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Original Article

ORIGINAL ARTICLE

Cystatin C–based estimated glomerular filtration rate and risk of stroke in the general population: a prospective cohort study

Jinlan Liao[1,*], Fei Xiao[1,2,*], Liuqiao Yang[3], Yanling Wei[4], Congying Song[4], Jing Li[1], Sike Yu[3], Yueqi Lu[3], Jingwen Zhang[1], Liang Dai[4], Wei Liang[1], Tao Li[3], Zuying Xiong[1], Yangfeng Wu[5], Meg J. Jardine[6,7,8], Juan Jesus Carrero[9,10], Ying Shan[3,4] and Xiaoyan Huang[1,4]

[1]Renal Division, Peking University Shenzhen Hospital, Peking University, Shenzhen, Guangdong Province, China, [2]Shantou University Medical College, Shantou, Guangdong Province, China, [3]BGI-Shenzhen, Shenzhen, Guangdong Province, China, [4]Clinical Research Academy, Peking University Shenzhen Hospital, Peking University, Shenzhen, Guangdong Province, China, [5]Peking University Clinical Research Institute, Peking University, Beijing, China, [6]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia, [7]Concord Repatriation General Hospital, Sydney, New South Wales, Australia, [8]Department of Medicine, Stanford Centre for Clinical Research, Stanford University School of Medicine, Stanford, CA, USA, [9]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden and [10]Division of Nephrology, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm 182 88, Sweden

*Jinlan Liao and Fei Xiao contributed equally to this work.
Correspondence to: Ying Shan; E-mail: sylvia.shanboo@gmail.com; Xiaoyan Huang; E-mail: huangxiaoyan@pku.org.cn

ABSTRACT

Background. Previous results on the association between the estimated glomerular filtration rate (eGFR) and stroke are mixed. Most studies derived the eGFR from serum creatinine, which is affected by non-kidney determinants and thus has possibly biased the association with stroke risk.

Methods. In this cohort study, we included 429 566 UK Biobank participants (94.5% white, 54% women, age 56 ± 8 years) free of stroke at enrollment. The $eGFR_{cys}$ and $eGFR_{cr}$ were calculated with serum cystatin C and creatinine, respectively. Outcomes of interest were risk of total stroke and subtypes. We investigated the linear and nonlinear associations using Cox proportional hazards models and restricted cubic splines, corrected for regression dilution bias.

Results. During an average follow-up of 10.11 years, 4427 incident strokes occurred, among which 3447 were ischemic and 1163 were hemorrhagic. After adjustment for confounders, the regression dilution-corrected hazard ratios (95% confidence intervals) for every 10 mL/min/1.73 m^2 decrement in $eGFR_{cys}$ were 1.10 (1.05–1.14) for total stroke and 1.11 (1.08–1.15) for ischemic stroke. A similar pattern was observed with $eGFR_{cr}$, although the association was weaker. When either type of eGFR was below 75 mL/min/1.73 m^2, the risks of total and ischemic stroke increased exponentially as eGFR decreased. A U-shaped relationship was witnessed if $eGFR_{cr}$ was used instead. There was a null association between eGFR and hemorrhagic stroke.

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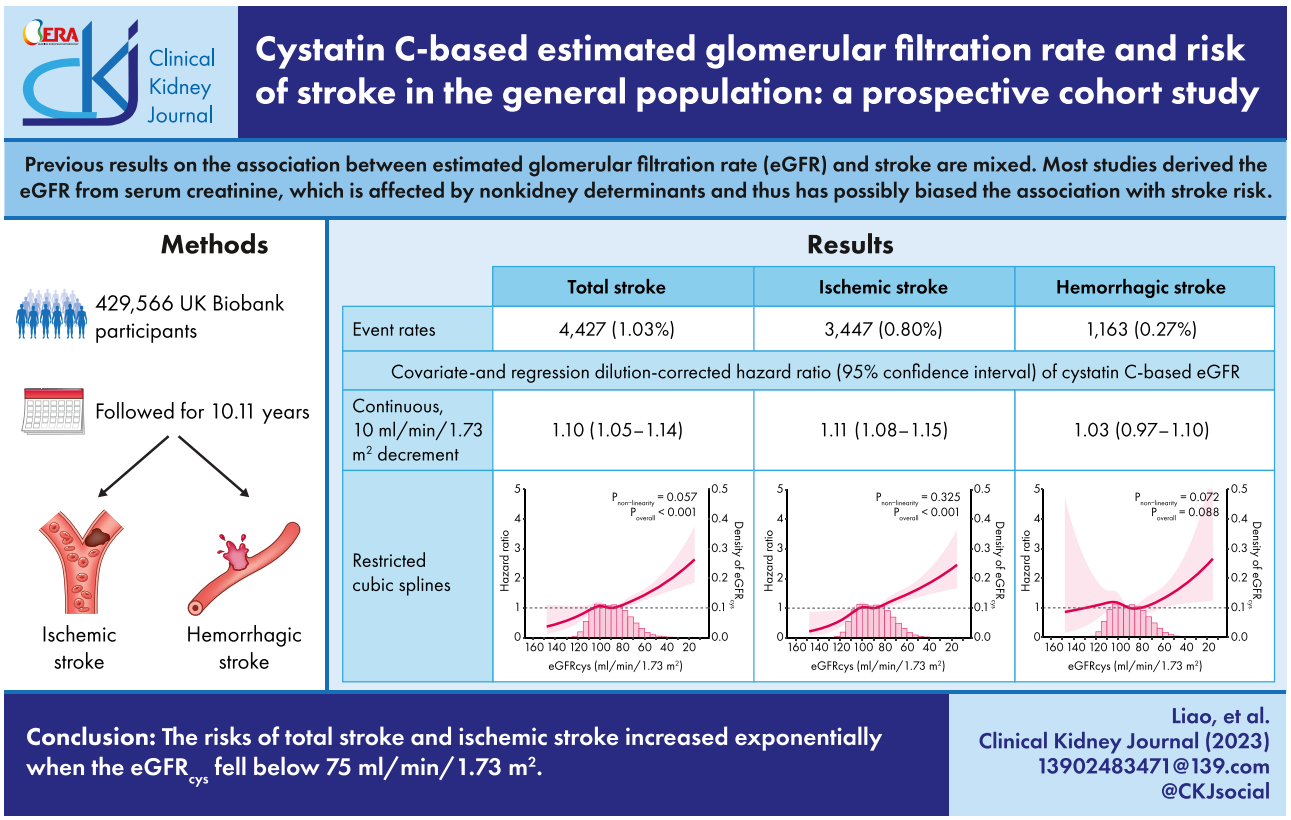
Conclusions. The risks of total stroke and ischemic stroke increased exponentially when the $eGFR_{cys}$ fell below 75 mL/min/1.73 m^2.

LAY SUMMARY

Previous research on the association between estimated glomerular filtration rate (eGFR) and stroke risk has produced mixed results, partly due to the use of serum creatinine–based eGFR ($eGFR_{cr}$), which may be influenced by non-kidney determinants and therefore introduce bias. To address this issue, we investigated the linear and nonlinear associations of cystatin C–based eGFR ($eGFR_{cys}$) with the incidence of total stroke, ischemic stroke, and hemorrhagic stroke in 429 566 community-dwelling UK Biobank participants. Our analysis revealed that $eGFR_{cys}$ below 75 mL/min/1.73 m^2 was associated with an increased risk of stroke, specifically ischemic stroke. Notably, the association between stroke and $eGFR_{cr}$ was weaker than that with $eGFR_{cys}$. Our findings highlight the importance of not underestimating stroke risk when an individual's eGFR is below 75 mL/min/1.73 m^2 in routine tests and suggest that $eGFR_{cys}$ is a superior marker for identifying those at increased risk of stroke.

GRAPHICAL ABSTRACT



Keywords: cystatin C, estimated glomerular filtration rate, regression dilution bias, stroke, UK Biobank

INTRODUCTION

Worldwide, stroke is the third leading cause of death and disability combined [1]. Many stroke survivors experience a range of disabilities, including physiological or psychological sequelae, which often affect their quality of life [2]. Stroke places an immense economic and social burden on public health; therefore, it is important to reduce the burden of stroke through primary prevention [1].

The decline in kidney function may contribute to the development of stroke by impairing cerebral autoregulation, remodeling the cerebral vasculature and reducing cerebral blood flow [3]. A meta-analysis of 33 prospective cohort studies proposed that a baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (also known as chronic kidney disease stage 3 to 5) was independently related to a higher risk of stroke [4]. Later, a subsequent meta-analysis including 63 cohort studies and 20 randomized controlled trials identified a linear relationship between eGFR and incident stroke [5]. However, in the Chronic Renal Insufficiency Cohort Study [6] and in a *post hoc* analysis of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [7], the eGFR was not

associated with an increased risk of stroke after adjustment for confounders. In most previous reports, it is worth noting that the eGFR was calculated using creatinine-based formulas. However, serum creatinine measurement does not provide an accurate eGFR, particularly in those with preserved kidney function [8]. Serum cystatin C, the use of which has become prevalent in the last decade, superiorly captures the level of kidney function independent of age and muscle mass [9]. In addition, most studies relied on a single evaluation of the exposure at baseline and thus neglected the random measurement error and variability of the eGFR [10], leading to an underestimation of the underlying association due to regression dilution bias [11–13]. As such, the inaccuracy of creatinine and regression dilution bias altogether might have flawed prior reports of this kind.

In this study, we hypothesized that eGFR was independently associated with the risk of stroke in the general population. Herein, we investigated the linear and nonlinear associations of the cystatin C–based eGFR ($eGFR_{cys}$) with the risk of total stroke and its subtypes in UK Biobank participants. Furthermore, we used repeated $eGFR_{cys}$ measurements to attenuate regression dilution bias. For comparison, we performed the analyses in parallel using the creatinine-based eGFR ($eGFR_{cr}$).

MATERIALS AND METHODS

Study design and participants

This was a prospective cohort study of participants from the UK Biobank. Details of the UK Biobank appear in the Supplementary Methods. We included participants who provided written informed consent to the UK Biobank and had not withdrawn from the study by 9 August 2021; had no history of stroke at baseline; and had undergone serum cystatin C measurement. We excluded participants with incomplete data for the calculation of the $eGFR_{cys}$, e.g. age or sex; those with malignant tumor or end-stage kidney disease prior to recruitment; and those who were diagnosed with acute kidney injury within 90 days prior to enrollment.

Exposures

All participants provided serum and random spot urine samples at baseline (2006–10), and a subsample of 15 245 participants provided additional samples as the repeated assessments between 2012 and 2013 (https://biobank.ctsu.ox.ac.uk/~bbdatan/Repeat_assessment_doc_v1.0.pdf). In the main analysis, the GFR was estimated from cystatin C using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [8]. In addition, we also examined the equations based on creatinine ($eGFR_{cr}$) as well as a combination of both creatinine and cystatin C ($eGFR_{cr\text{-}cys}$) [8]. Details of the measurement and calculation of the exposures, as well as covariates considered in this study, appear in the Supplementary Methods.

Outcomes

The primary outcome was any first incident stroke between baseline and 31 March 2019. The secondary outcomes were the risk of stroke subtypes, including ischemic and hemorrhagic strokes. Stroke events were ascertained from algorithmically defined outcomes obtained through algorithmic combinations of coded information from the UK Biobank's baseline assessment data collection (which included data from participants on their self-reported medical conditions, operations and medications) and data from hospital admissions (diagnoses and procedures) and death registries. Those who were lost to follow-up, died, dropped out or had no stroke on 31 March 2019 were censored.

Statistical analysis

First, we conducted a descriptive analysis by $eGFR_{cys}$ categories (>105, 90–105, 75–<90, 60–<75, <60 mL/min/1.73 m^2, in accordance with previous studies) [14–17]. In addition, we visualized histograms of $eGFR_{cys}$ and $eGFR_{cr}$ and Kaplan–Meier curves of survival probability according to the categories of $eGFR_{cys}$ and $eGFR_{cr}$. We also calculated the incidence rate per 100 000 person-years of stroke and its two subtypes by both $eGFR_{cys}$ and $eGFR_{cr}$ categories.

Next, we explored the associations between $eGFR_{cys}$ and outcomes. Considering the large sample size of the UK Biobank, we did not perform data imputation before modeling. We used the Cox proportional hazards models as the main analysis to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for $eGFR_{cys}$ with the outcomes. Simultaneously, we repeated the analyses with $eGFR_{cr}$ to read the disparity with $eGFR_{cys}$.

The $eGFR_{cys}$ and $eGFR_{cr}$ were entered into the model in three forms: a continuous form (per 10 mL/min/1.73 m^2 decrement, no conversion); a binary form (<60 mL/min/1.73 m^2 vs ≥60 mL/min/1.73 m^2); and a multicategorical form (with the 90–105 mL/min/1.73 m^2 category as the reference). The nonlinear association of $eGFR_{cys}$ and $eGFR_{cr}$ on a continuous scale with the outcomes were assessed by restricted cubic splines.

We constructed two types of models for each outcome: the crude model and the adjusted model. Covariates in the adjusted models included demographics, including age, sex, ethnicity, education and economic status (Townsend deprivation index); lifestyle factors, including smoking status, alcohol consumption and metabolic equivalents; physical measurements, including body mass index (BMI), systolic blood pressure, diastolic blood pressure; laboratory measurements, including glycated hemoglobin A1c, low-density lipoprotein, high-density lipoprotein, triglycerides, C-reactive protein and urine albumin-to-creatinine ratio; comorbid conditions, including hypertension, diabetes, cardiovascular diseases; and medications, including antihypertensive medications, hypoglycemic agents, lipid-lowering drugs and antiplatelet drugs.

Within-person variability and laboratory measurement errors (known as regression dilution bias) [11] of the exposure always lead to risk underestimation if the exposure was measured only once. Therefore, we used the McMahon–Peto method [18, 19] to correct the association estimates using the repeated cystatin C and creatinine measurements after 4.3 years (SD 0.9 years) since recruitment. We calculated the regression dilution ratios (RDRs) by dividing the difference in the mean $eGFR_{cys}$ and $eGFR_{cr}$ between the 5th and 1st quintiles in the repeat measurements by the equivalent mean differences in the baseline measurements. We divided the log HRs and standard errors in the crude and covariate-adjusted models by RDRs to obtain the corrected estimates.

We applied a series of sensitivity analyses to further test the robustness of the results. First, we considered any deaths prior to first stroke from baseline to 31 March 2019, as competing risks. As such, we confirmed all the analyses of $eGFR_{cys}$ with the Fine and Gray approach (subdistribution hazards models) as a substitute to manage the competing risks [20]. Second, to examine

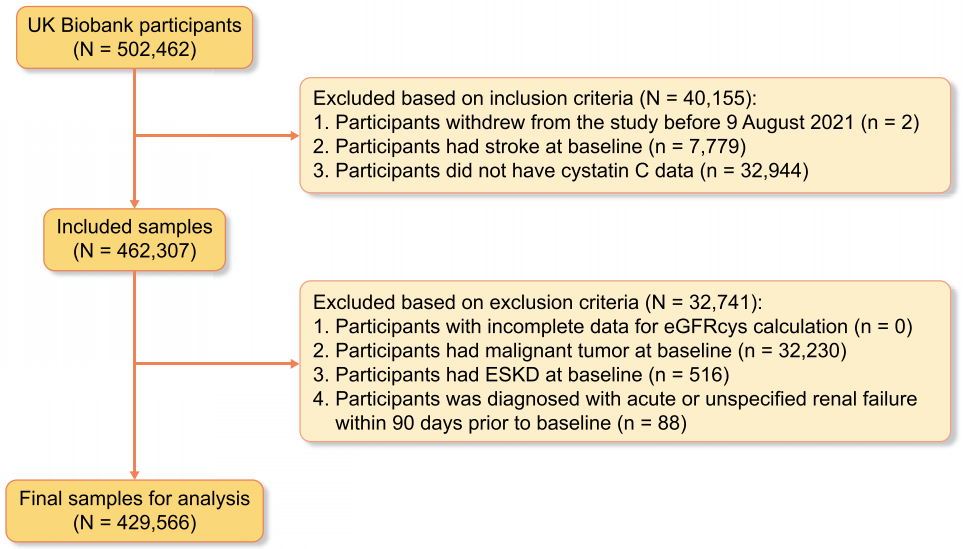


Figure 1: Flowchart of inclusion and exclusion. $eGFR_{cys}$, estimated glomerular filtration rate based on serum cystatin C calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

a particularly healthy subset, we assessed the association between the $eGFR_{cys}$ and the outcomes by excluding the participants who took certain medications or were diagnosed with cardiovascular diseases at baseline. Third, to minimize reverse causality, we excluded participants who developed stroke within 2 years after recruitment. Fourth, we confirmed the results by using $eGFR_{cr\text{-}cys}$ as the exposure [8]. Fifth, to further understand the relation between BMI and GFR_{cr}, we excluded underweight participants with a BMI <18.5 kg/m^2. Finally, we performed preplanned subgroup analyses to assess potential effect modifications between the $eGFR_{cys}$ and baseline characteristics.

All analyses were performed with R Statistical Software, version 4.0.3. All *P*-values were two-sided, and a *P*-value of $<.05$ was considered to indicate statistical significance. More information on the statistical analyses is provided in the Supplementary data.

RESULTS

Baseline characteristics

Of the 502 462 participants recruited, we included 462 307 participants meeting the inclusion criteria and further excluded 32 741 participants meeting the exclusion criteria. Thus, the study sample comprised 429 566 participants (Fig. 1). The distributions of $eGFR_{cys}$ and $eGFR_{cr}$ are depicted in Supplementary data, Fig. S1. Table 1 shows the baseline characteristics of participants in the five $eGFR_{cys}$ categories. The majority (94.5%) were of white ethnicity, and nearly half (54%) were women. The average age of the participants was 56 (SD 8) years. Overall, people with a lower $eGFR_{cys}$ level were older, with low education levels and unfavorable economic status. They were more likely to be smokers, physically inactive and obese, and also presented with more comorbid conditions.

Outcomes during follow-up

Of all the participants, 1101 (0.26%) were lost to follow-up or dropped out. During 10.11 years of mean follow-up, a total of 4427 (1.03%) incident strokes occurred, including 3447 (0.80%) ischemic and 1163 (0.27%) hemorrhagic cases. The incidence rates were 103.5, 80.6 and 27.1 per 100 000 person-years for total stroke, ischemic stroke and hemorrhagic stroke, respectively (Table 2).

Association between eGFR and risk of stroke

As shown in Fig. 2, Kaplan–Meier curves indicate that people in the lower $eGFR_{cys}$ or $eGFR_{cr}$ categories were more likely to develop incident stroke, with the risks being obvious for total and ischemic strokes (Fig. 2A–D) but largely diminishing for hemorrhagic stroke (Fig. 2E and F). Differences in stroke risks appeared more noticeable when the participants were divided according to the $eGFR_{cys}$.

Table 2 shows that a lower $eGFR_{cys}$ was independently associated with an increased risk of total stroke and ischemic stroke but not with hemorrhagic stroke after adjustment for potential confounders. When subsequently corrected for RDRs, the associations became slightly stronger. Such relationships generally held for all three forms of $eGFR_{cys}$ entered. For each 10 mL/min/1.73 m^2 decrement in the $eGFR_{cys}$, the risk increased by 10% (adjusted HR 1.10, 95% CI 1.05–1.14) and 11% (adjusted HR 1.11, 95% CI 1.08–1.15) for total stroke and ischemic stroke, respectively. However, the risk was not significantly increased for hemorrhagic stroke (adjusted HR 1.03, 95% CI 0.97–1.10). The binary analyses confirmed the same relationships. The multicategory analyses coupled with restricted cubic spline (Fig. 3A) suggested a cubic relationship between the $eGFR_{cys}$ and the risk of total stroke might exist, although not statistically significant (*P* for nonlinearity = 0.057). When $eGFR_{cys}$ was below 75 mL/min/1.73 m^2, stroke risk increased almost exponentially as $eGFR_{cys}$ decreased. However, when $eGFR_{cys}$ was above 75 mL/min/1.73 m^2, the risk did not significantly differ but seemingly decreased as the $eGFR_{cys}$ exceeded 105 mL/min/1.73 m^2. A similar mode of association was visualized for ischemic stroke (Fig. 3C) but not for hemorrhagic stroke (Fig. 3E).

As shown in Table 3, the continuous analyses indicated that the associations of $eGFR_{cr}$ with total stroke (adjusted HR 1.05,

Table 1: Baseline characteristics of participants.

Characteristics	Missing value, *n*	Whole population	$eGFR_{cys}$ (mL/min/1.73 m^2)				
			>105	90–105	75–<90	60–<75	<60
n (%)		429 566	72 155 (16.80)	141 078 (32.84)	131 305 (30.57)	67 316 (15.67)	17 712 (4.12)
Age, mean (SD), years	0	56 (8)	49 (6)	55 (8)	58 (7)	61 (6)	63 (5)
Women, *n* (%)	0	232 182 (54)	37 995 (53)	82 026 (58)	66 933 (51)	35 645 (53)	9583 (54)
Ethnicity, *n* (%)	2040						
White		403 862 (94.5)	65 533 (91.3)	132 955 (94.6)	124 831 (95.5)	63 982 (95.6)	16 561 (94.1)
Asian		10 130 (2.4)	1976 (2.8)	3012 (2.1)	2823 (2.2)	1650 (2.5)	669 (3.8)
Black		6934 (1.6)	2368 (3.3)	2301 (1.6)	1455 (1.1)	622 (0.9)	188 (1.1)
Others		6600 (1.5)	1927 (2.7)	2215 (1.6)	1584 (1.2)	686 (1.0)	188 (1.1)
Education[a], *n* (%)	5057						
Level 1		70 896 (17)	4831 (7)	17 412 (12)	24 317 (19)	18 009 (27)	6327 (36)
Level 2		71 919 (17)	12 103 (17)	23 948 (17)	22 033 (17)	11 000 (17)	2835 (16)
Level 3		140 920 (33)	24 673 (35)	47 070 (34)	43 036 (33)	21 086 (32)	5055 (29)
Level 4		140 774 (33)	29 841 (42)	51 326 (37)	40 338 (31)	16 124 (24)	3145 (18)
Townsend deprivation index, median (IQR)	536	–2.14 (–3.65, 0.53)	–2.04 (–3.62, 0.65)	–2.25 (–3.71, 0.26)	–2.22 (–3.68, 0.41)	–1.99 (–3.55, 0.83)	–1.33 (–3.24, 1.86)
Smoking status, *n* (%)	2136						
Never		235 834 (55)	43 931 (61)	81 426 (58)	69 923 (54)	32 767 (49)	7787 (44)
Previous		146 318 (34)	21 942 (31)	46 784 (33)	46 142 (35)	24 642 (37)	6808 (39)
Current		45 278 (11)	5993 (8)	12 305 (9)	14 588 (11)	9431 (14)	2961 (17)
Alcohol consumption, *n* (%)	956						
Never		33 833 (8)	4256 (6)	8991 (6)	10 270 (8)	7395 (11)	2921 (17)
Occasional		96 737 (23)	13 894 (19)	28 555 (20)	29 802 (23)	18 677 (28)	5809 (33)
Frequent		298 040 (70)	53 825 (75)	103 288 (73)	90 952 (69)	41 055 (61)	8920 (51)
Metabolic equivalents, median (IQR), min/week	81 728	1779 (812, 3572)	1884 (885, 3626)	1853 (873, 3590)	1760 (792, 3600)	1653 (702, 3492)	1386 (542, 3012)
BMI, *n* (%)	1633						
<25 kg/m^2		142 083 (33.2)	33 859 (47.1)	55 789 (39.7)	36 796 (28.1)	13 047 (19.5)	2 592 (14.8)
25–≤30 kg/m^2		182 274 (42.6)	28 581 (39.7)	59 774 (42.5)	58 984 (45.1)	28 679 (42.8)	6 256 (35.6)
>30 kg/m^2		103 576 (24.2)	9463 (13.2)	25 103 (17.8)	35 079 (26.8)	25 228 (37.7)	8703 (49.6)

Table 1: Continued

Characteristics	Missing value, *n*	Whole population	$eGFR_{cys}$ (mL/min/1.73 m^2)				
			>105	90–105	75–<90	60–<75	<60
SBP, mean (SD), mmHg	24 082	138 (19)	131 (17)	136 (18)	140 (18)	142 (19)	142 (19)
DBP, mean (SD), mmHg	24 079	82 (10)	81 (10)	82 (10)	83 (10)	83 (10)	82 (11)
Hypertension, *n* (%)	1	39 816 (9)	2572 (4)	8714 (6)	12 716 (10)	10 469 (16)	5345 (30)
Diabetes, *n* (%)	1871	21 538 (5)	2635 (4)	5294 (4)	6142 (5)	4717 (7)	2750 (16)
Cardiovascular diseases, *n* (%)	0	37 181 (9)	2988 (4)	8712 (6)	12 052 (9)	9147 (14)	4282 (24)
Antihypertensive medications, *n* (%)	0	91 462 (21)	6568 (9)	21 668 (15)	29 941 (23)	23 110 (34)	10 175 (57)
Hypoglycemic agents, *n* (%)	0	13 281 (3)	1557 (2)	3134 (2)	3767 (3)	3037 (5)	1786 (10)
Lipid-lowering drugs, *n* (%)	0	81 222 (19)	7083 (10)	21 514 (15)	26 949 (21)	18 465 (27)	7211 (41)
Antiplatelet drugs, *n* (%)	0	56 881 (13)	5032 (7)	14 431 (10)	18 756 (14)	13 329 (20)	5333 (30)
Glycated hemoglobin A1c, median (IQR), mmol/mol	22 133	35.2 (32.7, 37.8)	33.7 (31.4, 36.1)	34.8 (32.4, 37.2)	35.5 (33.2, 38.1)	36.4 (33.9, 39.2)	37.6 (34.8, 41.3)
LDL, mean (SD), mmol/L	1097	3.57 (0.86)	3.40 (0.80)	3.59 (0.84)	3.64 (0.87)	3.60 (0.91)	3.37 (0.96)
HDL, mean (SD), mmol/L	36 450	1.45 (0.38)	1.50 (0.37)	1.51 (0.39)	1.43 (0.37)	1.36 (0.35)	1.27 (0.35)
Triglycerides, median (IQR), mmol/L	613	1.48 (1.04, 2.14)	1.19 (0.85, 1.79)	1.37 (0.98, 1.99)	1.58 (1.13, 2.24)	1.73 (1.25, 2.41)	1.86 (1.36, 2.58)
CRP, median (IQR), mg/L	1205	1.31 (0.65, 2.72)	0.84 (0.43, 1.74)	1.08 (0.56, 2.20)	1.46 (0.76, 2.88)	2.03 (1.04, 3.95)	2.82 (1.45, 5.64)
UACR, *n* (%)	25 361						
<30 mg/g		386 140 (95.5)	64 787 (96.5)	127 180 (96.4)	119 686 (96.2)	60 230 (94.2)	14 257 (85.3)
30–<300 mg/g		16 573 (4.1)	2254 (3.4)	4490 (3.4)	4519 (3.6)	3401 (5.3)	1909 (11.4)
≥300 mg/g		1492 (0.4)	125 (0.2)	228 (0.2)	257 (0.2)	324 (0.5)	558 (3.3)

[a]Level 1, none of the above; level 2, O-levels/GCSEs or equivalent or CSEs or equivalent; level 3, A-levels/AS-levels or equivalent or National Vocational Qualification or Higher National Diploma or Higher National Certificate or equivalent, or other professional qualifications; level 4, college or university degree.

SBP, systolic blood pressure; DBP, diastolic blood pressure; $eGFR_{cys}$, estimated glomerular filtration rate based on serum cystatin C calculated with the Chronic Kidney Disease Epidemiology Collaboration equation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; UACR, urine albumin-to-creatinine ratio.

Table 2: Association between cystatin C–based eGFR and stroke with Cox proportional hazards models.

$eGFR_{cys}$	Incidence rate, per 100 000 person-years	Events (%)	Crude model		Fully adjusted model	
			HRs (95% CIs)	RDR-adjusted HRs (95% CIs)	HRs (95% CIs)	RDR-adjusted HRs (95% CIs)
Total stroke						
Continuous, 10 mL/min/1.73 m^2 decrement	103.5	4427 (1.03)	1.39 (1.37–1.41)	1.43 (1.41–1.47)	1.09 (1.05–1.12)	1.10 (1.05–1.14)
Binary						
≥60 mL/min/1.73 m^2	94.4	3879 (0.94)	Reference	Reference	Reference	Reference
<60 mL/min/1.73 m^2	327.9	548 (3.09)	3.45 (3.16–3.77)	3.89 (3.52–4.29)	1.31 (1.14–1.50)	1.34 (1.15–1.56)
Multicategory						
>105 mL/min/1.73 m^2	41.0	298 (0.41)	0.55 (0.48–0.63)	0.52 (0.45–0.60)	0.82 (0.69–0.98)	0.80 (0.67–0.98)
90–105 mL/min/1.73 m^2	74.5	1054 (0.75)	Reference	Reference	Reference	Reference
75–<90 mL/min/1.73 m^2	103.9	1358 (1.03)	1.39 (1.29–1.51)	1.44 (1.32–1.57)	1.01 (0.91–1.12)	1.01 (0.90–1.13)
60–<75 mL/min/1.73 m^2	177.3	1169 (1.74)	2.37 (2.18–2.57)	2.57 (2.35–2.82)	1.24 (1.10–1.39)	1.27 (1.11–1.43)
<60 mL/min/1.73 m^2	327.9	548 (3.09)	4.37 (3.94–4.84)	5.03 (4.49–5.64)	1.44 (1.23–1.69)	1.49 (1.25–1.78)
Ischemic stroke						
Continuous, 10 mL/min/1.73 m^2 decrement	80.6	3447 (0.80)	1.45 (1.43–1.47)	1.49 (1.47–1.54)	1.10 (1.06–1.14)	1.11 (1.08–1.15)
Binary						
≥60 mL/min/1.73 m^2	72.5	2981 (0.72)	Reference	Reference	Reference	Reference
<60 mL/min/1.73 m^2	278.5	466 (2.63)	3.82 (3.46–4.21)	4.34 (3.90–4.83)	1.30 (1.12–1.51)	1.33 (1.13–1.57)
Multicategory						
>105 mL/min/1.73 m^2	27.9	203 (0.28)	0.53 (0.45–0.62)	0.50 (0.42–0.59)	0.81 (0.66–1.00)	0.79 (0.63–1.00)
90-105 mL/min/1.73 m^2	52.8	747 (0.53)	Reference	Reference	Reference	Reference
75–<90 mL/min/1.73 m^2	81.8	1070 (0.81)	1.55 (1.41–1.70)	1.62 (1.46–1.79)	1.08 (0.96–1.22)	1.09 (0.96–1.24)
60–<75 mL/min/1.73 m^2	145.6	961 (1.43)	2.75 (2.50–3.02)	3.03 (2.73–3.36)	1.29 (1.13–1.48)	1.32 (1.14–1.54)
<60 mL/min/1.73 m^2	278.5	466 (2.63)	5.24 (4.67–5.88)	6.14 (5.41–6.97)	1.51 (1.26–1.80)	1.57 (1.29–1.90)
Hemorrhagic stroke						
Continuous, 10 mL/min/1.73 m^2 decrement	27.1	1163 (0.27)	1.23 (1.20–1.28)	1.27 (1.22–1.32)	1.03 (0.97–1.09)	1.03 (0.97–1.10)
Binary						
≥60 mL/min/1.73 m^2	25.6	1054 (0.26)	Reference	Reference	Reference	Reference
<60 mL/min/1.73 m^2	64.5	109 (0.62)	2.51 (2.06–3.05)	2.74 (2.20–3.40)	1.25 (0.93–1.69)	1.28 (0.92–1.78)
Multicategory						
>105 mL/min/1.73 m^2	14.1	103 (0.14)	0.58 (0.46–0.72)	0.55 (0.43–0.70)	0.80 (0.60–1.07)	0.78 (0.57–1.08)
90–105 mL/min/1.73 m^2	24.5	347 (0.25)	Reference	Reference	Reference	Reference
75–<90 mL/min/1.73 m^2	25.5	335 (0.26)	1.04 (0.90–1.21)	1.05 (0.89–1.23)	0.82 (0.67–1.00)	0.80 (0.64–1.00)
60–<75 mL/min/1.73 m^2	40.5	269 (0.40)	1.65 (1.41–1.93)	1.73 (1.45–2.06)	1.08 (0.86–1.35)	1.09 (0.85–1.39)
<60 mL/min/1.73 m^2	64.5	109 (0.62)	2.62 (2.11–3.25)	2.87 (2.27–3.63)	1.20 (0.86–1.67)	1.22 (0.85–1.75)

Covariates in the fully adjusted model included age, sex, ethnicity, education, Townsend deprivation index, smoking status, alcohol consumption, metabolic equivalents, BMI, systolic blood pressure, diastolic blood pressure, glycated hemoglobin A1c, low-density lipoprotein, high-density lipoprotein, triglycerides, C-reactive protein, urine albumin-to-creatinine ratio, hypertension, diabetes, cardiovascular diseases, antihypertensive medications, hypoglycemic agents, lipid-lowering drugs and antiplatelet drugs. The regression dilution ratio was 0.91.

The proportional hazards assumption was checked for all the models using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. Time-dependent covariates were constructed in those where the proportional hazards assumption was violated (diastolic blood pressure in the models for total stroke; systolic blood pressure and diastolic blood pressure in the models for ischemic stroke; C-reactive protein in the models for hemorrhagic stroke). Variance inflation factor values were below 5 for all the models presented, indicating a low risk of multicollinearity.

$eGFR_{cys}$, estimated glomerular filtration rate based on serum cystatin C calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

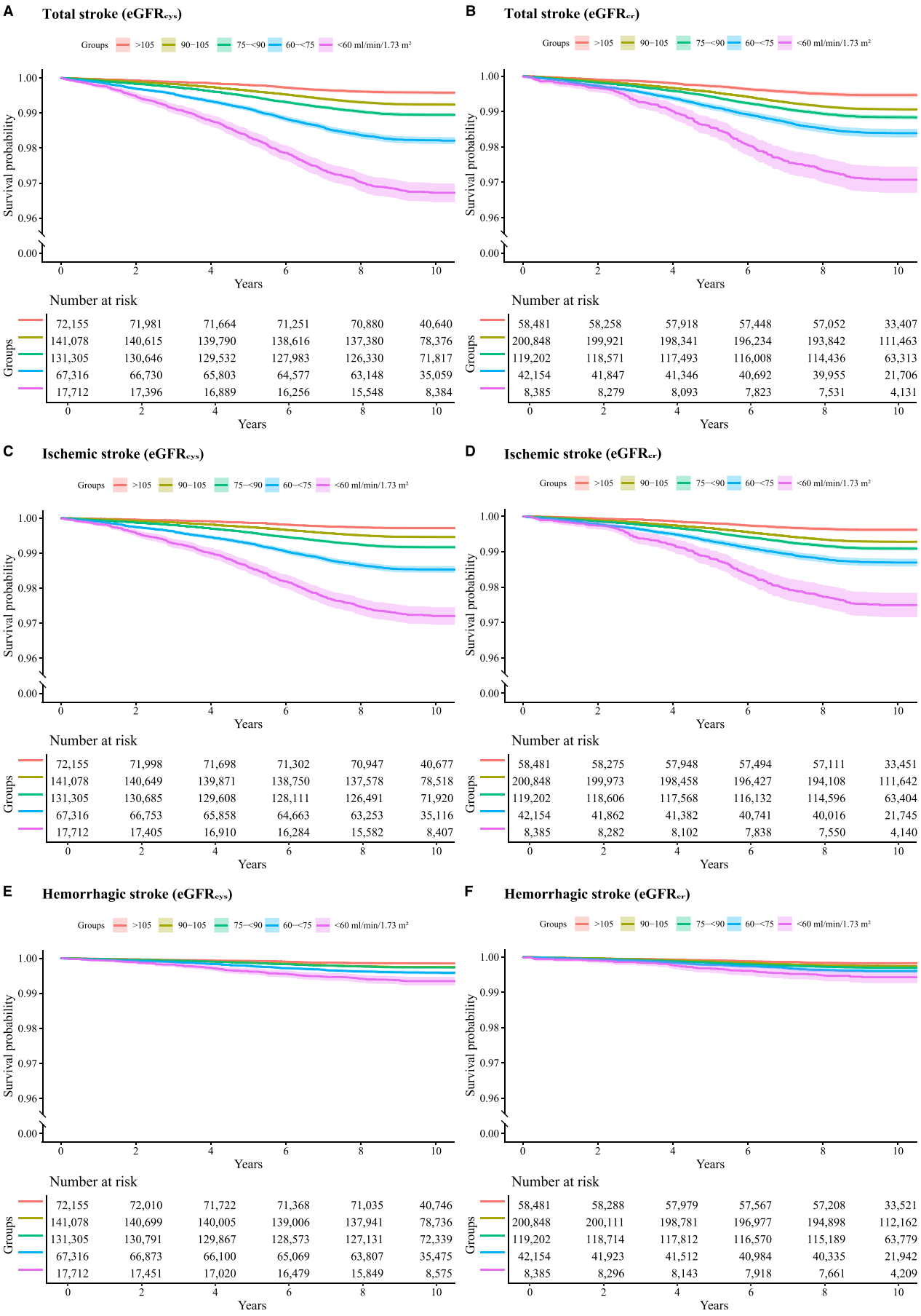

A
Total stroke (eGFRcys)
B
Total stroke (eGFRcr)
C
Ischemic stroke (eGFRcys)
D
Ischemic stroke (eGFRcr)
E
Hemorrhagic stroke (eGFRcys)
F
Hemorrhagic stroke (eGFRcr)
Groups >105 90–105 75–<90 60–<75 <60 ml/min/1.73 m²
Survival probability
Years
Number at risk
Groups
72,155 71,981 71,664 71,251 70,880 40,640
141,078 140,615 139,790 138,616 137,380 78,376
131,305 130,646 129,532 127,983 126,330 71,817
67,316 66,730 65,803 64,577 63,148 35,059
17,712 17,396 16,889 16,256 15,548 8,384
58,481 58,258 57,918 57,448 57,052 33,407
200,848 199,921 198,341 196,234 193,842 111,463
119,202 118,571 117,493 116,008 114,436 63,313
42,154 41,847 41,346 40,692 39,955 21,706
8,385 8,279 8,093 7,823 7,531 4,131
72,155 71,998 71,698 71,302 70,947 40,677
141,078 140,649 139,871 138,750 137,578 78,518
131,305 130,685 129,608 128,111 126,491 71,920
67,316 66,753 65,858 64,663 63,253 35,116
17,712 17,405 16,910 16,284 15,582 8,407
58,481 58,275 57,948 57,494 57,111 33,451
200,848 199,973 198,458 196,427 194,108 111,642
119,202 118,606 117,568 116,132 114,596 63,404
42,154 41,862 41,382 40,741 40,016 21,745
8,385 8,282 8,102 7,838 7,550 4,140
72,155 72,010 71,722 71,368 71,035 40,746
141,078 140,699 140,005 139,006 137,941 78,736
131,305 130,791 129,867 128,573 127,131 72,339
67,316 66,873 66,100 65,069 63,807 35,475
17,712 17,451 17,020 16,479 15,849 8,575
58,481 58,288 57,979 57,567 57,208 33,521
200,848 200,111 198,781 196,977 194,898 112,162
119,202 118,714 117,812 116,570 115,189 63,779
42,154 41,923 41,512 40,984 40,335 21,942
8,385 8,296 8,143 7,918 7,661 4,209

Figure 2: Kaplan–Meier curves of survival probability by eGFR categories. Survival probability for primary (**A** and **B** for total stroke) and secondary outcomes (**C** and **D** for ischemic stroke; **E** and **F** for hemorrhagic stroke) according to the categories of $eGFR_{cys}$ and $eGFR_{cr}$. The median follow-up period for total stroke was 10.11 (IQR 9.39–10.81) years, that for ischemic stroke was 10.11 (IQR 9.40–10.81) years and for hemorrhagic stroke was 10.11 (IQR 9.40–10.82) years. In the participants who experienced stroke, the median follow-up periods were 5.01 (IQR 2.98–6.62), 5.04 (IQR 3.01–6.66) and 4.92 (IQR 2.90–6.55) years for total stroke, ischemic stroke and hemorrhagic stroke, respectively. The median follow-up period for participants who did not develop stroke was 10.17 (IQR 9.48–10.84) years. $eGFR_{cr}$, estimated glomerular filtration rate based on serum creatinine calculated with the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{cys}$, estimated glomerular filtration rate based on serum cystatin C calculated with the Chronic Kidney Disease Epidemiology Collaboration equation; IQR, interquartile range.

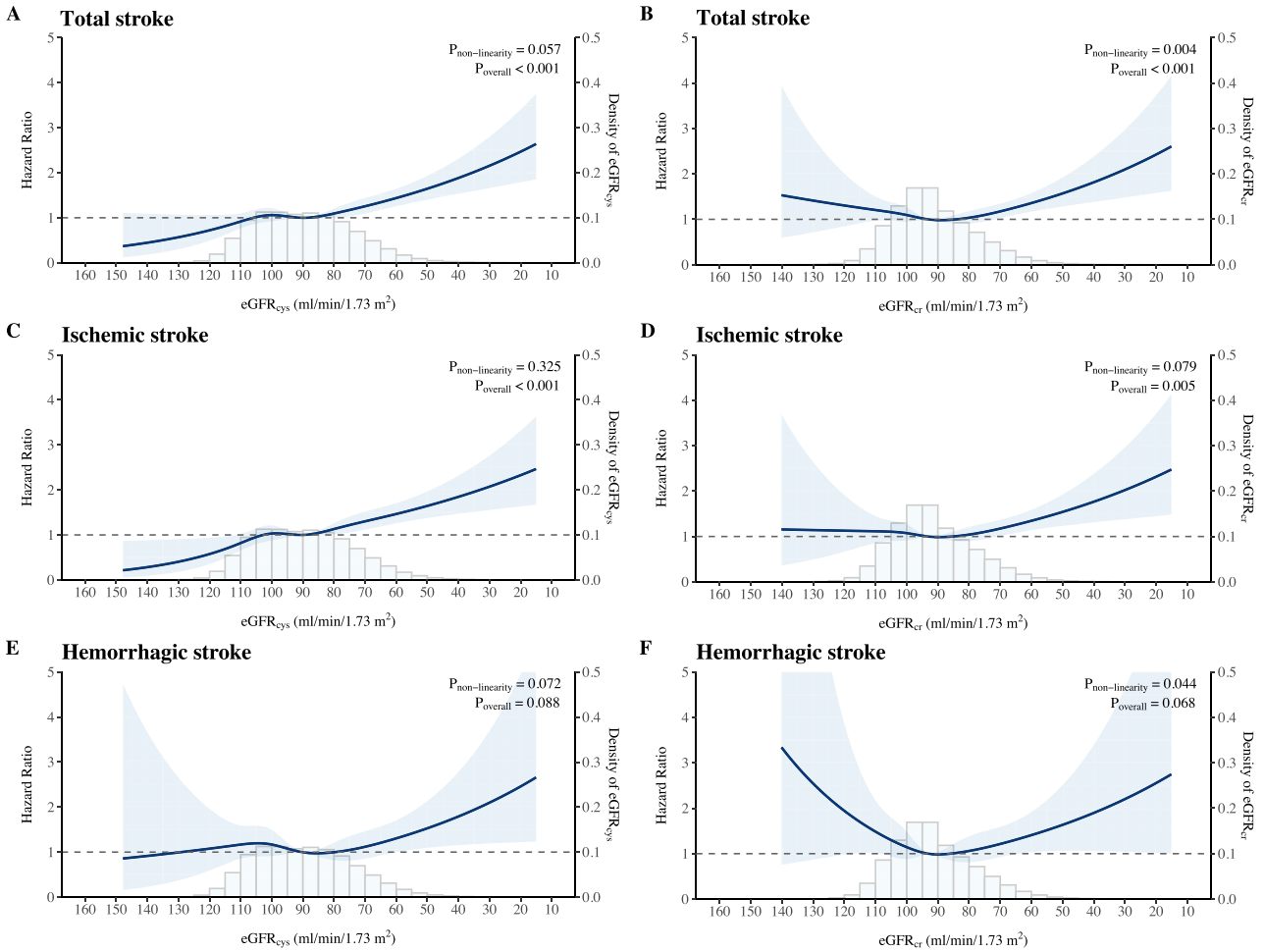


Figure 3: Restricted cubic splines for total stroke, ischemic stroke and hemorrhagic stroke. The adjusted restricted cubic splines were defined with five knots at the 5th, 27.5th, 50th, 72.5th and 95th percentiles, conditional on the median values of the covariates. HRs were adjusted for age, sex, ethnicity, education, Townsend deprivation index, smoking status, alcohol consumption, metabolic equivalents, BMI, systolic blood pressure, diastolic blood pressure, glycated hemoglobin A1c, low-density lipoprotein, high-density lipoprotein, triglycerides, C-reactive protein, urine albumin-to-creatinine ratio, hypertension, diabetes, cardiovascular diseases, antihypertensive medications, hypoglycemic agents, lipid-lowering drugs and antiplatelet drugs, and additionally corrected for regression dilution bias of the estimates. The regression dilution ratio was 0.91. The 95% CIs were derived by bootstrap resampling, the times of which were equal to the numbers of observations. Each point on the curve is the pointwise average HR. Shaded areas represent 95% CIs. The horizontal dashed line indicates an HR of 1. $eGFR_{cr}$, estimated glomerular filtration rate based on serum creatinine calculated with the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{cys}$, estimated glomerular filtration rate based on serum cystatin C calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

95% CI 1.01–1.10) and ischemic stroke (adjusted HR 1.06, 95% CI 1.01–1.11) were weaker than those of $eGFR_{cys}$. Contrary to the results of $eGFR_{cys}$, the multicategory analyses revealed that compared with the reference group, participants in the highest $eGFR_{cr}$ category (>105 mL/min/1.73 m^2) paradoxically exhibited an increased risk of stroke: adjusted HRs (95% CIs) were 1.20 (0.98–1.50) for total stroke, 1.29 (1.00–1.67) for ischemic stroke and 1.09 (0.73–1.60) for hemorrhagic stroke, respectively. A U-shaped relationship was observed in the restricted cubic splines (Fig. 3B, D and F).

Sensitivity analyses and subgroup analyses

All the sensitivity analyses revealed consistent results with the main analysis. When the Fine and Gray approach was applied to account for competing risks, the results were altered little (Supplementary data, Table S1). Similarly, the findings remained constant to a large extent in the diverse scenarios that we tested (Supplementary data, Tables S2 and S3). In the subgroup analyses (Supplementary data, Fig. S2), we found no significant differences in the associations of $eGFR_{cys}$ with risk of total stroke

Table 3: Association between creatinine-based eGFR and stroke with Cox proportional hazards models.

$eGFR_{cr}$	Incidence rate, per 100 000 person-years	Events (%)	Crude model		Fully adjusted model	
			HRs (95% CIs)	RDR-adjusted HRs (95% CIs)	HRs (95% CIs)	RDR-adjusted HRs (95% CIs)
Total stroke						
Continuous, 10 mL/min/1.73 m^2 decrement	103.5	4422 (1.03)	1.28 (1.25–1.30)	1.35 (1.33–1.39)	1.04 (1.01–1.08)	1.05 (1.01–1.10)
Binary						
≥60 mL/min/1.73 m^2	99.9	4 187 (1.00)	Reference	Reference	Reference	Reference
<60 mL/min/1.73 m^2	292.9	235 (2.80)	2.92 (2.56–3.32)	3.77 (3.20–4.44)	1.31 (1.08–1.58)	1.40 (1.10–1.76)
Multicategory						
>105 mL/min/1.73 m^2	52.6	310 (0.53)	0.57 (0.51–0.64)	0.50 (0.43–0.58)	1.16 (0.98–1.39)	1.20 (0.98–1.50)
90–105 mL/min/1.73 m^2	92.4	1853 (0.92)	Reference	Reference	Reference	Reference
75–<90 mL/min/1.73 m^2	115.0	1360 (1.14)	1.24 (1.16–1.33)	1.31 (1.20–1.43)	0.99 (0.90–1.08)	0.99 (0.88–1.10)
60–<75 mL/min/1.73 m^2	160.3	664 (1.58)	1.72 (1.58–1.88)	1.97 (1.76–2.19)	1.16 (1.03–1.30)	1.20 (1.04–1.38)
<60 mL/min/1.73 m^2	292.9	235 (2.80)	3.15 (2.75–3.61)	4.15 (3.51–4.91)	1.35 (1.11–1.64)	1.45 (1.14–1.85)
Ischemic stroke						
Continuous, 10 mL/min/1.73 m^2 decrement	80.6	3443 (0.80)	1.32 (1.30–1.35)	1.41 (1.37–1.45)	1.05 (1.01–1.09)	1.06 (1.01–1.11)
Binary						
≥60 mL/min/1.73 m^2	77.3	3242 (0.77)	Reference	Reference	Reference	Reference
<60 mL/min/1.73 m^2	250.1	201 (2.40)	3.22 (2.79–3.71)	4.27 (3.57–5.09)	1.30 (1.06–1.60)	1.38 (1.07–1.79)
Multicategory						
>105 mL/min/1.73 m^2	37.3	220 (0.38)	0.53 (0.46–0.61)	0.46 (0.38–0.54)	1.23 (1.00–1.51)	1.29 (1.00–1.67)
90–105 mL/min/1.73 m^2	70.7	1418 (0.71)	Reference	Reference	Reference	Reference
75–<90 mL/min/1.73 m^2	90.1	1066 (0.89)	1.27 (1.17–1.38)	1.35 (1.22–1.49)	0.99 (0.90–1.10)	0.99 (0.88–1.13)
60–<75 mL/min/1.73 m^2	129.7	538 (1.28)	1.83 (1.65–2.02)	2.11 (1.87–2.39)	1.16 (1.01–1.32)	1.20 (1.01–1.41)
<60 mL/min/1.73 m^2	250.1	201 (2.40)	3.52 (3.03–4.08)	4.76 (3.96–5.72)	1.34 (1.09–1.66)	1.44 (1.11–1.88)
Hemorrhagic stroke						
Continuous, 10 mL/min/1.73 m^2 decrement	27.1	1162 (0.27)	1.19 (1.14–1.23)	1.23 (1.18–1.30)	1.02 (0.96–1.09)	1.02 (0.95–1.11)
Binary						
≥60 mL/min/1.73 m^2	26.5	1116 (0.27)	Reference	Reference	Reference	Reference
<60 mL/min/1.73 m^2	56.8	46 (0.55)	2.13 (1.58–2.86)	2.55 (1.77–3.68)	1.26 (0.84–1.90)	1.33 (0.81–2.22)
Multicategory						
>105 mL/min/1.73 m^2	17.1	101 (0.17)	0.69 (0.56–0.86)	0.64 (0.49–0.83)	1.07 (0.78–1.46)	1.09 (0.73–1.60)
90–105 mL/min/1.73 m^2	24.8	498 (0.25)	Reference	Reference	Reference	Reference
75–<90 mL/min/1.73 m^2	29.8	354 (0.30)	1.20 (1.05–1.38)	1.25 (1.06–1.49)	0.98 (0.82–1.17)	0.98 (0.78–1.22)
60–<75 mL/min/1.73 m^2	39.1	163 (0.39)	1.57 (1.32–1.88)	1.75 (1.41–2.18)	1.20 (0.95–1.51)	1.25 (0.94–1.67)
<60 mL/min/1.73 m^2	56.8	46 (0.55)	2.28 (1.68–3.08)	2.78 (1.91–4.04)	1.30 (0.85–1.98)	1.38 (0.82–2.33)

Covariates in the fully adjusted model included age, sex, ethnicity, education, Townsend deprivation index, smoking status, alcohol consumption, metabolic equivalents, BMI, systolic blood pressure, diastolic blood pressure, glycated hemoglobin A1c, low-density lipoprotein, high-density lipoprotein, triglycerides, C-reactive protein, urine albumin-to-creatinine ratio, hypertension, diabetes, cardiovascular diseases, antihypertensive medications, hypoglycemic agents, lipid-lowering drugs and antiplatelet drugs. The regression dilution ratio was 0.81.

The proportional hazards assumption was checked for all the models using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. Time-dependent covariates were constructed in those where the proportional hazards assumption was violated (diastolic blood pressure in the models for total stroke; systolic blood pressure, diastolic blood pressure, cardiovascular diseases in the models for ischemic stroke; C-reactive protein in the models for hemorrhagic stroke). Variance inflation factor values were below 5 for all the models presented, indicating a low risk of multicollinearity.

$eGFR_{cr}$, estimated glomerular filtration rate based on serum creatinine calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

across the prespecified strata, accompanied by null interaction between $eGFR_{cys}$ and all the stratified factors.

DISCUSSION

In this large cohort study, we observed a cubic relationship between the $eGFR_{cys}$ and the risk of total and ischemic strokes. The associations were generally stronger after the calibration of regression dilution bias and remained consistent in various sensitivity and subgroup analyses. However, when the $eGFR_{cr}$ was used as a proxy of kidney function, the mode of the associations appeared to be U-shaped. We found null association between $eGFR_{cys}$ and hemorrhagic stroke.

The robust nature of our results is apparent from the overall consistency of the results achieved using multiple approaches. Remarkably, in a community-based population, we found that the risk of stroke started to increase exponentially as the eGFR was below 75 mL/min/1.73 m^2, which is significantly higher than the literature reported threshold of 60 mL/min/1.73 m^2 [4]. As the relationship between a reduced eGFR and stroke risk is still debated, our results strengthen the evidence from several previous studies, including two systematic reviews [4, 5]. One meta-analysis including 284 672 participants and 7863 stroke events showed that the stroke risk increased among participants with an $eGFR_{cr}$ <60 mL/min/1.73 m^2 (relative risk 1.43, 95% CI 1.31–1.57) [4]. Another meta-analysis including 2 156 147 participants with 30 392 stroke events revealed that each 10 mL/min/1.73 m^2 decrement in $eGFR_{cr}$ increased the risk of stroke by 7% (relative risk 1.07, 95% CI 1.04–1.09) [5]. In contrast, another pooled analysis of four community-based studies reported null association between a low $eGFR_{cr}$ and stroke [21]. It is worth noting that in many publications, a single eGFR evaluated at baseline was merely entered into the models as a dichotomous variable (<60 mL/min/1.73 m^2 vs ≥60 mL/min/1.73 m^2) or as a continuous variable. In this regard, neither a potential nonlinear relationship nor the correction for regression dilution bias could be addressed. Our results indeed support the nonlinearity of the association between kidney function and stroke risk. Thus, the simplistic analysis strategy may have underestimated the true association.

Creatinine is not sufficiently sensitive to detect mild to moderate kidney function impairment (40–70 mL/min/1.73 m^2) [9]. This possibly leads to misclassification as the reference group in the $eGFR_{cr}$ analysis. Earlier studies in the general population have been inevitably limited by these unpredictable pitfalls related to creatinine. Moreover, an apparently higher $eGFR_{cr}$ was related to stroke risks, a clinically counterintuitive phenomenon being presented for all three outcomes in our analysis. We observed distinct results between $eGFR_{cys}$ (or $eGFR_{cys\text{-}cr}$) and $eGFR_{cr}$ mainly in the highest category (above 105 mL/min/1.73 m^2), which likely reflects differences in the accuracy of the two measures of kidney function. Both the accuracy and precision of $eGFR_{cr}$ are compromised compared with those of $eGFR_{cys}$ and $eGFR_{cys\text{-}cr}$, especially when kidney function is relatively normal [8]. Pseudo-elevated $eGFR_{cr}$ may mirror the loss of lean muscle mass and poor nutrition [22], all of which are associated with adverse outcomes [23].

Evidence for the association of impaired kidney function with hemorrhagic stroke risk is conflicting. We did not find a detrimental association between a lower eGFR and hemorrhagic stroke risk. In line with our results, a pooled analysis of four studies showed that a low $eGFR_{cr\text{-}cys}$ was significantly associated with an increased risk of ischemic stroke but not hemorrhagic stroke [17]. Recently, a nationwide cohort study in South Korea also reported null association between $eGFR_{cr}$ and the risk of hemorrhagic stroke [24]. The opposite result was reported in the Rotterdam Study using $eGFR_{cr}$ calculated by the Cockcroft–Gault equation [25]. Dissimilarities in these findings may be attributed to the case mix, the spectrum of kidney function, and the equations employed [26, 27]. Nevertheless, the relationship between kidney function and the risk of hemorrhagic stroke appears less clear than that for ischemic stroke and thus warrants further elucidation.

The kidneys and the brain vasculature have many mutual anatomical and functional properties [28] and share similar risk factors [29]. The putative homeostatic mechanisms of a lower eGFR and stroke include cerebral autoregulation, blood flow and vessel remodeling [3]. Impaired kidney function can lead to instability in the regulation of cerebral blood flow, which relies on a constant and adequate supply [30].

From a public health point of view, both stroke and kidney disease are noncommunicable diseases. The current study strengthened the evidence for the relationship between kidney function and stroke risks, and it was shown that screening for kidney function with serum cystatin C may help risk stratification for stroke in the general population. Moreover, our findings highlight that when individuals have an eGFR below 75 mL/min/1.73 m^2 in routine laboratory tests, the risk of stroke should not be underestimated. With the Kidney Disease: Improving Global Outcomes (KDIGO) guideline promoting the measurement of cystatin C [31], more widespread use of cystatin C could expectedly reduce the bias of eGFR in studying adverse outcomes [32, 33].

This study has several limitations that should be considered. First, given the nature of observational studies, we can only suggest an association but cannot ascertain causality. Second, the participants who volunteered were mainly whites aged 40–69 years; therefore, the generalizability of our findings to other ethnic and age groups may be limited. Third, our estimated GFR relied on serum biomarkers rather than the gold standard method of measured GFR [34], which may introduce some uncertainty. Although cystatin C testing is available in many laboratories, it is more expensive than creatinine testing due to the cost of reagents [35] and may be influenced by non-kidney factors such as thyroid function [36, 37] or glucocorticoid use [38]. We were unable to adjust for these confounding factors. The inclusion of participants with such conditions may have overestimated the impact of $eGFR_{cys}$ on outcomes. Fourth, because GFR is estimated using a single measure of cystatin C or creatinine at baseline, we cannot provide GFR values at the time of the stroke or information on GFR progression over time. Finally, due to the lack of data on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification in the UK Biobank [39], we were unable to specify the relationship between eGFR and etiological types of stroke and thereby provide mechanistic insights [40].

In conclusion, we observed a nonlinear relationship between $eGFR_{cys}$ and the risk of total and ischemic strokes in this population-based study. The risks of stroke progressively increased as $eGFR_{cys}$ decreased below 75 mL/min/1.73 m^2. In contrast, the $eGFR_{cr}$-related results were likely to be biased. Our findings emphasize the importance of monitoring kidney function in patients and suggest that $eGFR_{cys}$ should be considered the preferred marker for assessing stroke risk.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

X.H., J.Liao and Z.X. conceptualized the study; J.Liao and X.H. contributed to methodology; L.Y. and Y.S. had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; L.Y. contributed to visualization; X.H. and Y.S. contributed to validation; Y.S., X.H. and Z.X. provided supervision; Y.Wei, C.S., J.Li, S.Y., Y.L., J.Z., L.D., W.L. and T.L. provided resources; J.Liao and F.X. wrote the original draft; Y.Wu, M.J.J. and J.J.C. provided critical feedback on interpretation; and all authors reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were obtained from the UK Biobank (https://www.ukbiobank.ac.uk/). The corresponding author will make the code used for all analyses available upon reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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