HDL-cholesterol, and triglyceride

Table 3-2. Hazard ratio and 95% confidence intervals for incident CKD based on baseline RGS quartile

	Women (pre-menopause)				Women (post-menopause)			
	$Q_1 \leq$ 0.96	0.96 < Q_2 ≤ 1.09	1.09 < Q_3 ≤ 1.24	1.24 < Q_4	$Q_1 \leq$ 0.80	0.80 < Q_2 ≤ 0.95	0.95 < Q_3 ≤ 1.10	1.10 < Q_4
N	2140	2143	2141	2141	3766	3768	3766	3765
Unadjusted	1.00	1.32 (0.91 – 1.92)	1.11 (0.75 – 1.64)	1.11 (0.75 – 1.64)	1.00	0.98 (0.76 – 1.26)	0.78 (0.60 – 1.02)	0.72 (0.55 – 0.96)
Model 1	1.00	1.28 (0.88 – 1.86)	1.06 (0.72 – 1.57)	1.02 (0.68 – 1.52)	1.00	1.04 (0.81 – 1.35)	0.88 (0.67 – 1.15)	0.86 (0.65 – 1.15)
Model 2	1.00	1.27 (0.87 – 1.84)	1.05 (0.71 – 1.55)	1.00 (0.67 – 1.50)	1.00	1.04 (0.81 – 1.35)	0.88 (0.67 – 1.15)	0.86 (0.65 – 1.15)
Model 3	1.00	1.26 (0.87 – 1.84)	1.04 (0.70 – 1.55)	1.03 (0.69 – 1.56)	1.00	1.06 (0.82 – 1.37)	0.88 (0.67 – 1.16)	0.92 (0.69 – 1.24)

Model 1: adjusted for age; Model 2: adjusted for age, regular exercise, alcohol intake, and smoking status; Model 3: adjusted for age, regular exercise, alcohol intake, smoking status, SBP, DBP, AST, ALT, total cholesterol, HDL-cholesterol, and triglyceride

5. Analysis of eGFR changes in CKD patients according to baseline handgrip strength quartile

Values of eGFR at baseline and follow-up in CKD patients according to baseline RGS quartiles are tabulated in Table 4. eGFR values gradually increased according to RGS quartiles in both male and female groups, which were statistically significant. On the other hand, the results of both baseline and follow-up eGFR were statistically insignificant in the pre-menopause group. The follow-up results of eGFR were significantly increased in the post-menopause group. However, the baseline results of eGFR were insignificant.

Table 5 suggests eGFR changes in CKD patients according to baseline absolute handgrip strength quartiles. The results in Table 5 are trending similar to those in Table 4.

Table 4. Analysis of eGFR changes in CKD patients according to baseline RGS quartile

	Men	$Q_1 \leq 1.28$	$1.28 < Q_2 \leq 1.51$	$1.51 < Q_3 \leq 1.77$	$1.77 < Q_4$	*p*-value
N	553	138	139	138	138	
eGFR	76.3 ± 24.0	69.9 ± 22.0	72.6 ± 22.6	80.7 ± 22.6	81.9 ± 26.7	< 0.001
eGFR	73.0 ± 25.3	66.5 ± 22.5	68.7 ± 26.0	78.3 ± 22.5	78.6 ± 27.7	< 0.001
	Women	$Q_1 \leq 0.82$	$0.82 < Q_2 \leq 0.98$	$0.98 < Q_3 \leq 1.15$	$1.15 < Q_4$	*p*-value
N	873	218	218	219	218	
eGFR	89.1 ± 22.9	84.7 ± 24.9	87.8 ± 22.8	88.6 ± 23.7	95.4 ± 18.4	< 0.001
eGFR	87.4 ± 23.6	80.3 ± 27.5	86.2 ± 23.4	89.0 ± 22.4	93.9 ± 18.2	< 0.001
	Women (pre-menopause)	$Q_1 \leq 0.92$	$0.92 < Q_2 \leq 1.06$	$1.06 < Q_3 \leq 1.23$	$1.23 < Q_4$	*p*-value
N	305	76	77	76	76	
eGFR	100.4 ± 16.8	100.3 ± 19.8	100.1 ± 16.1	101.8 ± 15.8	99.5 ± 15.3	0.847
eGFR	99.2 ± 16.8	97.7 ± 20.9	99.9 ± 16.7	101.4 ± 12.0	97.6 ± 16.4	0.456
	Women (post-menopause)	$Q_1 \leq 0.79$	$0.79 < Q_2 \leq 0.94$	$0.94 < Q_3 \leq 1.09$	$1.09 < Q_4$	*p*-value
N	567	141	143	141	142	
eGFR	83.1 ± 23.4	80.6 ± 23.3	80.5 ± 24.2	85.7 ± 23.1	85.6 ± 22.7	0.081
eGFR	81.0 ± 24.3	75.4 ± 25.7	79.5 ± 26.1	84.1 ± 21.1	85.2 ± 22.9	0.002

Table 5. Analysis of eGFR changes in CKD patients according to baseline absolute handgrip strength quartile

	Men	$Q_1 \leq 33.1$	$33.1 < Q_2 \leq 38.2$	$38.2 < Q_3 \leq 42.8$	$42.8 < Q_4$	*p*-value
N	553	141	137	138	137	
eGFR	76.3 ± 24.0	70.4 ± 22.2	70.6 ± 22.1	80.4 ± 22.6	83.9 ± 26.2	< 0.001
eGFR	73.0 ± 25.3	66.6 ± 24.1	67.3 ± 23.4	77.7 ± 23.4	80.7 ± 27.4	< 0.001
	Women	$Q_1 \leq 20.6$	$20.6 < Q_2 \leq 23.6$	$23.6 < Q_3 \leq 26.7$	$26.7 < Q_4$	*p*-value
N	873	224	220	212	217	
eGFR	89.1 ± 22.9	84.6 ± 25.0	88.2 ± 22.9	91.4 ± 22.3	92.5 ± 20.4	0.001
eGFR	87.4 ± 23.6	81.0 ± 27.0	87.1 ± 23.2	91.2 ± 20.3	90.5 ± 21.8	< 0.001
	Women (pre-menopause)	$Q_1 \leq 22.0$	$22.0 < Q_2 \leq 25.0$	$25.0 < Q_3 \leq 28.1$	$28.1 < Q_4$	*p*-value
N	305	77	77	76	75	
eGFR	100.4 ± 16.8	102.8 ± 16.1	99.3 ± 19.9	99.7 ± 17.7	99.9 ± 12.6	0.558
eGFR	99.2 ± 16.8	101.8 ± 14.8	97.2 ± 20.7	97.9 ± 17.5	99.8 ± 13.0	0.321
	Women (post-menopause)	$Q_1 \leq 19.9$	$19.9 < Q_2 \leq 23.0$	$23.0 < Q_3 \leq 25.5$	$25.5 < Q_4$	*p*-value
N	567	143	148	138	138	
eGFR	83.1 ± 23.4	79.7 ± 24.2	83.6 ± 22.4	83.3 ± 24.0	86.0 ± 22.9	0.155
eGFR	81.0 ± 24.3	75.3 ± 26.9	81.4 ± 23.0	83.7 ± 22.9	84.0 ± 23.5	0.009

6. Predictive power based on baseline RGS for incident CKD

ROC curves were generated to test whether RGS has predictive power for new-onset CKD (Figure 3). The AUC of Figure 3a is 0.597 (0.571 – 0.623) in men, the AUC of Figure 3b is 0.532 (0.509 – 0.555) in women, the AUC of Figure 3c is 0.506 (0.468 – 0.545) in pre-menopause women, which was statistically insignificant, and the AUC of Figure 3d is 0.541 (0.513 – 0.568) in post-menopause women, which suggests predictive power for CKD was higher in men than in women. Furthermore, predictive power was higher in post-menopause women than in pre-menopause women among women.

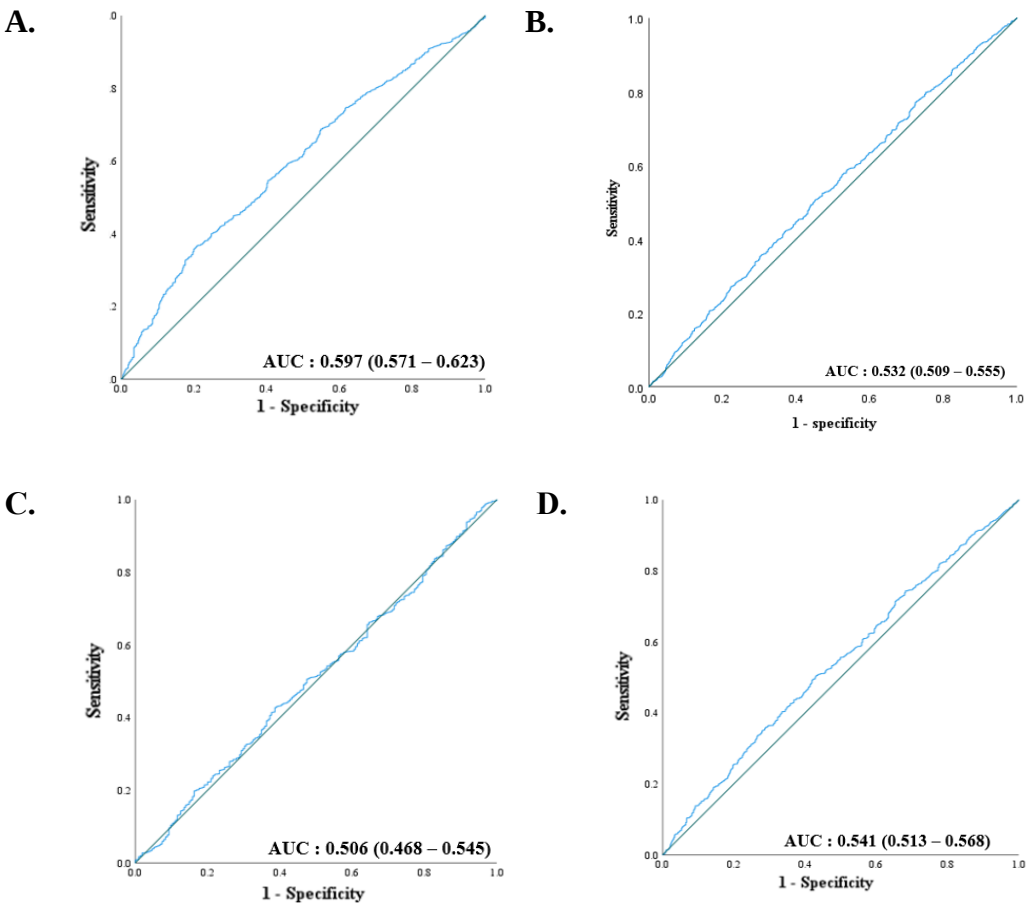


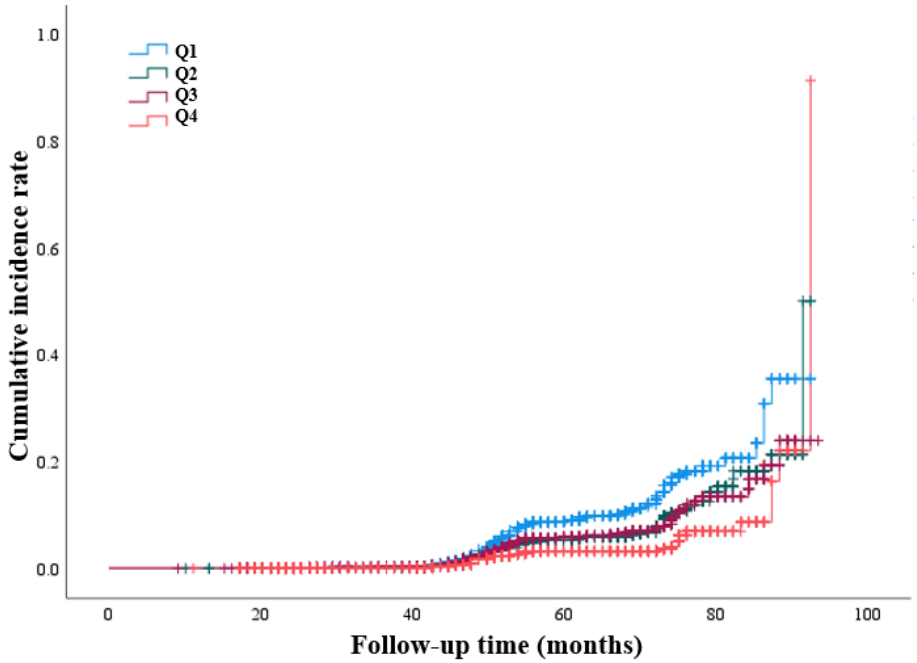
Figure 3. ROC curve showing the baseline RGS-based prediction power for new-onset CKD in men (A), in women (B) in pre-menopause women (C) and in post-menopause women (D)

7. Cumulative incidence of CKD according to RGS quartile during follow-up time

The cumulative incident rates for incident CKD were the highest in the Q1 group but declined progressively in both genders from Q2 to Q4 following the baseline survey (log-rank test, $p < 0.001$) (Figure 4). Moreover, Concordance indices were performed in order to suggest predictive power for CKD by using cox-regression analysis. The concordance index of 4a is 0.5759 (standard error = 0.0152) in men, the concordance index of Figure 4b is 0.5091 (standard error = 0.0134), the concordance index of Figure 4c is 0.5066 (standard error = 0.0219) in pre-menopause women, which was statistically insignificant, and the concordance index of Figure 4d is 0.5112 (standard error = 0.016) in post-menopause women, which suggests predictive power for CKD is still higher in men than in women even after reflecting follow-up time.

A.

Concordance index = 0.5759 (standard error = 0.0152)

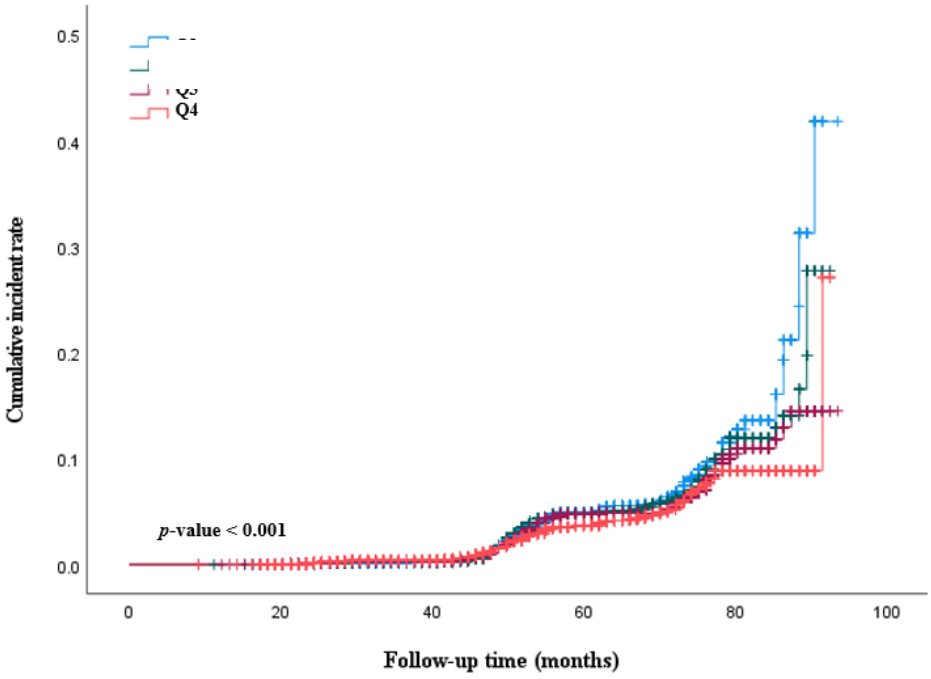


Number at risk

Q1	0	0	8	125	153	158
Q2	0	1	4	80	104	109
Q3	0	1	10	84	103	107
Q4	0	0	4	46	53	58

B.

Concordance index = 0.5091 (standard error = 0.0134)

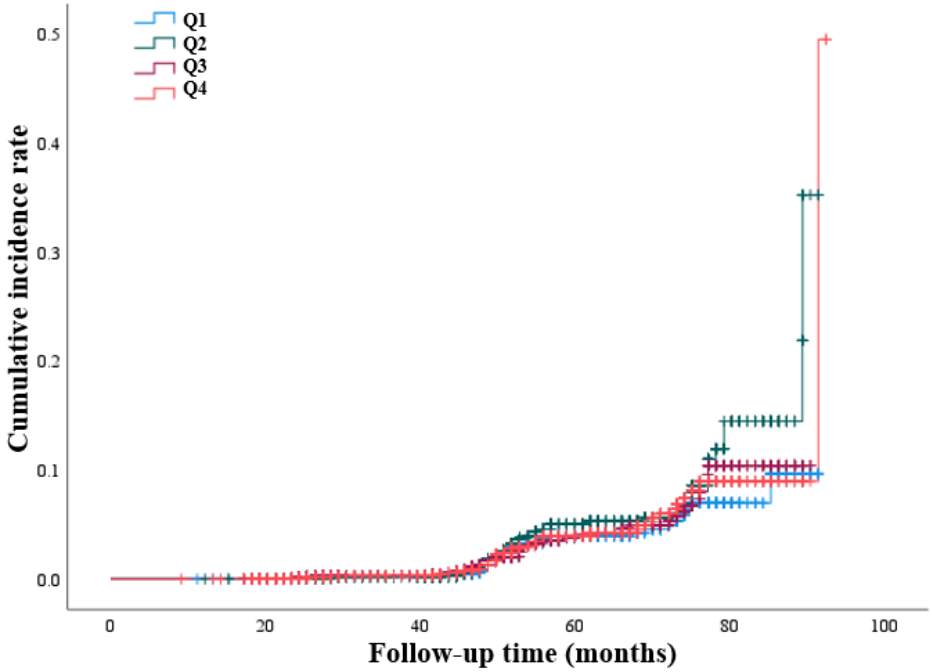


Number at risk

Q1	0	0	11	138	170	181
Q2	0	0	12	131	160	166
Q3	0	2	15	122	146	150
Q4	0	1	21	105	132	133

C.

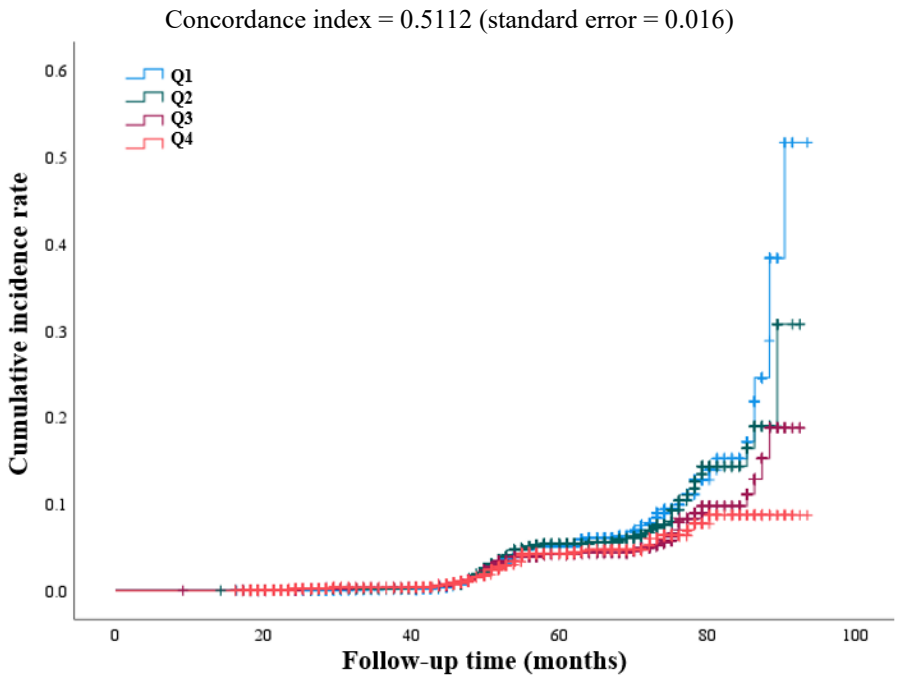
Concordance index = 0.5066 (standard error = 0.0219)



Number at risk

Q1	0	0	5	41	48	49
Q2	0	1	4	48	62	64
Q3	0	0	7	40	52	52
Q4	0	0	6	38	49	50

D.



Number at risk

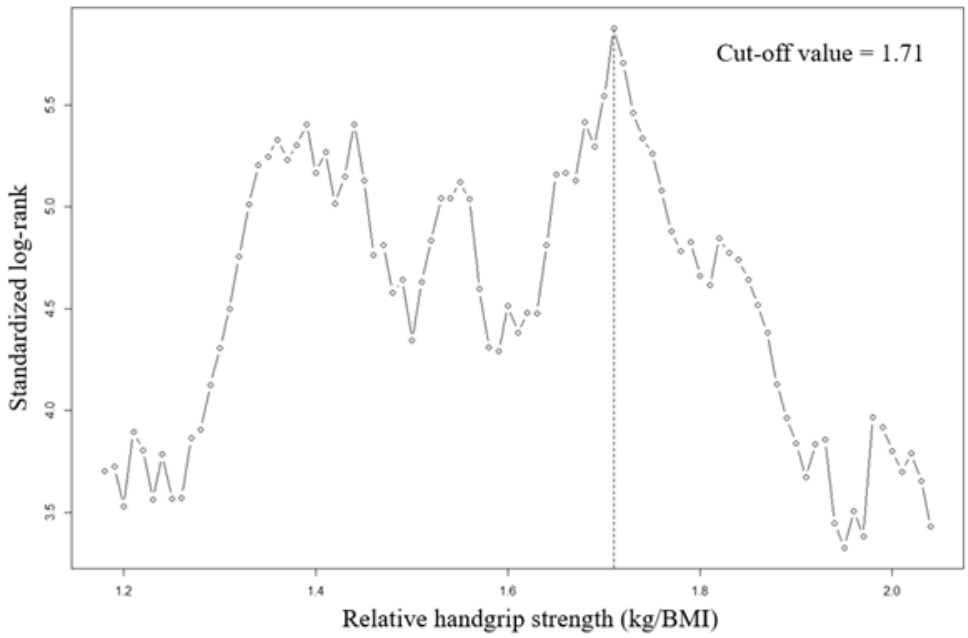
Q1	0	0	11	138	170	181
Q2	0	0	12	131	160	166
Q3	0	2	15	122	146	150
Q4	0	1	21	105	132	133

Figure 4. Kaplan Meier curves for new-onset CKD based on the baseline RGS quartile in men (A), in women (B) in pre-menopause women (C) and in post-menopause women (D).

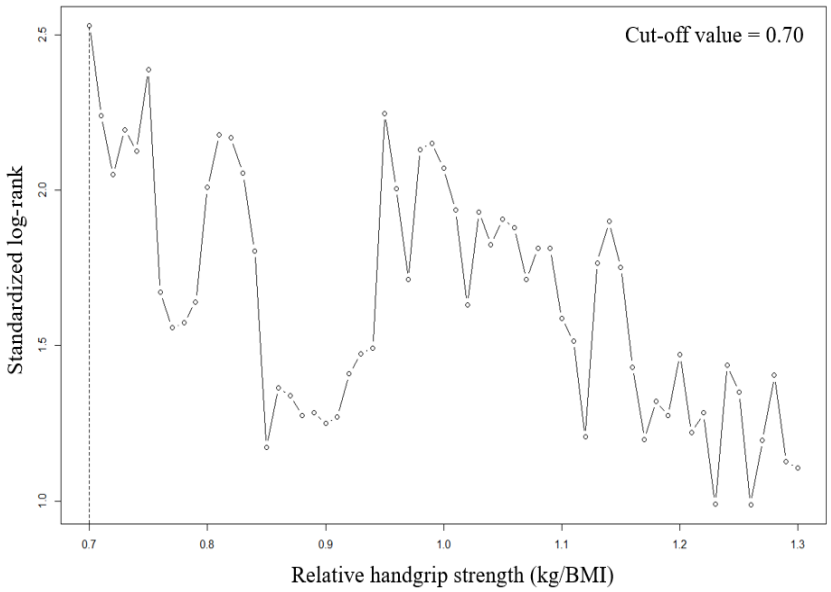
8. Optimized cut-off values for predicting incident CKD according to baseline RGS

Maximally selected log-rank tests were generated to find cutpoints for predicting incident CKD according to baseline RGS (Figure 5). The result of the cutpoint of Figure 5a is 1.71 in men, the cutpoint of Figure 5b is 0.70 in women, which was statistically insignificant, the cutpoint of Figure 5c is 0.92 in pre-menopause women, which was statistically insignificant, and the cutpoint of Figure 5d is 0.95 in post-menopause women, which was also insignificant.

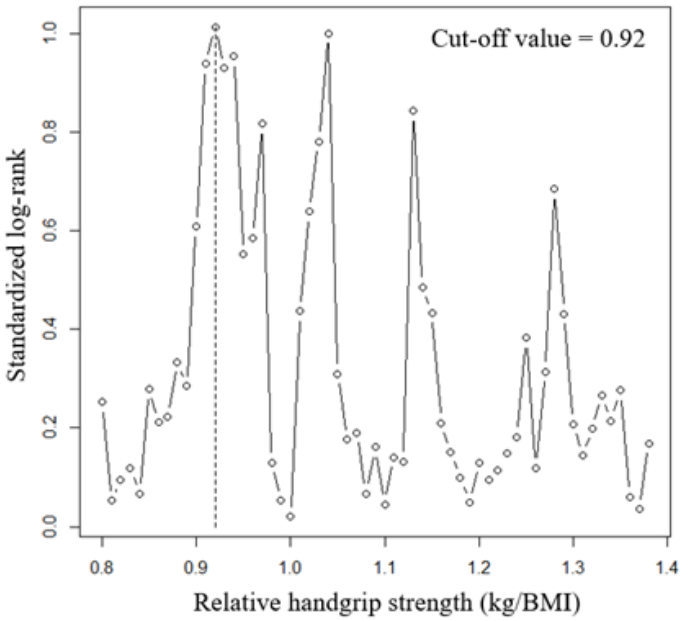
A.



B.



C.



D.

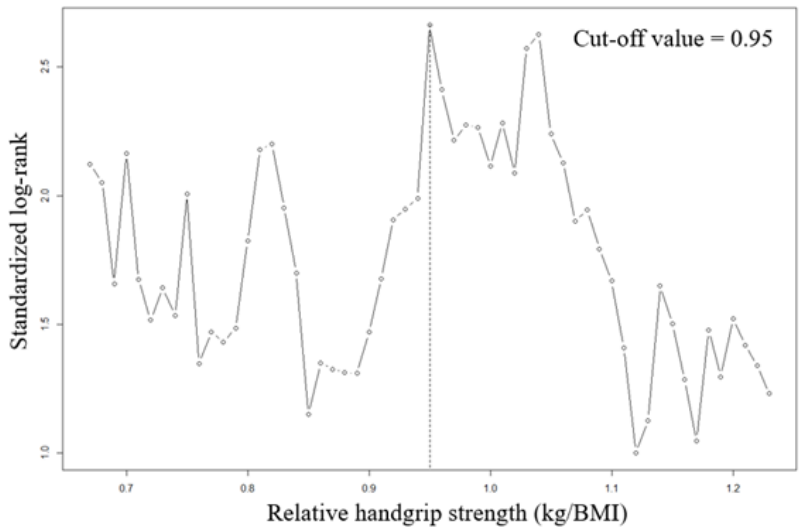


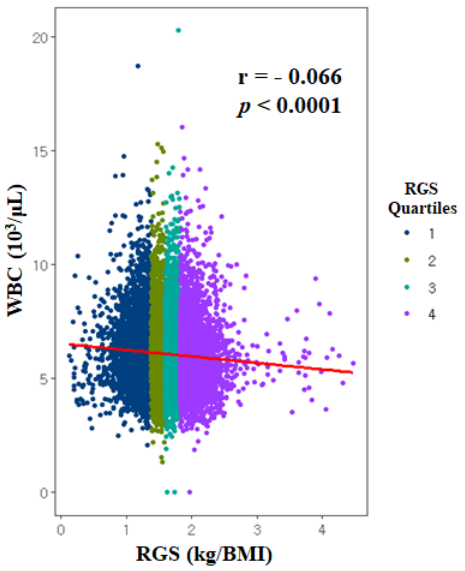
Figure 5. Maximally selected log-rank tests presenting the cut-off value for new-onset CKD based on baseline RGS in men (A), in women (B) in pre-menopause women (C) and in post-menopause women (D)

9. Association of baseline RGS with inflammatory markers and insulin resistance markers

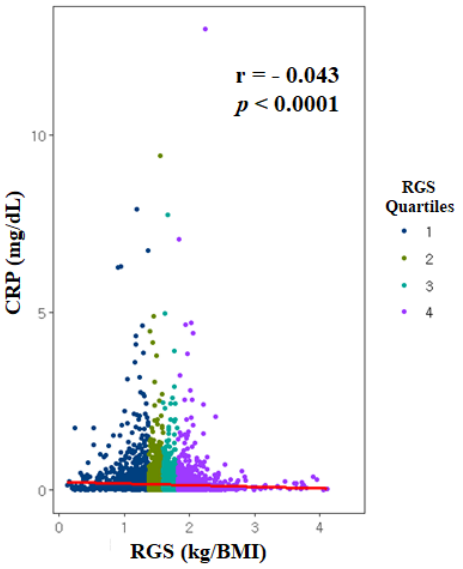
Scatter plots with least squares lines and Pearson correlation coefficients were illustrated to show the association of baseline RGS with inflammatory markers (WBC and CRP) and insulin resistance markers (TyG index and TG/HDL ratio) in Figure 6.

The results of the correlation coefficients of Figure 6a – 6d are - 0.066, - 0.043, - 0.105, and - 0.067 in men, the results of Figure 6e – 6h are -0.085, -0.074, -0.202, and -0.145, the results of Figure 6i – 6l are - 0.097, - 0.085, - 0.164, and - 0.127 in pre-menopause women and the results of Figure 6m – 6p are - 0.100, - 0.058, - 0.146, and - 0.107 in post-menopause women, which are statistically significant.

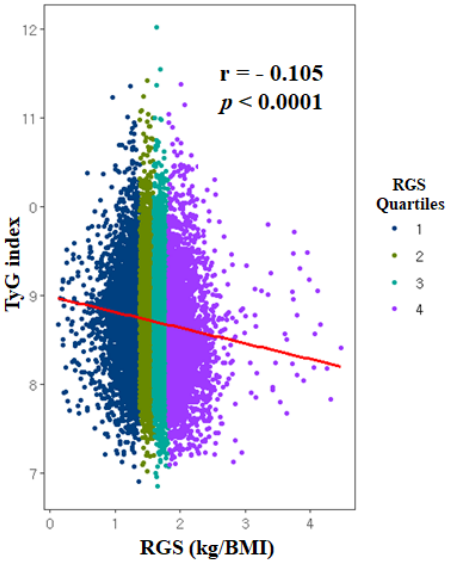
A.



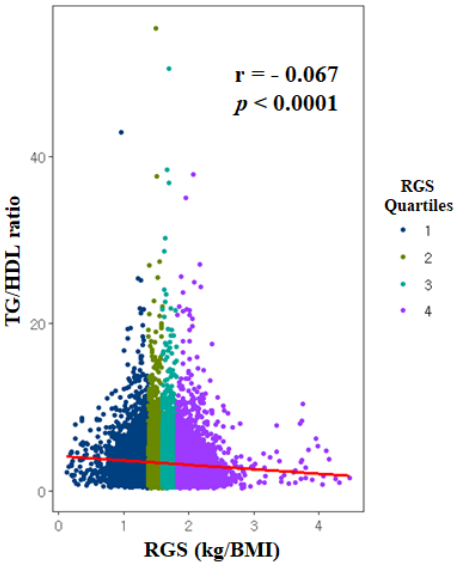
B.



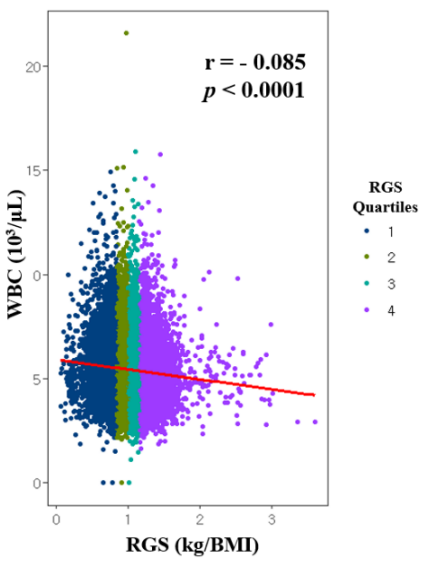
C.



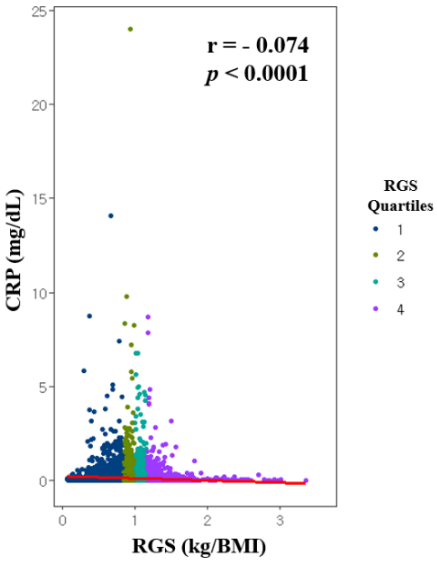
D.



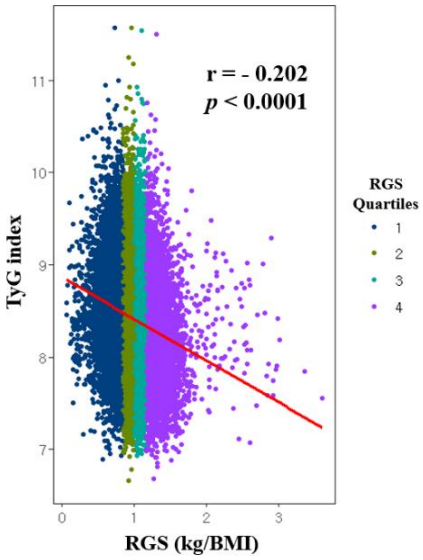
E.



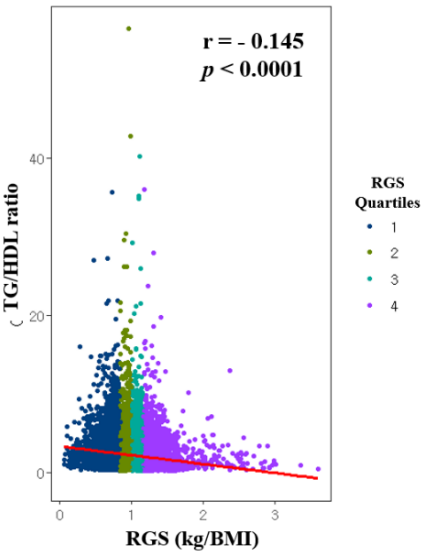
F.



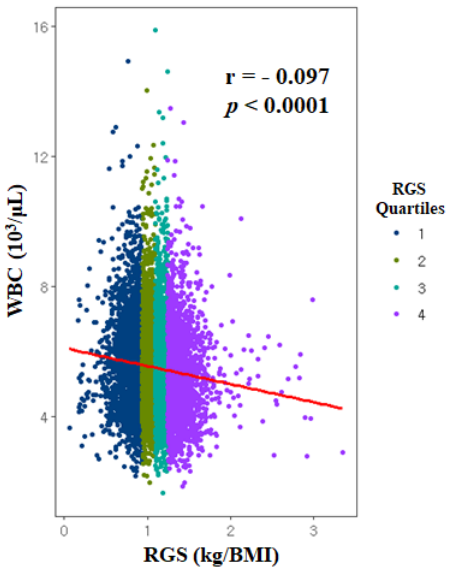
G.



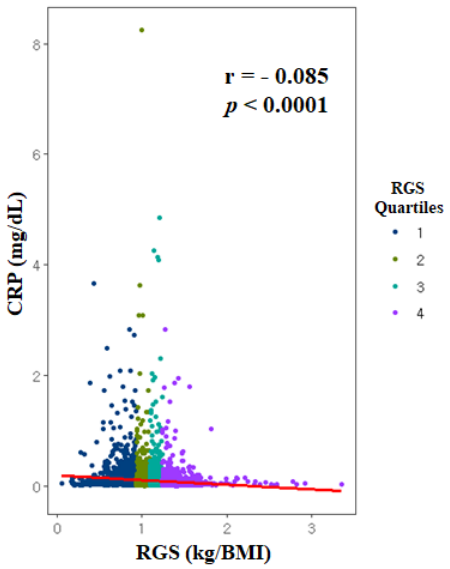
H.



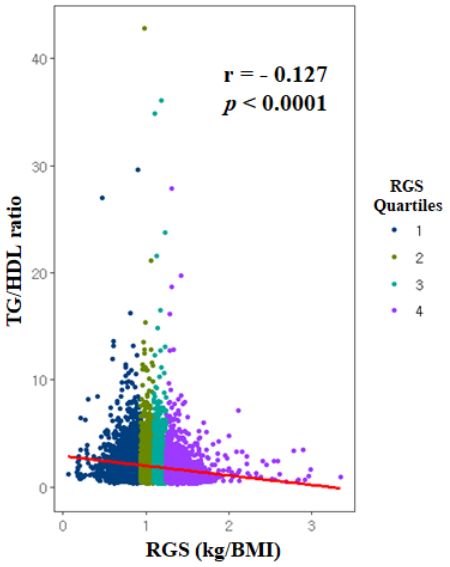
I.



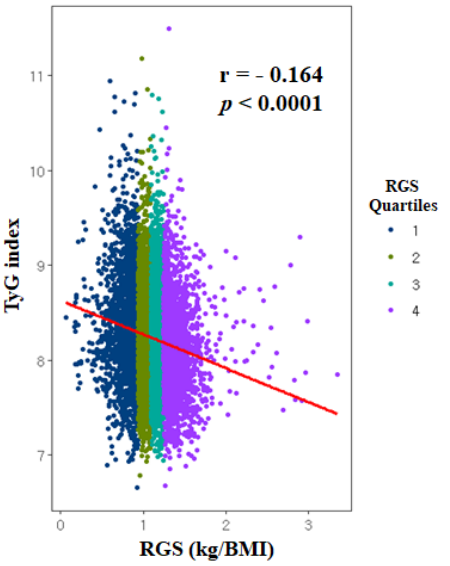
J.



K.



L.



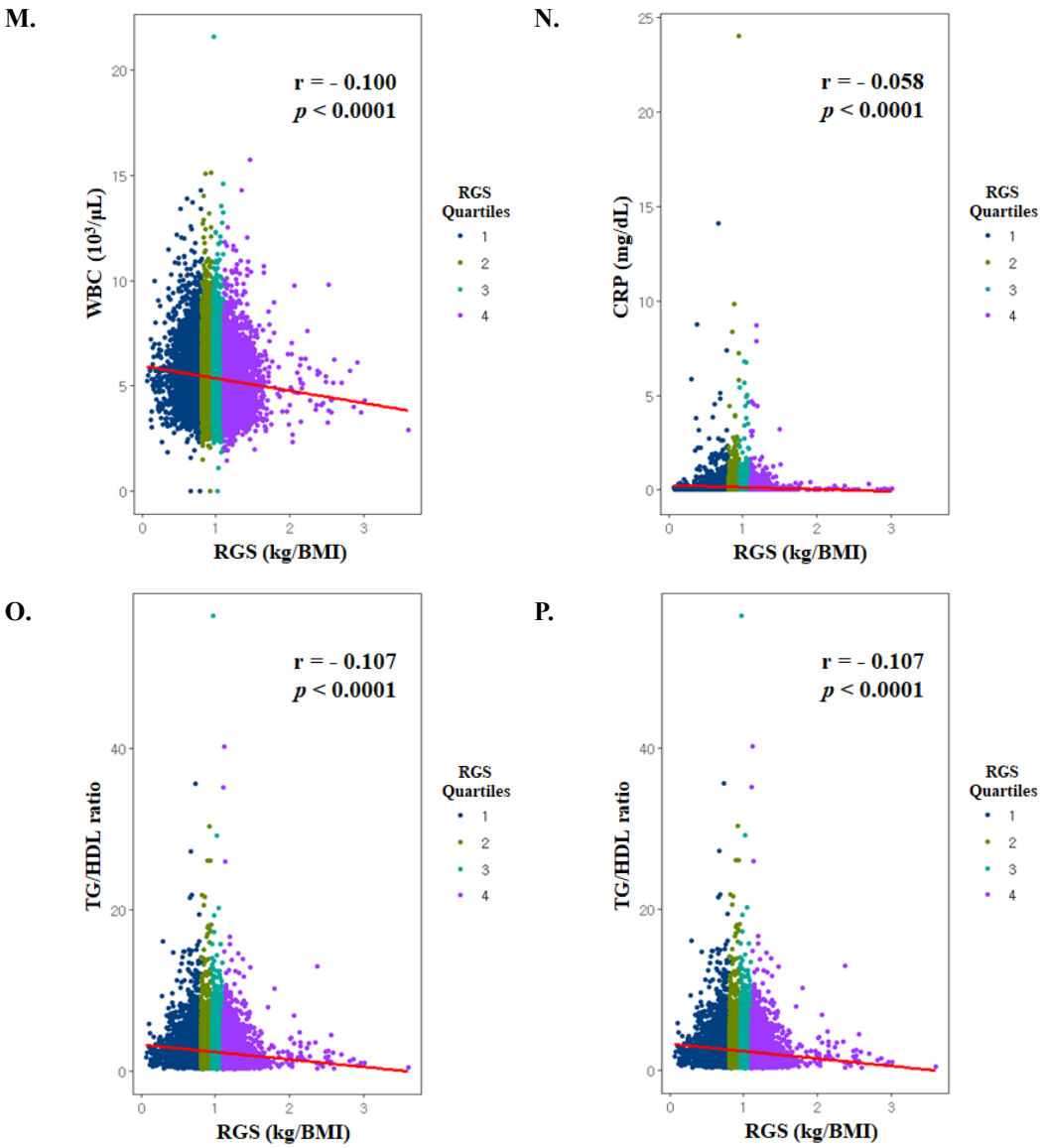


Figure 6. Scatter plots for inflammatory markers (WBC and CRP) and insulin resistance (TyG index and TG/HDL ratio) according to baseline RGS in men (A, B, C, D) in women (E, F, G, H), in pre-menopause women (I, J, K L) and in post-menopause women (M, N, O, P)

IV. DISCUSSION

The incidence of CKD was negatively related to RGS in the 12-year countrywide cohort study. In addition, relative handgrip strength, particularly in males, was an independent predictor of CKD, regardless of age, history of smoking, regular exercise, alcohol consumption, SBP, DBP, AST, ALT, TC, HDL-cholesterol, and triglyceride.

Handgrip strength is a predictor of diabetes, hypertension, and metabolic syndrome (14, 30, 31). However, rather than focusing on healthy populations, these studies frequently recommended that HGS be a useful tool to assess these comorbidities in high-risk groups. Furthermore, a number of studies have discovered a link between CKD and handgrip strength (32, 33). These investigations, however, only showed that HGS is a reliable indicator of renal function in individuals with CKD. A previous study found the usefulness of handgrip strength for the incidence of CKD based on KoGES data (34). However, we have further analysed the results by subdividing women into pre-menopausal and post-menopausal women, thereby finding that handgrip strength might be more useful in predicting CKD incidence in post-menopausal women than in pre-menopausal women. Moreover, we showed that RGS can still be used as a predictor

of CKD using various statistical methods. We have analysed the relationship between handgrip strength and mediators (WBC, CRP, TyG index, and TG/HDL ratio), further reinforcing our hypothesis of the association. Our findings are the first to show that RGS is a valuable technique for predicting incident CKD. We showed this by having a sizable sample size and by removing those who had CKD at baseline. Moreover, Kaplan Meier curves were conducted in order to find the trends for the cumulative incident rate of CKD according to baseline RGS quartiles. We also analysed both baseline and follow-up results of eGFR changes in CKD patients according to the baseline handgrip strength quartile.

Because it is inexpensive and simple to use, measuring handgrip strength is a useful method for assessing muscular strength (35). Sarcopenia is primarily caused by low muscular strength, not reduced muscle mass; muscle strength is a more accurate predictor of falls, fractures, and all-cause death than muscle mass (9, 36). As a result, handgrip strength is frequently utilized in sarcopenia diagnosis.

We found mechanisms through mediators of sarcopenia and CKD, inflammatory markers, and insulin resistance markers (37, 38). Muscles can play a role as endocrine organs by releasing myokines, cytokines secreted in muscle. Interleukin-6, one of the myokines released from muscle fibers by muscle contraction, increases as sarcopenia aggravates (39). IL-6 can lead to an inflammatory reaction on its own. Furthermore, when IL-6 reaches the liver through blood vessels, it produces

intrahepatic CRP, which is also an inflammatory marker (40). Various investigations have demonstrated elevated levels of inflammatory markers including CRP and IL-6, which can induce an increase of CRP as a pro-inflammatory cytokine (41). The inflammatory markers affect the maintenance of metabolic homeostasis (42, 43). In other words, increased IL-6 and CRP were found in inflammatory conditions such as cardiovascular diseases, rheumatoid arthritis, and metabolic syndrome (44). Since skeletal muscle makes up 40–50% of an adult's lean body mass and is the primary source of the body's insulin-stimulated glucose consumption, skeletal muscle plays a significant role in maintaining glucose homeostasis (45). Cell structure and biological activity in skeletal muscle may eventually deteriorate as a result of sarcopenia (46). It may affect glucose homeostasis by impairing insulin-stimulated glucose intake into muscle (45). Moreover, as described above, sarcopenia causes release of IL-6. When IL-6 is released into the blood, it causes an increase of glucose production in the liver (47). Furthermore, IL-6 has been reported to inhibit muscle protein synthesis and decrease insulin sensitivity by inhibiting AMP protein kinase activity (48). In summary, sarcopenia results in insulin resistance. Several sarcopenia-associated features such as mitochondrial dysfunction, decreased insulin sensitivity, and increased glucose level; these factors cause IR (49).

Inflammation and insulin resistance induced by sarcopenia can induce renal injury.

IL-6 and CRP lead to endothelial dysfunction in kidney, thereby inducing blood flow disorder as an effect of cytokine (50, 51). Furthermore, it can result in renal fibrosis through inflammatory reaction (52). Insulin is necessary for the metabolism of glucose and the kidney is an insulin target organ since the kidney is crucial for the clearance and breakdown of insulin (53). IR can cause CKD if cells, especially kidney cells, do not react to insulin. Additionally, IR can accelerate the development of dyslipidemia, obesity, fatty liver, hypertension, atherosclerosis, and dyslipidemia—all significant risk factors for CKD (13, 54-57).

Studies have shown that estrogen is associated with a slower progression of CKD in pre-menopausal women compared to men and that these protective effects disappear after menopause (58, 59). It has been demonstrated that endothelial dysfunction and decreased vasodilation caused by NO shortage might accelerate renal injury. However, estrogen promotes the release of NO. Moreover, estrogen reduces the production of renin and the enzyme angiotensin-converting enzyme (ACE), which can also diminish renal injury (60). Exposure to endogenous estrogen is linked to a decreased risk of developing CKD (61). Furthermore, the administration of continuous estradiol can prevent albuminuria and glomerulosclerosis (62). Accordingly, even if both pre-menopausal and post-menopausal women are significantly negatively associated with muscle strength and the mediators (inflammatory and insulin resistance markers), the protective

effect of estrogen for kidney can make the association of muscle strength with CKD insignificant in premenopausal women.

Despite having numerous benefits, our study has a few limitations. First, based on the KDOQI definition of CKD, a lower eGFR should be maintained for a minimum of three months (63). However, the diagnostic criteria was an eGFR of less than 60 at the first follow-up. The KoGES HEXA trial recruited a large number of patients across several clinics, making it challenging to evaluate the preservation of lowered eGFR via short-term follow-up. A number of earlier studies also used an eGFR of less than 60 to define CKD. This was true in one trial, even when there was a continued reduction in eGFR (64, 65). Furthermore, proteinuria should be present consistently in order to diagnose CKD; however only the first follow-up study was available. Proteinuria should also be collected by a quantitative test, 24-hour urine collection. However, it was diagnosed qualitatively with a urine dipstick test because 24-hr urine collection is not feasible for performing nationwide data. These two tests are not so different in detecting albuminuria (66). In addition, we could not exclude pre-menopause women who collect urine during menstrual periods because of lacking data on menstrual status. Third, even with the use of RGS adjusted for BMI, our analysis was unable to account for muscle mass since the KoGES does not have any data on muscle mass. Therefore, we were unable to

determine whether muscle mass had no bearing on the association between handgrip strength and CKD. However, handgrip strength was selected in our investigation since prior research found that this was a more valuable measure than muscle mass (36). Low muscle strength is considered a better indicator of sarcopenia than a loss of muscle mass (67, 68). Fourth, it's possible that the follow-up date and the CKD event date were not the same. The follow-up date and the incidence date did not always coincide since the follow-up cohort study was carried out independently of the onset of CKD. Furthermore, we were unable to include deceased individuals in our study since they were not followed up on. KoGES didn`t have the data whether participants were dead. Lastly, there is currently no appropriate index to delete the influence of body size (height, weight, and BMI) on handgrip strength. Dividing HGS by BMI cannot fully account for the effect of body size, even though RGS can decrease its influence (69). Nonetheless, RGS has been extensively applied to reduce the impacts of body size (14). For muscle strength-associated indices that are independent of body size, more research is required.

V. CONCLUSION

We discovered that RGS, particularly in men, was independently adversely correlated for incident CKD. The predictive power of handgrip strength with incident CKD is higher in men than in post-menopause women. The effect of handgrip strength was not significant in predicting CKD in pre-menopause women. RGS is a helpful method for estimating incident CKD. To identify CKD, handgrip strength should be measured regularly.

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국 문 요 약

성별에 따른 만성콩팥병의 발생에 대한 예측인자로서의 악력의 유용성: 한국인을 대상으로 한 코호트 연구를 기반으로

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악력 (Handgrip strength) 은 폐렴, 심혈관 질환 및 암과 같은 많은 질병의 지표이다. 악력은 만성 신장 질환 (CKD) 환자의 신장 기능도 예측할 수 있는 것으로 알려져있지만 아직까지 새롭게 발병하는 만성콩팥병의 예측 인자로서의 악력의 가치는 알려진 바가 없다.

전국적인 코호트 조사를 통하여 173,195명의 피험자를 모집하여 4.1년간 추적 관찰했다. 특정 기준에 따라 대상을 제외한 후 35,636명의 참가자가 최종 연구에 포함되었으며 추적 기간 동안 1062명에서 만성콩팥병이 발생했다. 생활 습관, 인체 측정 및 실험실 데이터는 만성콩팥병 위험과 관련하여 평가되었다.

참가자들은 상대 악력에 따라 4분위수로 세분화되었다. 절대악력은 양측의 악력값 중 최대값으로 정의하였으며, 상대악력은 절대악력을 체질량 지수 (BMI) 로 나눈 값으로 정의하였다. 다변량 콕스 회귀 분석 결과, 상대악력은 만성콩팥병의 발생과 반비례하는 것으로 나타났다. 최하위 사분위수 (Q1) 와 비교했을 때, 공변량을 조정한 후 최상위 사분위수 (Q4)의 만성콩팥병 발생 위험비 (hazard ratio) [95% 신뢰구간(CI)]는 남성에서 0.62 (0.45 - 0.86), 여성에서 0.92 (0.72 – 1.17) 폐경 전 여성에서 1.03 (0.69 - 1.56) 폐경 후 여성에서 0.92 (0.69 – 1.24)

이었다. 만성콩팥병의 발생률은 상대악력이 증가함에 따라 감소했다. ROC 곡선은 기준 상대악력 (baseline RGS) 이 새로 발병한 만성콩팥병에 대한 예측력을 가지고 있음을 보여주었다. 곡선하 면적 (AUC) (95% 신뢰구간) 은 남성에서 0.597 (0.571 - 0.623), 여성에서 0.532 (0.509 – 0.555), 폐경 전 여성에서 0.506 (0.468 - 0.545), 폐경 후 여성에서 0.541 (0.513 – 0.568) 이었다. 카플란 마이어 곡선에서는 기준 상대악력 사분위수에 따른 누적 만성콩팥병 발생률 차이의 추세가 추적 관찰 기간 동안 변하지 않는 것으로 나타났다.

이 연구는 상대악력이 만성콩팥병의 발생률과 관련이 있음을 보여주는 새로운 연구다. 특히, 상대악력과 만성콩팥병의 발생률간의 관계는 남성에서 더 유의하게 나타났다. 악력의 CKD 발생 예측력은 폐경 후 여성보다 남성에서 더 높았다. 폐경 전 여성에서 CKD를 예측하는 데 있어서 악력의 영향력은 유의하지 않았다. 결론적으로 상대악력은 임상에서 신장 예후를 평가하는 데 사용할 수 있다. 만성콩팥병을 감지하려면 주기적으로 악력을 측정하는 것이 중요하다.

핵심 되는 말: 악력, 근육감소증, 신장 기능, 만성 콩팥병, 성별간 차이