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Cardiovascular and Mortality Risks in Young Health Screening Examinees With Marginal Estimated GFR

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Introduction: Additional evidence is necessary to interpret kidney function parameters in young adults, particularly in those with marginal estimated glomerular filtration rate (eGFR) values. Therefore, we aimed to investigate the association between eGFR and adverse outcomes in general young adults.

Methods: We performed a nationwide retrospective cohort study using the health-screening database of South Korea. We included young adults aged 20–39 years without a history of major adverse cardiovascular events (MACE) or kidney failure, who underwent nationwide health screening in 2012. The study exposure was eGFR categorized into 15 ml/min per 1.73 m^2 intervals. The risks of all-cause mortality and MACE were calculated using Cox regression analysis, adjusted for various clinicodemographic characteristics.

Results: In total, 3,132,409 young adults were included in this study. During a median follow-up of 7.3 years, marginal eGFR (60–75 ml/min per 1.73 m^2) was not significantly associated with a higher risk of all-cause mortality (adjusted hazard ratio [aHR], 0.80 [0.74–0.87]). The results were similar for MACE outcomes (aHR, 0.94 [0.87-1.01]). Although the presence of dipstick albuminuria had a significant interaction with the association between eGFR categories and all-cause mortality (interaction term $P = 0.028$), the risks of all-cause mortality were not significantly higher (aHR, 0.98 [0.62, 1.55]) in those with albuminuria and eGFR 60–75 ml/min per 1.73 m^2.

Conclusion: Marginal eGFR was not associated with higher risks of all-cause mortality and MACE in general young adults. Additional clinical investigations for incidentally found marginal eGFR values may be discouraged in general young adults.

Kidney Int Rep (2023) **8,** 2709–2719; https://doi.org/10.1016/j.ekir.2023.09.008
KEYWORDS: chronic kidney disease; epidemiology; glomerular filtration rate; major cardiovascular events; mortality; young adult

The prevalence and socioeconomic burden of chronic kidney disease (CKD) have increased over the past decades along with the global aging trend.[1,2] The current definition of CKD in adults is based on the 2012 Kidney Disease Improving Global Outcomes guidelines. According to this guideline, the criteria for the definition of CKD include glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2 or the presence of markers of kidney damage, often determined by elevated albuminuria, persisting for at least 3 months.[3]

Although it has already been over 2 decades since the current definition of CKD was used, there have been continuous discussions about an absolute threshold of GFR <60 ml/min per 1.73 m^2, regardless of age. The main issue related to the current definition of CKD is that the criteria do not consider the physiological decline in GFR that occurs with normal healthy aging.[4] In addition, a substantial number of healthy

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Received 4 January 2023; revised 7 June 2023; accepted 4 September 2023; published online 7 September 2023

elderly individuals have a GFR <60 ml/min per 1.73 m^2 in other studies.[5–7] Because of these phenomena, some addressed that the current definition of CKD with fixed criteria of GFR may lead to overdiagnosis of CKD, especially in older adults.[8]

In contrast, some considered that the threshold of GFR below 60 ml/min per 1.73 m^2 may be too low to diagnose CKD in young adults <40 years of age.[9] Considering that the average GFR in healthy young adults is about 100–110 ml/min per 1.73 m^2, the current CKD definition may underestimate the prevalence of CKD in young adults.[6,9] Although the GFR threshold to define CKD is determined by its association with mortality or cardiovascular risks, a previous study ascertained the risk of mortality according to categories of age and identified that eGFR below 75 ml/min per 1.73 m^2 is associated with increased mortality in general and in high risks cohorts with age <55 years.[10,11] Therefore, those who advocate for age-calibrated definition of CKD suggest that the GFR threshold of CKD for young adults should be raised to 75 ml/min per 1.73 m^2.[9,12] Despite the controversy, there have been few large-scale studies targeting general young adults that have investigated the association between incidentally found marginal eGFR and adverse outcomes. Such evidence would be important in advising clinicians on whether to pay additional sociomedical resources for incidentally detected marginal eGFR (60–75 ml/min per 1.73 m^2) in general young adults.

In this study, we aimed to investigate the association between eGFR and the risk of mortality and MACE in a unique cohort of general young adults from a nationwide health screening database in South Korea. We hypothesized that young adults with marginal eGFR would exhibit a worse prognosis.

METHODS

Ethics Considerations

This study was approved by the Institutional Review Board of the Seoul National University Hospital (E-2112-048-1281). The Korean National Health Insurance Service (NHIS) database was approved by the relevant government organizations. The study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because this retrospective study used fully anonymous and unidentifiable data.

Study Setting

This study used nationwide health screening data from the Korean NHIS database, as described in our previous studies.[13,14] In South Korea, a nationwide health screening program that includes clinicodemographic assessments, lifestyle evaluations, and laboratory tests is provided to all Korean citizens. The data are also linked to the nationwide claims database, which included information on all insured medical services coded according to the International Classification of Diseases, Tenth Revision (ICD-10). The database has the benefit of availability of large-scale serum creatinine measurements, even for young adults, because schools and workplaces provide charge-free general health screenings for their members. In addition, complete follow-up information within the nation is available because health insurance is provided by a single insurer.

Study Population

As the main study target, we included young adults aged 20 to 39 years who underwent a national health screening conducted in 2012. The year 2012 was chosen to ensure both sufficient underlying disease screening period and certain follow-up duration, considering the data availability of the National Health Insurance Database. Those with missing data were excluded. Given that we aimed to investigate the incident risks of myocardial infarction and stroke, those with a history of outcomes before follow-up were excluded. Those previously diagnosed with kidney failure were also excluded because the kidney function parameters fluctuate among those who undergo dialysis or transplantation.

Study Outcomes

The primary outcome was all-cause mortality. All-cause mortality was defined using the claims database, which included nationwide mortality events collected from death certificates. The secondary outcome was the occurrence of MACE defined as a composite of myocardial infarction and stroke. As in a previous study,[15] myocardial infarction was recorded if an individual had ICD-10 code I21 or I22 during hospitalization. Stroke was defined using ICD-10 codes I63 or I64 during hospitalization, with claims information for brain magnetic resonance imaging or brain computed tomography imaging. All the participants were followed up from the date of the baseline health screening visit at which the initial eGFR was measured and censored on the last date of data availability or the date of death or cardiovascular events.

Ascertainment of eGFR Exposure

In this study, kidney function was assessed using eGFR, which was calculated using the Modification of Diet in Renal Disease equation based on the Jaffe serum creatinine value. The main exposure variable was eGFR, and the study participants were classified into 8 different groups by eGFR: <30, 30 to 45, 45 to 60, 60 to 75, 75 to

90, 90 to 105, 105 to 120, and ≥120 ml/min per 1.73 m^2. Considering that the average eGFR in healthy young adults is about 100 to 110 ml/min per 1.73 m^2,[6] we determined the eGFR 105 to 120 ml/min per 1.73 m^2 group as the reference group. An additional sensitivity analysis was performed with eGFR calculation equations that have been developed in recent periods, although a certain readjustment of serum creatinine levels was necessary. For the analysis, the traditional Jaffe serum creatinine values were recalibrated to current standard isotope dilution mass spectrometry traceable creatinine (IDMS-traceable Cr) values using the equation: Conventional serum creatinine (mg/dl) = (IDMS-traceable Cr)*1.065 + 0.067.[16] The eGFR was recalculated using the CKD Epidemiology Collaboration 2021[17] and the European Kidney Function Consortium equations.[18] Sensitivity analysis was performed in a similar manner to the Modification of Diet in Renal Disease eGFR.

Data Collection

The Korean NHIS dataset contains demographic, anthropometric, lifestyle factors, and laboratory data. The study outcomes and medical histories were obtained from the claims database. We collected baseline information, including age and sex, anthropometric data, including height, weight, waist circumference, and blood pressure, and laboratory data, such as baseline eGFR, presence of dipstick albuminuria (≥1+), fasting glucose, total cholesterol, high-density lipoprotein, and low-density lipoprotein. Information related to social and lifestyle factors, such as low-income status (<20th percentile of the country), current smoking history, alcohol intake (>0 g of alcohol intake per day), and regular physical activity (moderate-intensity physical activity ≥5 days or vigorous-intensity physical activity ≥3 days per week) was collected through a questionnaire used in the nationwide health screening program. Past medical histories included diabetes mellitus (ICD-10 codes E11-14 with relevant antidiabetic medication history), hypertension (ICD-10 codes I10-13 or I15 with relevant antihypertensive medication history), and dyslipidemia (ICD-10 code E78 with relevant dyslipidemia medication history).

Statistical Analysis

Categorical variables are presented as frequencies (percentages) and continuous variables are presented as means (± SDs). Incidence rates (events per 1000 person-years) were also calculated. The Kaplan-Meier survival curve was plotted to describe the incidence probability of all-cause mortality. Considering that all-cause mortality is a competing risk of MACE outcome, the cumulative incidence function curve was plotted to describe the incidence probability of MACE.

We performed Cox regression analysis to assess the risk of the study outcomes. In addition to a univariate model, considering potential confounding effects, a model adjusted for age and sex, and a multivariate model including various collected covariates were constructed. In the multivariate model, age, sex, income status, smoking, alcohol consumption, physical activity, history of diabetes mellitus, hypertension, dyslipidemia, and presence of dipstick albuminuria were adjusted.

In addition, to assess the clinical significance of the marginal eGFR values in the diverse subgroups, we performed subgroup analyses with stratification according to the presence of hypertension, diabetes, and dipstick albuminuria. Considering false positive rates of dipstick albuminuria test, we defined the presence of dipstick albuminuria as ≥1+ and ≥2+ and conducted subgroup analysis in both cases. Using interaction term analysis, we investigated whether comorbidities and proteinuria had a notable interaction with the association between eGFR categories and adverse outcome risks.

All statistical analyses were performed using SAS (version 9.4, SAS Institute), and 2-sided *P*-values <0.05 were considered statistically significant.

RESULTS

Study Population

We identified 12,310,276 individuals who underwent the national health screening in 2012. There were 3,436,758 individuals aged 20 to 39 years. After excluding individuals with missing information and those with previous myocardial infarction, stroke, or kidney failure, 3,132,409 individuals were finally included in the study (Figure 1).

Baseline Characteristics

The baseline characteristics of the study participants, according to eGFR, are presented in Table 1. Those with a lower eGFR tended to have a higher proportion of individuals with the presence of dipstick albuminuria and a history of diabetes, hypertension, and dyslipidemia. Comparing the 2 groups with eGFR of 60 to 75 ml/min per 1.73 m^2 and 105 to 120 ml/min per 1.73 m^2, individuals with eGFR 60 to 75 ml/min per 1.73 m^2 were older and had a higher proportion of individuals who were males. Comparing the eGFR 60 to 75 ml/min per 1.73 m^2 group with those with eGFR <60 ml/min per 1.73 m^2, individuals with eGFR 60 to 75 ml/min per 1.73 m^2 had a higher proportion of males, current smokers, and alcohol consumers. Those with low-income status were frequently identified in those with prominently low or high eGFR values.

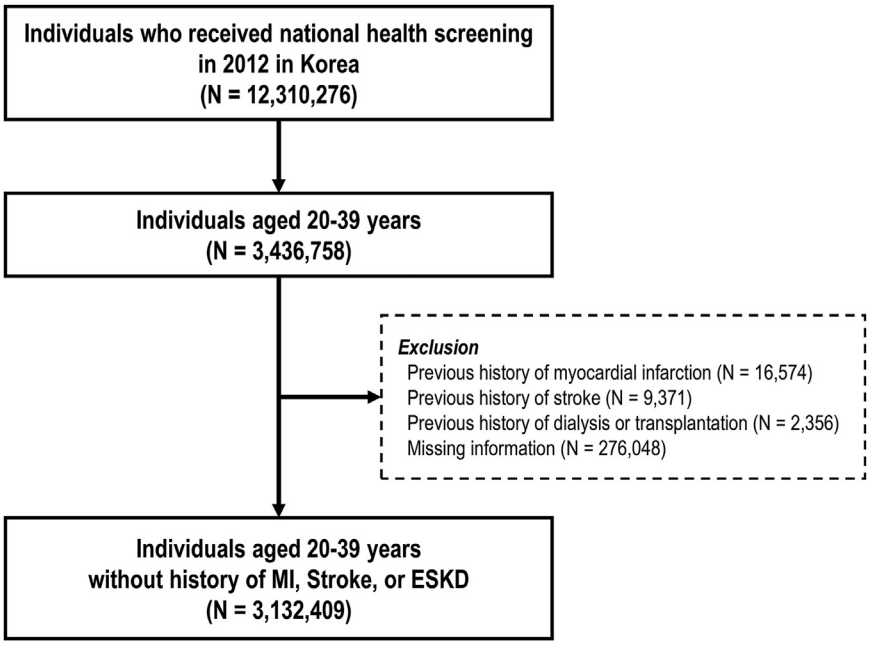

Figure 1. Flow chart of study population.

Table 1. Baseline characteristics of study population according to eGFR

	eGFR							
	<30	30–45	45–60	60–75	75–90	90–105	105–120	≥120
Variable	(*n* = 1089)	(*n* = 819)	(*n* = 12247)	(*n* = 277664)	(*n* = 893353)	(*n* = 1029555)	(*n* = 466425)	(*n* = 451257)
Age (yr)	32.42 ± 4.71	33.47 ± 4.34	33.53 ± 4.67	33.51 ± 4.46	32.57 ± 4.62	31.87 ± 4.33	29.82 ± 5.15	29.82 ± 4.44
20–29 yr	294 (27)	154 (19)	2721 (22)	53145 (19)	227737 (25)	281147 (27)	269801 (58)	213926 (47)
30–39 yr	795 (73)	665 (81)	9526 (78)	224519 (81)	665616 (75)	748408 (73)	196624 (42)	237331 (53)
Sex, Male	632 (58)	460 (56)	4631 (38)	186503 (67)	574672 (64)	714369 (69)	288779 (62)	189554 (42)
Anthropometric findings								
Height (cm)	168.04 ± 8.48	167.66 ± 8.5	166.08 ± 8.48	169.83 ± 8.18	169.25 ± 8.27	169.71 ± 8.12	168.65 ± 8.28	165.95 ± 8.4
Weight (kg)	66.33 ± 14.72	67.29 ± 15.45	64.67 ± 14.61	69.18 ± 13.94	67.41 ± 13.62	67.76 ± 13.60	65.66 ± 13.84	62.35 ± 13.57
BMI (kg/m^2)	23.3 ± 3.92	23.75 ± 4.25	23.27 ± 3.99	23.83 ± 3.68	23.38 ± 3.60	23.38 ± 3.63	22.93 ± 3.71	22.48 ± 3.70
Waist circumference (cm)	78.45 ± 10.99	79.07 ± 11.1	76.51 ± 10.81	79.4 ± 10.19	78.48 ± 10	78.98 ± 10.01	77.53 ± 10.29	75.92 ± 10.27
Systolic BP (mmHg)	121.32 ± 15.96	122.2 ± 18.05	117.04 ± 14.5	118.69 ± 13.33	118.05 ± 13.11	118.51 ± 13.04	117.66 ± 13.02	115.56 ± 12.99
Diastolic BP (mmHg)	76.6 ± 11.16	77.2 ± 12.42	73.97 ± 10.39	74.75 ± 9.67	74.21 ± 9.42	74.44 ± 9.36	73.8 ± 9.27	72.45 ± 9.30
Social and lifestyle factors								
Income, Lower 20 %	137 (13)	117 (14)	1859 (15)	24907 (9)	83219 (9)	93906 (9)	54749 (12)	59700 (13)
Current smoker	297 (27)	239 (29)	2611 (21)	96438 (35)	308188 (35)	397343 (39)	165711 (36)	115620 (26)
Alcohol intake (>0 g/day)	586 (54)	429 (52)	6597 (54)	179711 (65)	576844 (65)	686911 (67)	309535 (66)	259762 (58)
Regular physical activity[a]	164 (15)	119 (15)	2057 (17)	47198 (17)	137561 (15)	148649 (14)	65888 (14)	54762 (12)
Comorbidities								
Diabetes mellitus	62 (6)	70 (9)	387 (3)	6296 (2)	16803 (2)	20328 (2)	8670 (2)	7939 (2)
Hypertension	345 (32)	360 (44)	1521 (12)	24909 (9)	65570 (7)	77043 (7)	31855 (7)	25676 (6)
Dyslipidemia	217 (20)	239 (29)	1594 (13)	29722 (11)	74221 (8)	80184 (8)	28537 (6)	26686 (6)
Laboratory findings								
Fasting glucose (mg/dL)	93.62 ± 21.14	96.41 ± 29.59	93.21 ± 21.54	92.67 ± 16.06	91.71 ± 15.27	91.63 ± 16.13	90.57 ± 16.38	89.55 ± 16.78
Total cholesterol (mg/dL)	186.29 ± 38.18	195.47 ± 43.59	193.06 ± 37.13	193.12 ± 34.52	188.67 ± 33.69	187.28 ± 33.67	182.48 ± 33.01	180.62 ± 33.94
HDL (mg/dl)	55.98 ± 15.14	56.32 ± 16.26	60.06 ± 17.96	56.45 ± 18.56	56.79 ± 19.84	56.22 ± 19.35	57.54 ± 18.40	59.58 ± 16.68
LDL (mg/dl)	104.76 ± 33.59	110.47 ± 37.83	109.41 ± 35.46	111.32 ± 32.18	108.48 ± 31.28	107.52 ± 31.21	103.22 ± 30.28	100.49 ± 29.61
eGFR (mL/min/1.73m^2)	10.17 ± 8.22	39.34 ± 4.26	56.09 ± 3.42	70.23 ± 3.8	83.17 ± 4.31	97.21 ± 5.01	111.16 ± 4.92	143.94 ± 91.07
Urine albuminuria[b] (≥ 1+)	225 (21)	238 (29)	768 (6)	5890 (2)	13376 (2)	13355 (1)	6008 (1)	5930 (1)

eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.
[a]Regular physical activity was defined as moderate-intensity physical activity ≥5 days or vigorous-intensity physical activity ≥3 days per week.
[b]Urine albuminuria means the presence of dipstick albuminuria (≥1+).
Data are presented as the mean (1 SD) for continuous variables or number (%) for categorical variables.

Risks of All-Cause Mortality and MACE According to eGFR

During the median follow-up of 7.3 years (interquartile range: 7.13–7.55 years), 10,552 (0.34%) mortality, 8259 (0.26%) myocardial infarction, and 4622 (0.15%) stroke events were identified in the study population. The incidence rates and HRs of adverse outcomes in each eGFR group are shown in Table 2 and Figure 2. The risk of all-cause mortality was not significantly higher in the eGFR 60 to 75 ml/min per 1.73 m^2 group (HR, 0.96 [0.89–1.04]), whereas 3 groups with eGFR <60 ml/min per 1.73 m^2 had significantly higher risks of all-cause mortality. In the multivariable model adjusted for age, sex, and other clinicodemographic covariates, the HR was even lower (aHR, 0.80 [0.74–0.87]) (Figure 3).

In terms of the risks of MACE, a higher risk was only identified in the univariate analysis in the eGFR 60–75 ml/min per 1.73 m^2 group (HR, 1.24 [1.15–1.33]) when compared to the reference group. However, in the multivariable model, the risk of MACE was not significantly higher in the eGFR 60 to 75 ml/min per 1.73 m^2 group (aHR, 0.94 [0.87–1.01]) (Figure 3). In addition, those with extremely high eGFR (e.g., eGFR ≥120 ml/min per 1.73 m^2) showed higher risks for all-cause mortality (aHR, 1.08 [1.00–1.16]) and MACE (aHR, 1.08 [1.00–1.15]) compared to the reference group.

Subgroup Analysis

The presence of dipstick albuminuria had a significant interaction with the association between eGFR categories and all-cause mortality (interaction term $P = 0.028$) (Table 3). However, the risks of all-cause mortality were not significantly higher in those with eGFR 60 to 75 ml/min per 1.73 m^2, regardless of the presence of dipstick albuminuria (Figure 4). In addition, the risks of ischemic stroke (aHR, 2.31 [1.17–4.54]) and MACE (aHR, 1.58 [1.02–2.45]) were significantly higher in the eGFR 60–75 ml/min per 1.73 m^2 group in those with dipstick albuminuria, although the presence of dipstick albuminuria did not have a significant

Table 2. Risk of adverse outcomes according to eGFR

						Univariable model		Age, sex adjusted model		Multivariable model[a]	
Outcome	eGFR	*N*	Events	Duration (PY)	IR (/1000 PY)	HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
All-cause mortality	<30	1089	11	7899	1.39	2.99 (1.65, 5.41)	<0.001	2.67 (1.48, 4.84)	0.001	2.04 (1.13, 3.70)	0.019
	30–45	819	9	5960	1.51	3.25 (1.69, 6.25)	<0.001	2.82 (1.46, 5.42)	0.002	1.82 (0.94, 3.51)	0.07
	45–60	12247	62	89466	0.69	1.49 (1.15, 1.92)	0.002	1.45 (1.12, 1.87)	0.004	1.34 (1.04, 1.73)	0.025
	60–75	277664	912	2035123	0.45	0.96 (0.89, 1.04)	0.33	0.77 (0.71, 0.84)	<0.001	0.80 (0.74, 0.87)	<0.001
	75–90	893353	2952	6552209	0.45	0.97 (0.91, 1.03)	0.26	0.83 (0.78, 0.89)	<0.001	0.87 (0.81, 0.92)	<0.001
	90–105	1029555	3569	7554259	0.47	1.01 (0.95, 1.07)	0.68	0.89 (0.83, 0.94)	<0.001	0.91 (0.86, 0.96)	0.001
	105–120	466425	1598	3423838	0.47	1 (Reference)		1 (Reference)		1 (Reference)	
	≥120	451257	1439	3307722	0.44	0.93 (0.87, 1.00)	0.05	1.09 (1.01, 1.17)	0.026	1.08 (1.00, 1.16)	0.046
Myocardial infarction	<30	1089	3	7892	0.38	1.12 (0.36, 3.49)	0.84	0.98 (0.32, 3.03)	0.97	0.66 (0.21, 2.04)	0.47
	30–45	819	6	5948	1.01	2.98 (1.34, 6.64)	0.008	2.48 (1.11, 5.54)	0.026	1.40 (0.63, 3.12)	0.41
	45–60	12247	40	89374	0.45	1.32 (0.96, 1.81)	0.09	1.22 (0.89, 1.67)	0.22	1.07 (0.78, 1.47)	0.68
	60–75	277664	810	2033119	0.4	1.17 (1.07, 1.28)	0.001	0.91 (0.83, 0.99)	0.035	0.92 (0.84, 1.00)	0.06
	75–90	893353	2408	6546122	0.37	1.08 (1.01, 1.16)	0.035	0.91 (0.84, 0.97)	0.006	0.93 (0.87, 1.00)	0.05
	90–105	1029555	2772	7547432	0.37	1.08 (1.00, 1.15)	0.037	0.93 (0.87, 0.99)	0.032	0.95 (0.88, 1.01)	0.12
	105–120	466425	1169	3420929	0.34	1 (Reference)		1 (Reference)		1 (Reference)	
	≥120	451257	1051	3305248	0.32	0.93 (0.86, 1.01)	0.10	1.08 (0.99, 1.17)	0.08	1.06 (0.98, 1.16)	0.16
Stroke	<30	1089	11	7876	1.4	7.81 (4.31, 14.18)	<0.001	6.28 (3.46, 11.39)	<0.001	3.36 (1.84, 6.13)	<0.001
	30–45	819	7	5944	1.18	6.59 (3.13, 13.87)	<0.001	4.91 (2.33, 10.35)	<0.001	2.19 (1.03, 4.64)	0.041
	45–60	12247	34	89364	0.38	2.13 (1.51, 3.01)	<0.001	1.67 (1.18, 2.36)	0.004	1.40 (0.99, 1.98)	0.06
	60–75	277664	507	2033476	0.25	1.39 (1.24, 1.57)	<0.001	0.99 (0.88, 1.11)	0.84	1.00 (0.89, 1.13)	0.99
	75–90	893353	1381	6547979	0.21	1.18 (1.07, 1.30)	0.001	0.92 (0.84, 1.01)	0.10	0.96 (0.87, 1.05)	0.36
	90–105	1029555	1479	7549951	0.2	1.09 (1.00, 1.20)	0.06	0.92 (0.84, 1.01)	0.07	0.95 (0.86, 1.04)	0.25
	105–120	466425	613	3421976	0.18	1 (Reference)		1 (Reference)		1 (Reference)	
	≥120	451257	590	3305955	0.18	1.00 (0.89, 1.12)	0.95	1.13 (1.00, 1.26)	0.042	1.11 (0.99, 1.24)	0.08
MACE	<30	1089	13	7871	1.65	3.23 (1.87, 5.57)	<0.001	2.73 (1.58, 4.70)	<0.001	1.68 (0.97, 2.91)	0.06
	30–45	819	12	5938	2.02	3.99 (2.27, 7.01)	<0.001	3.19 (1.82, 5.62)	<0.001	1.62 (0.92, 2.87)	0.10
	45–60	12247	72	89277	0.81	1.57 (1.24, 1.99)	<0.001	1.37 (1.08, 1.73)	0.009	1.18 (0.94, 1.50)	0.16
	60–75	277664	1293	2031521	0.64	1.24 (1.15, 1.33)	<0.001	0.93 (0.86, 1.00)	0.046	0.94 (0.87, 1.01)	0.09
	75–90	893353	3728	6542020	0.57	1.11 (1.05, 1.17)	0.001	0.91 (0.86, 0.96)	0.001	0.94 (0.88, 0.99)	0.021
	90–105	1029555	4184	7543269	0.55	1.08 (1.02, 1.14)	0.010	0.92 (0.87, 0.97)	0.003	0.94 (0.89, 0.99)	0.029
	105–120	466425	1764	3419100	0.52	1 (Reference)		1 (Reference)		1 (Reference)	
	≥120	451257	1625	3303507	0.49	0.95 (0.89, 1.02)	0.17	1.09 (1.02, 1.17)	0.011	1.08 (1.01, 1.15)	0.033

CI, confidence interval; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiovascular event.
[a]Multivariable model was adjusted for age, sex, current-smoking, drinking alcohol consumption, regular physical activity, low-income status, history of diabetes mellitus, hypertension, dyslipidemia, presence of dipstick albuminuria.

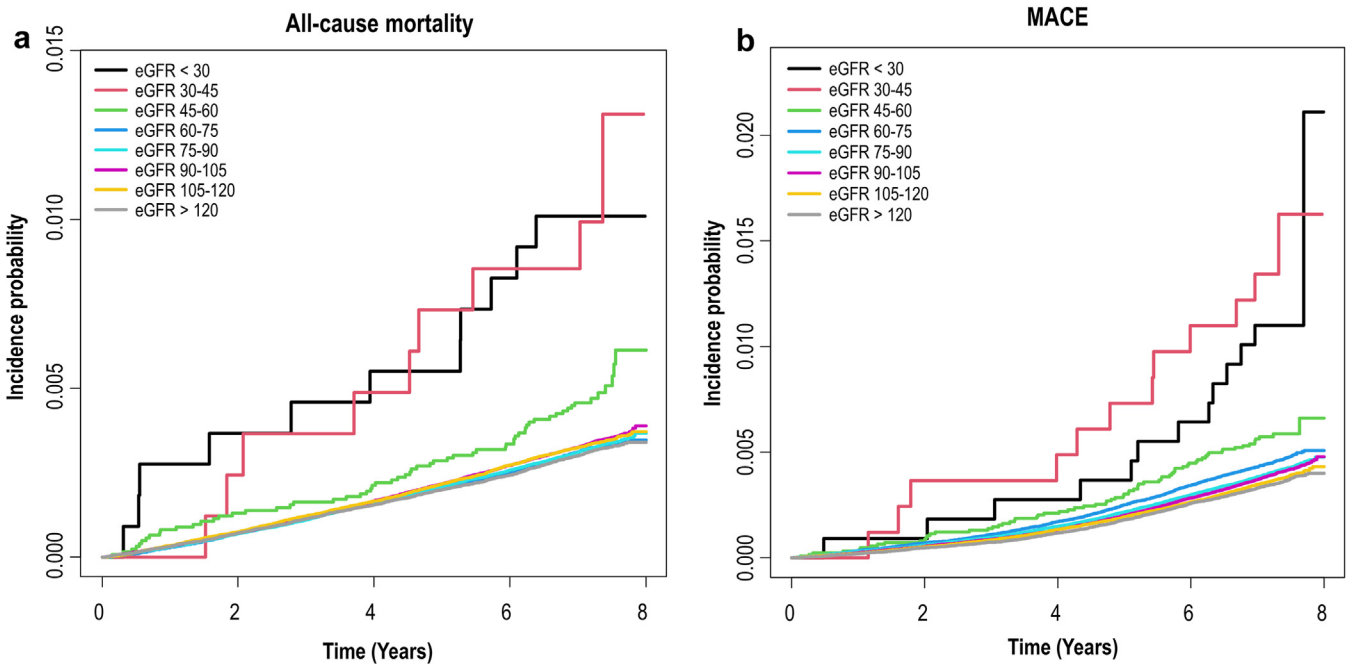

Figure 2. Incidence probability of all-cause mortality and major adverse cardiovascular events according to eGFR. (a) Kaplan Meier survival curve for all-cause mortality, (b) Cumulative incidence function curve for MACE. The x-axes indicate the time (years). The y-axes indicate the incidence probability of the adverse outcomes. eGFR, estimated glomerular filtration rate.

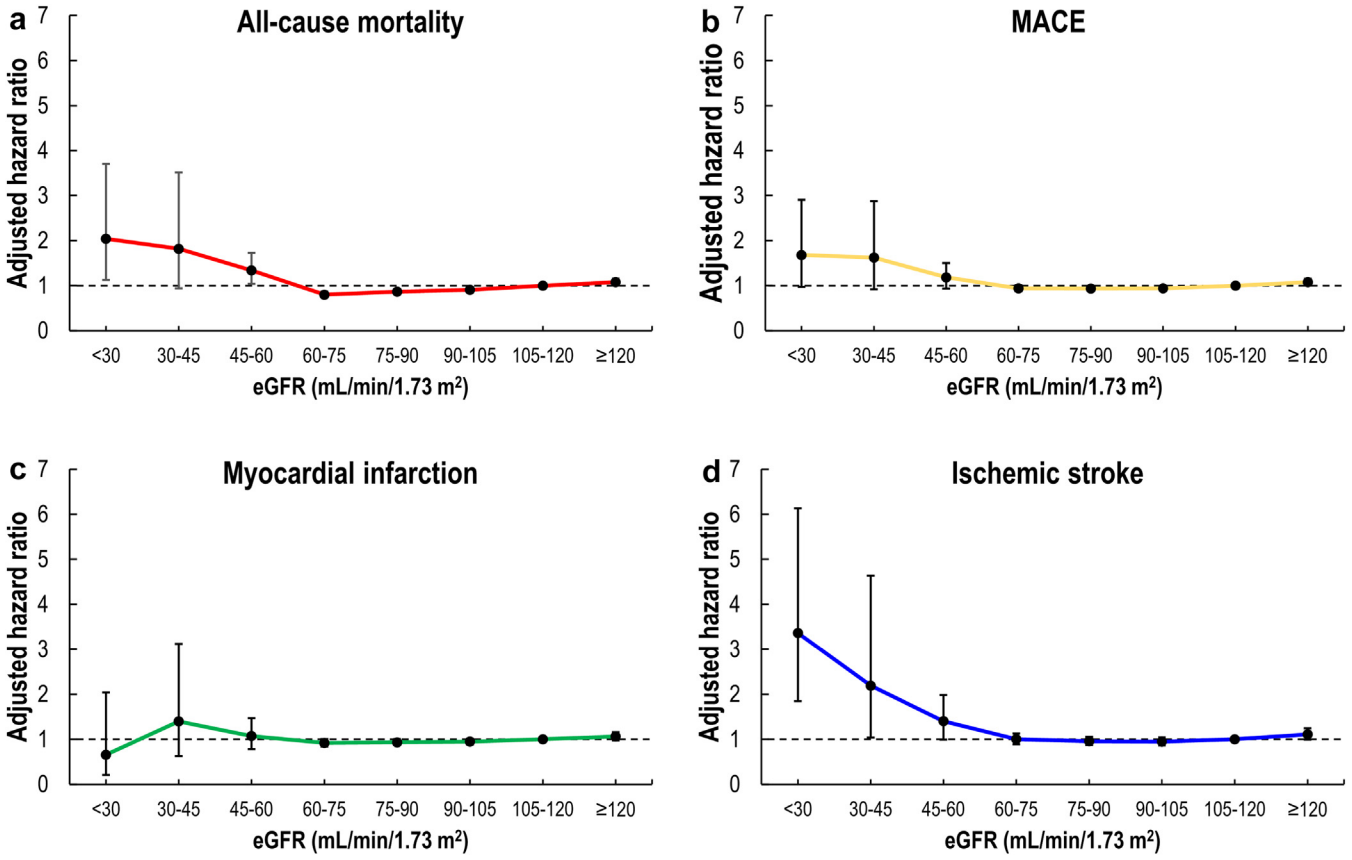

Figure 3. Risks of the adverse outcomes according to eGFR. (a) All-cause mortality, (b) MACE, (c) Myocardial infarction, (d) Ischemic stroke. The y-axes indicate the multivariable adjusted hazard ratios of the adverse outcomes, and x-axes indicate eGFR categories. A multivariable model was adjusted for age, sex, income status, smoking, alcohol consumption, physical activity, history of diabetes mellitus, hypertension, and dyslipidemia, and presence of dipstick albuminuria. eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event.

Table 3. Risk of adverse outcomes according to eGFR in subgroups stratified by the presence of dipstick albuminuria

Outcome			All-cause mortality				Myocardial infarction				Ischemic Stroke				MACE			
Sub group	eGFR	N	Event	Duration	IR	aHR (95% CI)	Event	Duration	IR	aHR (95% CI)	Event	Duration	IR	aHR (95% CI)	Event	Duration	IR	aHR (95% CI)
ALB. (−)[a]	<30	864	7	6254	1.12	2.05 (0.98, 4.31)	3	6246	0.48	1.07 (0.35, 3.34)	8	6238	1.28	4.64 (2.32, 9.31)	10	6233	1.60	2.24 (1.20, 4.17)
	30–45	581	3	4241	0.71	1.13 (0.36, 3.51)	5	4229	1.18	2.13 (0.88, 5.12)	3	4233	0.71	1.95 (0.63, 6.06)	7	4226	1.66	1.83 (0.87, 3.84)
	45–60	11479	47	83905	0.56	1.16 (0.87, 1.55)	35	83831	0.42	1.06 (0.76, 1.49)	28	83829	0.33	1.35 (0.93, 1.98)	61	83760	0.73	1.15 (0.89, 1.49)
	60–75	271774	872	1992002	0.44	0.79 (0.73, 0.86)	782	1990071	0.39	0.91 (0.83, 1.00)	472	1990471	0.24	0.97 (0.86, 1.09)	1231	1988587	0.62	0.92 (0.86, 1.00)
	75–90	879977	2898	6454061	0.45	0.87 (0.82, 0.93)	2350	6448129	0.36	0.93 (0.86, 1.00)	1342	6449957	0.21	0.95 (0.86, 1.05)	3633	6444152	0.56	0.93 (0.88, 0.99)
	90–105	1016200	3491	7456300	0.47	0.91 (0.85, 0.96)	2713	7449609	0.36	0.94 (0.88, 1.01)	1443	7452105	0.19	0.94 (0.85, 1.03)	4092	7445546	0.55	0.94 (0.88, 0.99)
	105–120	460417	1564	3379784	0.46	1 (Reference)	1150	3376933	0.34	1 (Reference)	602	3377954	0.18	1 (Reference)	1734	3375137	0.51	1 (Reference)
	≥120	445327	1403	3264355	0.43	1.07 (1.00, 1.15)	1032	3261917	0.32	1.06 (0.98, 1.16)	572	3262636	0.18	1.09 (0.98, 1.23)	1588	3260224	0.49	1.07 (1.00, 1.15)
ALB. (+)[b]	<30	225	4	1646	2.43	2.05 (0.73, 5.77)	0	1646	0.00	-	3	1638	1.83	2.88 (0.80, 10.31)	3	1638	1.83	1.19 (0.36, 3.91)
	30–45	238	6	1718	3.49	2.65 (1.11, 6.32)	1	1718	0.58	0.61 (0.08, 4.56)	4	1711	2.34	3.60 (1.15, 11.29)	5	1711	2.92	1.82 (0.71, 4.70)
	45–60	768	15	5561	2.70	2.62 (1.43, 4.82)	5	5543	0.90	1.34 (0.50, 3.59)	6	5535	1.08	2.38 (0.88, 6.45)	11	5517	1.99	1.78 (0.89, 3.54)
	60–75	5890	40	43121	0.93	0.98 (0.62, 1.55)	28	43049	0.65	1.16 (0.65, 2.07)	35	43006	0.81	2.31 (1.17, 4.54)	62	42934	1.44	1.58 (1.02, 2.45)
	75–90	13376	54	98149	0.55	0.65 (0.42, 0.99)	58	97994	0.59	1.21 (0.72, 2.04)	39	98022	0.40	1.33 (0.68, 2.60)	95	97868	0.97	1.23 (0.82, 1.86)
	90–105	13355	78	97959	0.80	0.92 (0.61, 1.37)	59	97824	0.60	1.23 (0.74, 2.07)	36	97846	0.37	1.29 (0.65, 2.53)	92	97724	0.94	1.21 (0.80, 1.83)
	105–120	6008	34	44054	0.77	1 (Reference)	19	43996	0.43	1 (Reference)	11	44021	0.25	1 (Reference)	30	43963	0.68	1 (Reference)
	≥120	5930	36	43367	0.83	1.19 (0.75, 1.90)	19	43330	0.44	1.12 (0.59, 2.12)	18	43319	0.42	1.80 (0.85, 3.81)	37	43283	0.85	1.37 (0.85, 2.22)
P value for interaction						0.028				0.84				0.13				0.28

aHR, adjusted hazard ratio; CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular event.
[a]ALB. (−) means dipstick albuminuria negative or trace (±).
[b]ALB. (+) means the presence of dipstick albuminuria (≥1+).
Hazard ratios were adjusted for age, sex, current-smoking, drinking alcohol consumption, regular physical activity, low-income status, history of diabetes mellitus, hypertension, and dyslipidemia.

interaction with the association between the eGFR categories and ischemic stroke (interaction term $P = 0.13$) or MACE (interaction term $P = 0.28$). When the presence of dipstick albuminuria was defined as dipstick albuminuria (≥2+), the presence of dipstick albuminuria did not have a significant interaction with the association between eGFR categories and stroke (interaction term $P = 0.05$) or MACE (interaction term $P = 0.20$) (Supplementary Table S1).

The presence of hypertension showed a significant interaction only with the association between eGFR categories and all-cause mortality (interaction term $P = 0.001$) (Supplementary Table S2). Nevertheless, the risk of all-cause mortality was not significantly higher in the marginal eGFR range, regardless of the presence of hypertension.

Underlying diabetes showed a significant interaction only with the association between eGFR categories and ischemic stroke (interaction term $P = 0.0497$) (Supplementary Table S3). However, the risk of ischemic stroke was not significantly higher in the eGFR 60 to 75 ml/min per 1.73 m^2 group, regardless of the presence of diabetes. In addition, the risk of other adverse outcomes was not higher in the marginal eGFR range, even in the diabetes subgroup.

Sensitivity Analysis

In a sensitivity analysis, the CKD Epidemiology Collaboration 2021 and European Kidney Function Consortium equations were used to estimate the GFR, and the risks of adverse outcomes were assessed, according to the eGFR ranges (Supplementary Tables S4 and S5). The risk of all-cause mortality was not significantly higher in the eGFR 60 to 75 ml/min per 1.73 m^2 group using either the CKD Epidemiology Collaboration 2021 equation (aHR, 0.86 [0.77–0.96]) or the European Kidney Function Consortium equation (aHR, 0.83 [0.76–0.90]), whereas the 3 groups with eGFR <60 ml/min per 1.73 m^2 had significantly higher risks of all-cause mortality in both cases (Supplementary Figure S1). The risks of MACE also were not significantly higher in the eGFR 60 to 75 ml/min per 1.73 m^2 group using either the CKD Epidemiology Collaboration 2021 equation (aHR, 1.01 [0.92–1.11]) or the European Kidney Function Consortium equation (aHR, 0.98 [0.91–1.05]) (Supplementary Figure S2). In addition, those with an extremely high eGFR calculated by both equations showed higher risks of all-cause mortality and MACE compared to the reference group.

In the subgroup analyses stratified according to the presence of albuminuria, the presence of dipstick albuminuria did not have a significant interaction with the association between study outcomes and

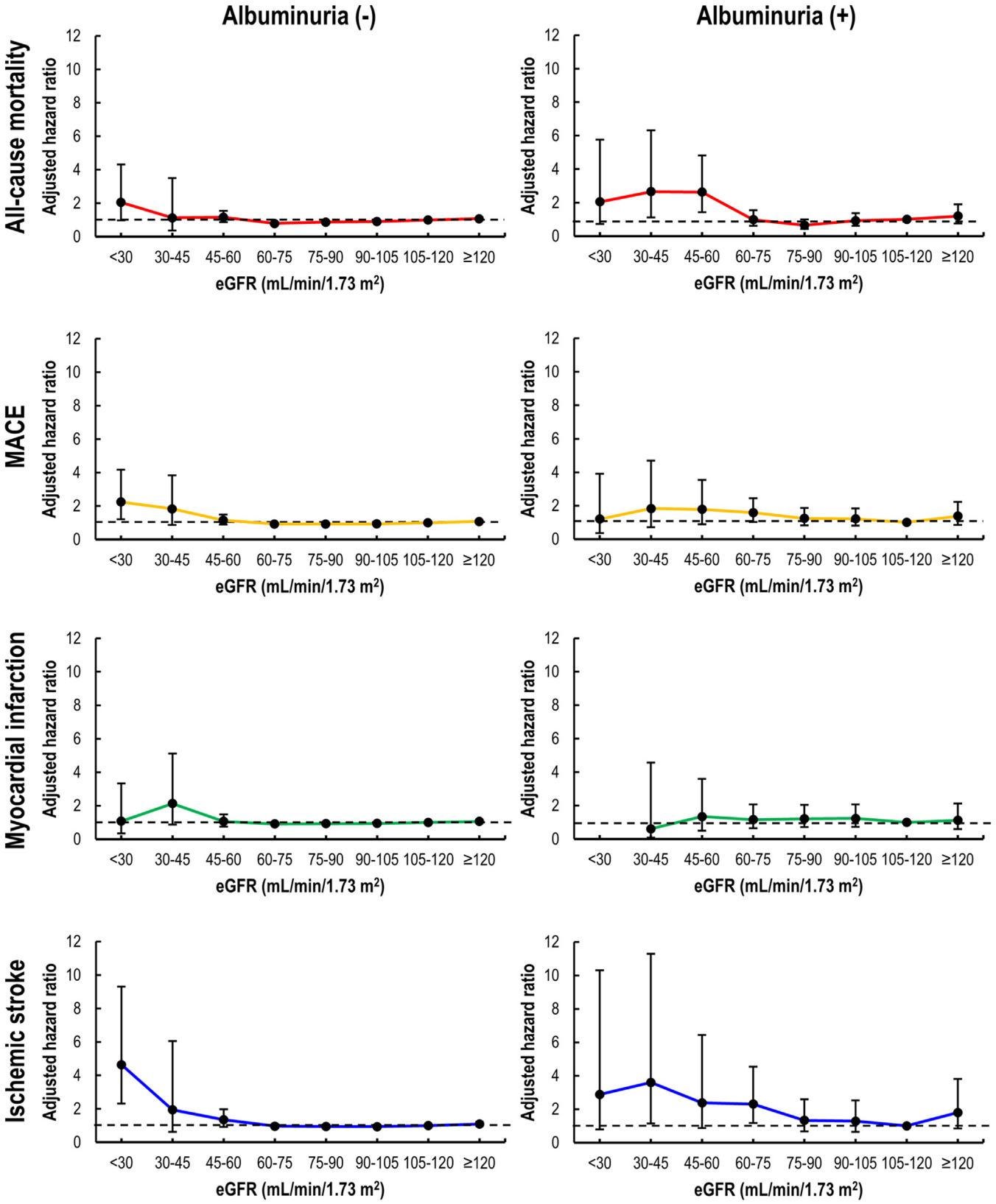

Figure 4. Risks of the adverse outcomes according to eGFR in subgroups stratified by the presence of dipstick albuminuria. Albuminuria (−) means dipstick albuminuria negative or trace (±). Albuminuria (+) means the presence of dipstick albuminuria (≥1+). The y-axes indicate the multivariable adjusted hazard ratios of the adverse outcomes, and x-axes indicate eGFR categories. A multivariable model was adjusted for age, sex, income status, smoking, alcohol consumption, physical activity, history of diabetes mellitus, hypertension, and dyslipidemia, and presence of dipstick albuminuria. eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event.

eGFR categories calculated using both equations (Supplementary Tables S6 and S7). Furthermore, the risks of all-cause mortality and MACE were not significantly higher in the eGFR 60 to 75 ml/min per 1.73 m^2 group, regardless of the presence of dipstick albuminuria.

DISCUSSION

In this observational study using a unique large-scale nationwide cohort of young adults, we demonstrated that an eGFR of 60 to 75 ml/min per 1.73 m^2 was not associated with a higher risk of all-cause mortality and MACE in those aged <40 years. In addition, we also demonstrated that an eGFR of 60 to 75 ml/min per 1.73 m^2 was not significantly associated with a higher risk of all-cause mortality even when albuminuria was present, and albuminuria did not have a significant interaction with the association between eGFR and MACE. Although the classical high-risk eGFR categories including low eGFR (e.g., <60 ml/min per 1.73 m^2) or supranormal eGFR (≥120 ml/min per 1.73 m^2) was reconfirmed in the young adults, there was no evidence of higher risk of the adverse outcomes in young adults with marginal eGFR levels. Therefore, our study suggests that young adults with a marginal eGFR of 60 to 75 ml/min per 1.73 m^2 should be considered to have clinically benign findings.

The current definition of CKD suggested in the Kidney Disease Improving Global Outcomes guideline uses a fixed GFR threshold identified through previous studies that considered the association between eGFR and various health outcomes.[19–21] However, there have been debates about applying a fixed threshold for various populations, particularly considering the age ranges. First, those who address the necessity of age-calibrated definition of CKD, rather than the fixed one, suggest that the risk of mortality associated with GFR is different according to age groups, which is supported by a previous study.[11] They suggested that elderly patients with marginally low eGFR (45–60 ml/min per 1.73 m^2) may be considered to have normal kidney function, and that youths with marginally high eGFR (60–75 ml/min per 1.73 m^2) may have clinically relevant kidney dysfunction. Second, those who advocate for the current fixed-eGFR CKD definition suggest that a decreased GFR is associated with an increased risk in all age categories and should not be regarded as a normal aging kidney. This point of view is supported by a large-scale meta-analysis,[10] or a Mendelian randomization study, which suggested that eGFR reflects telomere length and is not a mere parameter related to chronologic ageing.[22] In addition, those who support the fixed diagnostic criteria of GFR highlight that the definition is simpler to use and age-calibrated definition may lead to "birthday paradox," in which a patient's disease classification could be changed because of age without a change in health status.[23]

Large-scale general health screening data, including creatinine and urinalysis measurements, are necessary to determine whether clinicians should consider true kidney function impairments related to adverse outcome risks among general young adults with incidentally detected marginal eGFR values. The general health screening data of the Korean NHIS are a unique source for such investigations, as general free-of-charge health screening is delivered to the nationwide population, including even young adults. In addition, the data included complete nationwide follow-up information, including all insured medical services throughout the country, and long-term follow-up information for a median of >7 years was available. In our analysis, we identified that eGFR between 60 to 75 ml/min per 1.73 m^2 was not significantly associated with the risk of all-cause mortality or MACE in young adults. Because similar results were identified even in the multivariate model, our findings support that the overall risk of adverse outcomes is not increased in young adults with marginal eGFR values (60–75 ml/min per 1.73 m^2). Because the young adults included in the current study underwent health screenings for social obligations but not for medical purposes, the study data would reflect those with incidental findings of marginal eGFR in real-world practice. Therefore, our study suggests that paying additional sociomedical resources for incidental findings of marginal eGFR may be discouraged in young adults.

Although the risks of all-cause mortality were not significantly higher in the marginal eGFR group even when albuminuria was present and the interaction terms of albuminuria with the association between eGFR and MACE were not significant; those with both marginal eGFR values and albuminuria may have the potential risk of adverse outcomes considering our results. Albuminuria is already known as a risk factor and an early marker of mortality and cardiovascular disease in general population.[19,24] In addition, in previous studies, albuminuria was found to increase the risks of all-cause mortality and MACE in healthy middle-aged and young adults.[25,26] However, because there is a paucity of the study about the association between albuminuria and adverse outcomes conducted in young adults, further studies are needed. Furthermore, considering that young adults defined as having CKD more frequently have elevated urine albuminuria and GFR >60 ml/min per 1.73 m^2,[27,28] clinicians may carefully assess the

future risk of overt CKD in young adults with combined findings of marginal eGFR and albuminuria.

Although our study focused on the marginal eGFR ranges of young adults, we additionally identified that the risks of all-cause mortality and MACE were significantly higher in those with extremely high eGFR (e.g., eGFR ≥120 ml/min per 1.73 m^2). These results are consistent with those of previous studies that demonstrated the clinical significance of extremely high eGFR values in the general population.[29–31] Although the definition of kidney hyperfiltration is not firmly determined, our findings suggest that the possible clinical significance of kidney hyperfiltration may exist in healthy young individuals, as in our study cohort.

This study has several limitations. First, the possibility of residual confounding factors remains due to the retrospective nature of this study. Second, quantitative proteinuria results were unavailable, precluding direct investigation of the current definition of CKD. Third, the study was performed using single-nation data; thus, further studies with diverse ethnic groups are necessary to expand the generalizability of the findings. Fourth, the median follow-up of 7.3 years was relatively short, given that the study population consisted of healthy young adults and the number of events was low. Lastly, the study data included general health screening examinees; thus, the results may not apply to young adults who visit clinics for medical investigations or those with high-risk characteristics.

In conclusion, eGFR between 60 and 75 ml/min per 1.73 m^2 was not associated with higher risks of all-cause mortality and MACE in general young adults in Korea. For the general young adults without additional evidence of kidney function impairment, incidental findings of eGFR 60 to 75 ml/min per 1.73 m^2 may not be considered as a notable risk factor for major adverse outcomes.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This research was supported by a grant funded by Seoul National University Hospital (grant number: 3020-210020). This research was supported by a 2022 Young Investigator grant by the Korean Society of Nephrology.

Data Availability Statement

This study used data from the National Health Insurance Service of Republic of Korea. Data is available from the Korean National Health Insurance Sharing Service. Researchers who wish to access the data can apply at https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Kaplan–Meier survival curve for the incidence probability of all-cause mortality according to GFR estimated by CKD Epidemiology Collaboration 2021 equation and the European Kidney Function Consortium equation.

Figure S2. Kaplan–Meier survival curve for the incidence probability of MACE according to GFR estimated by CKD Epidemiology Collaboration 2021 equation and the European Kidney Function Consortium equation.

Table S1. Risk of adverse outcomes according to eGFR in subgroups stratified by the presence of dipstick albuminuria (≥ 2+).

Table S2. Risk of adverse outcomes according to eGFR in subgroups stratified by the presence of hypertension.

Table S3. Risk of adverse outcomes according to eGFR in subgroups stratified by the presence of diabetes mellitus.

Table S4. Risk of adverse outcomes according to eGFR estimated by CKD Epidemiology Collaboration 2021 equation.

Table S5. Risk of adverse outcomes according to eGFR estimated by the European Kidney Function Consortium equation.

Table S6. Risk of adverse outcomes according to eGFR estimated by CKD Epidemiology Collaboration 2021 equation in subgroups stratified by the presence of dipstick albuminuria.

Table S7. Risk of adverse outcomes according to eGFR estimated by the European Kidney Function Consortium equation in subgroups stratified by the presence of dipstick albuminuria.

REFERENCES

1. Tonelli M, Riella M. Chronic kidney disease and the ageing population. *Nephron Clin Pract*. 2014;128:319–322. https://doi.org/10.1159/000362458
2. Bikbov B, Purcell CA, Levey AS. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395:709–733. https://doi.org/10.1016/S0140-6736(20)30045-3
3. Levin A, Stevens PE, Bilous RW, et al. Kidney disease: improving global outcomes (KDIGO) CKD work group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3:1–150.
4. Hommos MS, Glassock RJ, Rule AD. Structural and functional changes in human kidneys with healthy aging. *J Am Soc Nephrol*. 2017;28:2838–2844. https://doi.org/10.1681/ASN.2017040421
5. Baba M, Shimbo T, Horio M, et al. Longitudinal study of the decline in renal function in healthy subjects. *PLoS One*. 2015;10:e0129036. https://doi.org/10.1371/journal.pone.0129036
6. Pottel H, Delanaye P, Weekers L, et al. Age-dependent reference intervals for estimated and measured glomerular

filtration rate. *Clin Kidney J*. 2017;10:545–551. https://doi.org/10.1093/ckj/sfx026

7. van den Brand JA, van Boekel GA, Willems HL, Kiemeney LA, den Heijer M, Wetzels JF. Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population. *Nephrol Dial Transplant*. 2011;26:3176–3181. https://doi.org/10.1093/ndt/gfr003
8. Delanaye P. Too much nephrology? The CKD epidemic is real and concerning. A CON view. *Nephrol Dial Transplant*. 2019;34:581–584. https://doi.org/10.1093/ndt/gfy331
9. Delanaye P, Glassock RJ, Pottel H, Rule AD. An age-calibrated definition of chronic kidney disease: rationale and benefits. *Clin Biochem Rev*. 2016;37:17–26.
10. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA*. 2012;308:2349–2360. https://doi.org/10.1001/jama.2012.16817
11. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis*. 2016;23:19–28. https://doi.org/10.1053/j.ackd.2015.08.004
12. Pottel H, Hoste L, Delanaye P. Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 ml/min/1.73 m^2. *Pediatr Nephrol*. 2014;30:821–828. https://doi.org/10.1007/s00467-014-3002-5
13. Seong SC, Kim YY, Park SK, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open*. 2017;7:e016640. https://doi.org/10.1136/bmjopen-2017-016640
14. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the National Health Information database of the National Health Insurance Service in South Korea. *Int J Epidemiol*. 2017;46:799–800. https://doi.org/10.1093/ije/dyw253
15. Kim MK, Han K, Park YM, et al. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation*. 2018;138:2627–2637. https://doi.org/10.1161/CIRCULATIONAHA.118.034978
16. Ortho-Clinical Diagnostics. Updated Information for IDMS Traceable VITROS® Chemistry Products CREA Slides. 2008. Accessed January 4, 2023. http://clincalc.com/Downloads/OrthoClinicalDiagnostics-IDMS_20080612.pdf
17. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. https://doi.org/10.1056/NEJMoa2102953
18. Pottel H, Bjork J, Courbebaisse M, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate : a cross-sectional analysis of pooled data. *Ann Intern Med*. 2021;174:183–191. https://doi.org/10.7326/M20-4366
19. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081. https://doi.org/10.1016/S0140-6736(10)60674-5
20. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80:93–104. https://doi.org/10.1038/ki.2010.531
21. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79:1341–1352. https://doi.org/10.1038/ki.2010.536
22. Park S, Lee S, Kim Y, et al. A Mendelian randomization study found causal linkage between telomere attrition and chronic kidney disease. *Kidney Int*. 2021;100:1063–1070. https://doi.org/10.1016/j.kint.2021.06.041
23. Levey AS, Inker LA, Coresh J. Chronic kidney disease in older people. *JAMA*. 2015;314:557–558. https://doi.org/10.1001/jama.2015.6753
24. de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. *J Am Soc Nephrol*. 2006;17:2100–2105. https://doi.org/10.1681/ASN.2006050517
25. Ohsawa M, Fujioka T, Ogasawara K, et al. High risks of all-cause and cardiovascular deaths in apparently healthy middle-aged people with preserved glomerular filtration rate and albuminuria: a prospective cohort study. *Int J Cardiol*. 2013;170:167–172. https://doi.org/10.1016/j.ijcard.2013.10.076
26. Choi Y, Jacobs DR Jr, Shroff GR, Kramer H, Chang AR, Duprez DA. Progression of chronic kidney disease risk categories and risk of cardiovascular disease and total mortality: coronary artery risk development in young adults cohort. *J Am Heart Assoc*. 2022;11:e026685. https://doi.org/10.1161/JAHA.122.026685
27. James MT, Hemmelgarn BR, Wiebe N, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet*. 2010;376:2096–2103. https://doi.org/10.1016/S0140-6736(10)61271-8
28. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038–2047. https://doi.org/10.1001/jama.298.17.2038
29. Park M, Yoon E, Lim YH, Kim H, Choi J, Yoon HJ. Renal hyperfiltration as a novel marker of all-cause mortality. *J Am Soc Nephrol*. 2015;26:1426–1433. https://doi.org/10.1681/ASN.2014010115
30. Reboldi G, Verdecchia P, Fiorucci G, et al. Glomerular hyperfiltration is a predictor of adverse cardiovascular outcomes. *Kidney Int*. 2018;93:195–203. https://doi.org/10.1016/j.kint.2017.07.013
31. Tonelli M, Klarenbach SW, Lloyd AM, et al. Higher estimated glomerular filtration rates may be associated with increased risk of adverse outcomes, especially with concomitant proteinuria. *Kidney Int*. 2011;80:1306–1314. https://doi.org/10.1038/ki.2011.280