Kidney Diseases

Research Article

Kidney Dis 2024;10:274–283
DOI: 10.1159/000539289

Received: September 26, 2023
Accepted: May 6, 2024
Published online: May 20, 2024

Association of Estimated Glomerular Filtration Rate Trajectories with Atrial Fibrillation Risk in Populations with Normal or Mildly Impaired Renal Function

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Keywords
Estimated glomerular filtration rate · Trajectory · Atrial fibrillation · Cohort study · Risk prediction

Abstract

Introduction: The association between the longitudinal patterns of estimated glomerular filtration rate (eGFR) and risk of atrial fibrillation (AF) in populations with normal or mildly impaired renal function is not well characterized. We sought to explore the eGFR trajectories in populations with normal or mildly impaired renal function and their association with AF. ***Methods:*** This prospective cohort study included 62,407 participants who were free of AF, cardiovascular diseases, and moderate to severe renal insufficiency (eGFR <60 mL/min/1.73 m^2) before 2010. The eGFR trajectories were developed using latent mixture modeling based on examination data in 2006, 2008, and 2010. Incident AF cases were identified in biennial electrocardiogram assessment and a review of medical insurance data and discharge registers. We used Cox regression models to estimate the hazard ratios and 95% confidence intervals (CIs) for incident AF. ***Results:*** According to survey results for the range and changing pattern of eGFR during 2006–2010, four trajectories were identified: high-stable (range, 107.47–110.25 mL/min/1.73 m^2; n = 11,719), moderate-increasing (median increase from 83.83 to 100.37 mL/min/1.73 m^2; n = 22,634), high-decreasing (median decrease from 101.72 to 89.10 mL/min/1.73 m^2; n = 7,943), and low-stable (range, 73.48–76.78 mL/min/1.73 m^2; n = 20,111). After an average follow-up of 9.63 years, a total of 485 cases of AF were identified. Compared with the high-stable trajectory, the adjusted hazard ratios of AF were 1.70 (95% CI, 1.09–2.66) for the moderate-increasing trajectory, 1.92 (95% CI, 1.18–3.13) for the high-decreasing trajectory, and 2.28 (95% CI, 1.46–3.56) for the low-stable trajectory. The results remained consistent across a number of sensitivity analyses. ***Conclusion:*** The trajectories of eGFR were associated with subsequent AF risk in populations with normal or mildly impaired renal function.

Plain Language Summary

The relation between estimated glomerular filtration rate (eGFR) within the normal or mildly impaired range and risk of atrial fibrillation (AF) in former studies is controversial, and

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data on longitudinal pattern of eGFR in such topic is sparse. In this cohort study, we identified 4 trajectories of eGFR in populations with normal or mildly impaired renal function. Relative to populations with high-stable pattern of eGFR, those with low-stable pattern, high-decreasing pattern and moderate-increasing pattern were associated with 128%, 92%, and 70% higher risk of AF, respectively. These findings suggested that monitoring eGFR trajectories is an important approach for AF prediction in populations with normal or mildly impaired renal function. Decreasing and consistently low eGFR trajectories within the currently designated normal or mildly impaired range may still significantly increase the risk of AF.

Introduction

Atrial fibrillation (AF) is a major cause of cardiovascular disease and mortality, affecting 33.5 million people worldwide [1]. The prevalence of AF in the adult population is 0.7–1.6% in China [2, 3] and 1.9–2.9% in European countries [4]. With aging of the population and an increasing prevalence of risk factors, the morbidity of AF is anticipated to continue to rise [1], placing higher burdens on public health and socioeconomic development. Therefore, early identification and precise prevention for individuals at high risk of AF are urgently needed.

Some cohort studies have suggested that individuals with moderate to severe renal insufficiency (eGFR <60 mL/min/1.73 m^2, chronic kidney disease [CKD] stage 3–5) are predisposed to incident AF [5, 6]. A recent study on the association between estimated glomerular filtration rate (eGFR) within the normal to mildly impaired range (eGFR ≥60 mL/min/1.73 m^2, CKD stage 1–2) and incident AF indicated that mild renal insufficiency could also increase AF risk [7]. However, several other studies did not find differential AF risks between CKD stage 1 and stage 2 [8–10]. The inconsistent findings may result from the fact that these studies were limited to single measurement of eGFR. However, because reduced renal function is a modifiable risk factor, we believe that exploring the longitudinal patterns in eGFR can better characterize the relationship between renal function and AF. Previous cohort studies have suggested that long-term changes in eGFR are associated with mortality risk beyond current eGFR [11, 12]; however, few studies have explored the timing of eGFR within the normal to mildly impaired range in relation to AF risk. Therefore, the aim of this study was to investigate the association between trajectories of eGFR over a 4-year period and subsequent AF risk in a population with normal or mildly impaired renal function using data from the Kailuan cohort. We hypothesized that multiple eGFR trajectory patterns existed among participants in the Kailuan Study, and those with lower levels of eGFR and decreasing trajectories of eGFR had a higher risk of AF.

Methods

Study Design and Population

The Kailuan Study is a community-based prospective cohort study conducted in Tangshan, China. The detailed study design and procedure have been previously described [13]. In brief, a total of 101,510 participants were enrolled from 11 hospitals affiliated with the Kailuan community from July 2006 to October 2007. All participants underwent a questionnaire interview (including demographic characteristics, medical comorbidities, medication history, and lifestyle factors), physical examinations, and laboratory tests. Follow-up surveys were conducted biennially after the initial survey in 2006.

In the current study, eGFR trajectories were identified using data from 2006, 2008, and 2010 surveys. We excluded 1,638 participants without serum creatinine data in 2006 and 14,980 participants without serum creatinine data in 2008 and 2010. We further excluded 17,084 participants who had a diagnosis of moderate to severe renal insufficiency (CKD stage 3–5) during 2006–2010, 4,904 participants who had a history of AF or cardiovascular diseases (including myocardial infarction, stroke, heart failure, and a detected murmur on cardiac auscultation) before 2010, 44 participants who had a history of hyperthyroidism before 2010, and 453 participants who died during 2006–2010. Ultimately, a total of 62,407 participants were included in the current study (shown in Fig. 1).

Assessment of eGFR and Potential Covariates

Blood and urine samples were collected after an overnight fast by all participants. Concentrations of serum creatinine, fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), and C-reactive protein (CRP) were analyzed on the same day as blood collection using an auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan). Serum creatinine was measured with the sarcosine oxidase assay method. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation. FBG was measured with the hexokinase/glucose-6-phosphate dehydrogenase method. TG and TC were measured using the enzymatic colorimetric method. CRP was measured using the high-sensitivity particle-enhanced immunonephelometric assay. Proteinuria was examined using dipstick urine analysis (DIRUI N-600; Changchun Dirui Medical Technology Co. Ltd, Changchun, China). Test results of "1+" and above were defined as proteinuria [14]. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. Smoking status and drinking status were classified according to three categories: never, past, and current. Blood pressure measurement was according to the seventh Joint National Committee recommendation, as described in detail elsewhere [13]. Heart rate was determined using a 12-lead electrocardiogram (ECG).

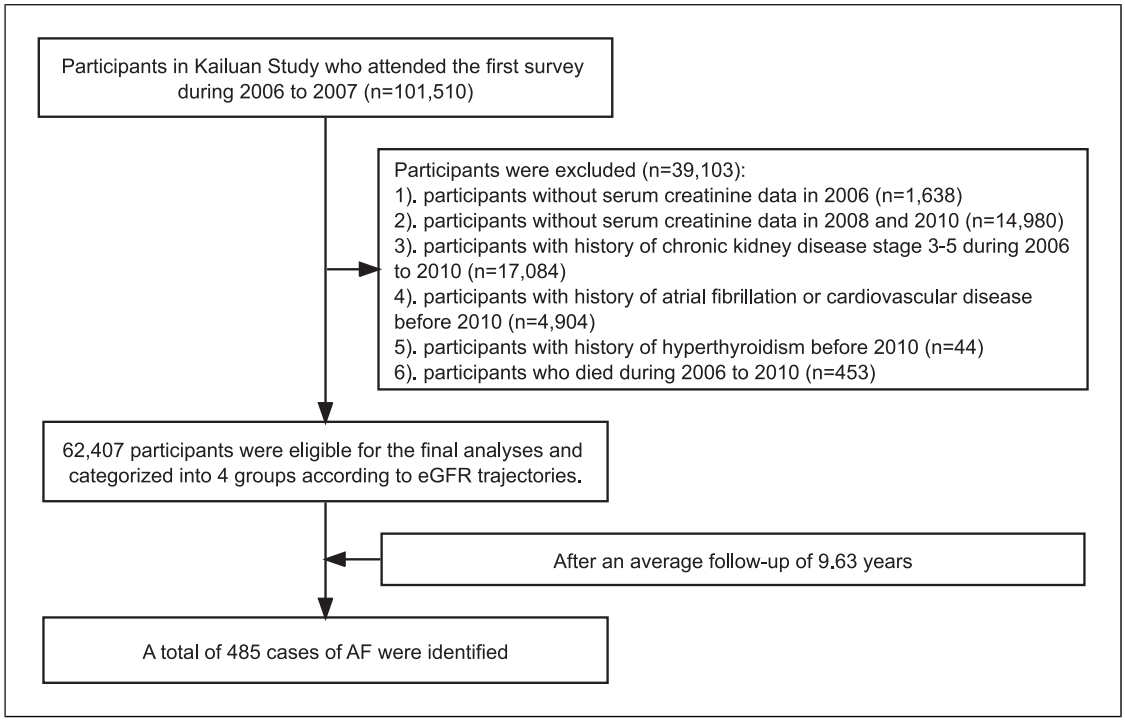

Fig. 1. Flowchart of the eligibility of 62,407 participants included in the final analyses.

Assessment of Incident AF

An incident AF case was defined as the first occurrence of AF during follow-up. The identification of AF was based on the results of 12-lead ECG during follow-up visits every 2 years, with the following diagnostic criteria: (1) irregular RR intervals; (2) absence of distinct *P* waves, with the possibility of regular atrial electrical activity in some ECG leads; and (3) atrial cycle length being usually variable and <200 ms (>300 beats/min) [15]. All ECGs were reviewed independently by two cardiologists. Additional information on AF diagnosis was collected via medical records from the Municipal Social Insurance Institution database and discharge registers from all 11 hospitals in Kailuan community, which covered all participants in the Kailuan Study. The participants were monitored for AF or death until December 31, 2020.

Statistical Analysis

The primary exposure in the current study was eGFR trajectories during 2006–2010. Latent mixture modeling within the PROC TRAJ procedure [16–18] was used to identify subgroups that shared similar changing patterns of eGFR. A censored normal model appropriate for continuous data was used to estimate multiple trajectories. Model fit was assessed using the Bayesian information criterion (BIC). We initially conducted a model with five trajectories and then compared the BIC with models having 4, 3, 2, and 1 trajectory patterns. The model with four trajectories achieved optimal fit.

Continuous variables were compared using analysis of variance or the Kruskal-Wallis test according to their distribution, and categorical variables were compared using the χ^2 test. Cox proportional hazards regression models were used to examine the association between eGFR trajectories and the risk of developing AF. The fully adjusted models included age, sex, smoking status, drinking status, use of antihypertensive agents, proteinuria, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, FBG, TG, TC, and CRP. The models met the proportional assumption based on Schoenfeld residuals. Missing data on covariates were handled by multiple imputation.

To test the robustness of our results, we further performed several sensitivity analyses. To investigate whether the association between eGFR trajectories and incident AF could be explained by single measurement of eGFR during 2006–2010, we additionally adjusted for eGFR in 2006 and 2010, one at a time. To examine whether this eGFR trajectory-AF association was attributable to a change in covariates, we further adjusted for the annual change in BMI, SBP, DBP, heart rate, FBG, TG, TC, and CRP (defined as the slope of the measurements in 2006, 2008, and 2010, using a simple linear regression model). In a sensitivity analysis, we excluded participants with a history of atrial/junctional/ventricular tachycardia, frequent premature atrial/ventricular contractions, Wolff-Parkinson-White syndrome, and second-degree or third-degree atrioventricular block before the follow-up period. To minimize potential reverse causation, we excluded AF events that occurred within the first year of follow-up. Finally, we further tested the results taking into account the competing risk of death. Stratified analyses were performed to assess the potential statistical interaction between eGFR trajectories and age (<50 years vs. ≥50 years), sex, proteinuria (yes vs. no), diabetes mellitus (yes vs. no), and CRP level (<1 mg/L vs. ≥1 mg/L). We also performed a stratified analysis according to antihypertensive medication use (yes vs. no) because

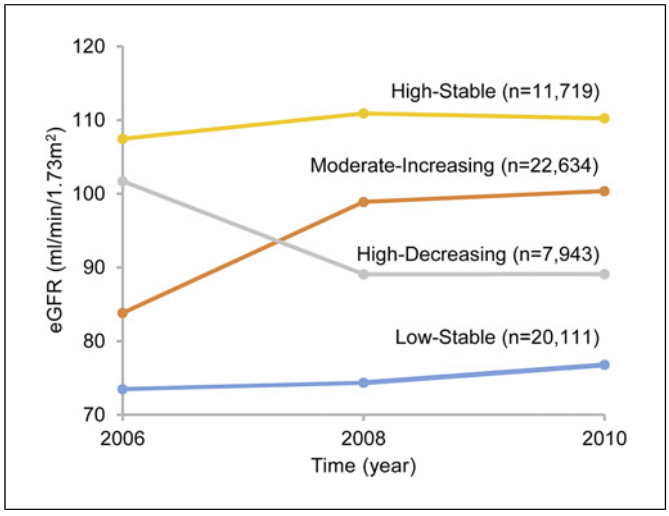

Fig. 2. eGFR trajectories of 62,407 participants during 2006–2010. Four distinct trajectories of eGFR during 2006–2010 were identified: high-stable, eGFR ranged from 107.47 to 110.25 mL/min/1.73 m^2; moderate-increasing, mean eGFR increased from 83.83 to 100.37 mL/min/1.73 m^2; high-decreasing, mean eGFR decreased from 101.72 to 89.10 mL/min/1.73 m^2; low-stable, eGFR ranged from 73.48 to 76.78 mL/min/1.73 m^2. eGFR, estimated glomerular filtration rate.

the cardiac and renal protective effect of antihypertensive medications may modify the eGFR trajectories and their impact on AF. In the secondary analyses, we used the eGFR in 2010, cumulative average of eGFR, and the change in proteinuria during 2006–2010 as secondary exposures.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided $p < 0.05$ was considered statistically significant.

Results

Of 62,451 participants included in the current study (median [interquartile range] age at baseline, 49.50 [41.61, 55.83] years), 49,230 (78.89%) were men and 13,177 (21.11%) were women. We identified four distinct trajectories according to the changes in eGFR from 2006 to 2010 (shown in Fig. 2): 18.78% (n = 11,719) of participants had consistently high levels of eGFR (median eGFR ranged from 107.47 to 110.25 mL/min/1.73 m^2 during 2006–2010, referred to as "high-stable"); 36.27% (n = 22,634) of participants had a moderate level of eGFR but experienced an increase (median eGFR increased from 83.83 to 100.37 mL/min/1.73 m^2 during 2006–2010, referred to as "moderate-increasing"); 12.73% (n = 7,943) of participants had a high level of eGFR in 2006, but experienced a decrease (median eGFR decreased from 101.72 to 89.10 mL/min/1.73 m^2 during 2006–2010, referred to as "high-decreasing"); and, 32.23% (n = 20,111) of participants had consistently low levels of eGFR (median eGFR ranged from 73.48 to 76.78 mL/min/1.73 m^2 during 2006–2010, referred to as "low-stable"). The baseline characteristics according to eGFR trajectory groups were presented in Table 1. All continuous variables have skewed distribution according to Kolmogorov-Smirnov test and are presented as median (interquartile range). Participants with the low-stable trajectory were older and included a higher proportion of men. This group also had higher proportions of proteinuria and antihypertensive medication use, lower TG, and higher BMI, SBP, DBP, and FBG. The highest CRP levels were found in participants with the high-decreasing trajectory.

During the average follow-up period of 9.63 years, 485 cases of incident AF were identified. The group with low-stable trajectory had the highest incidence rate of AF, followed by those with the high-decreasing trajectory, moderate-increasing trajectory, and high-stable trajectory (shown in Table 2; Fig. 3). After adjusting for potential confounders, eGFR trajectories were significantly associated with the risk of AF. The participants with low-stable eGFR had the highest risk of AF among all four trajectories. Relative to the high-stable trajectory, the adjusted hazard ratios were 1.70 (95% confidence interval [CI], 1.09–2.66) for the moderate-increasing trajectory, 1.92 (95% CI, 1.18–3.13) for the high-decreasing trajectory, and 2.28 (95% CI, 1.46–3.56) for the low-stable trajectory (Table 2). The results did not substantially change across the sensitivity analyses (Table 2).

In the stratified analyses, no significant interactions were found between eGFR trajectories and sex, antihypertensive medication use, proteinuria, diabetes mellitus, or CRP level. However, the moderate-increasing trajectory exhibited a relatively higher risk of AF in participants aged ≥50 years, but no significantly higher risk in younger participants, as compared with the high-stable trajectory (Table 3). In the secondary analyses, lower eGFR in 2010 and lower cumulative average eGFR during 2006–2010 were associated with a higher risk of AF. Additionally, participants with proteinuria changing from absence to presence had a 65% higher risk of AF compared with those who maintained an absence of proteinuria (Table 4).

Discussion

In this prospective cohort study, we identified four heterogeneous eGFR trajectories in participants without significant renal insufficiency, and these trajectories were found to be associated with altered AF risk. Relative to

Table 1. Characteristics of 62,407 participants according to eGFR trajectories

Variables	High-stable	Moderate-increasing	High-decreasing	Low-stable	*p* value[a]
Participants, *n*	11,719	22,634	7,943	20,111	
Age, median (IQR), years	40.58 (32.30, 46.83)	49.98 (42.90, 55.40)	50.74 (43.30, 55.82)	53.25 (45.76, 60.73)	<0.001
Men, *n* (%)	16,366 (81.38)	17,060 (75.37)	6,348 (79.92)	9,456 (80.69)	<0.001
Smoking status, *n* (%)					<0.001
Never	12,549 (62.40)	12,400 (54.78)	5,107 (64.30)	5,956 (50.82)	
Past	1,119 (5.56)	1,305 (5.77)	366 (4.61)	491 (4.19)	
Current	6,443 (32.04)	8,929 (39.45)	2,470 (31.10)	5,272 (44.99)	
Drinking status, *n* (%)					<0.001
Never	12,625 (62.78)	11,463 (50.65)	5,056 (63.65)	5,191 (44.30)	
Past	653 (3.25)	783 (3.46)	193 (2.43)	297 (2.53)	
Current	6,833 (33.98)	10,388 (45.90)	2,694 (33.92)	6,231 (53.17)	
Antihypertensive medications use, *n* (%)	3,862 (19.20)	3,967 (17.53)	1,292 (16.27)	1,179 (10.06)	<0.001
Diabetes mellitus, *n* (%)	2,375 (11.81)	2,352 (10.39)	964 (12.14)	817 (6.97)	<0.001
Proteinuria, *n* (%)	2,800 (13.92)	2,773 (12.25)	1,041 (13.11)	1,570 (13.40)	<0.001
eGFR in 2006, median (IQR), mL/min/1.73 m^2	107.47 (101.50, 114.55)	83.83 (76.44, 90.25)	101.72 (97.83, 106.63)	73.48 (67.41, 80.91)	<0.001
eGFR in 2008, median (IQR), mL/min/1.73 m^2	110.92 (105.50, 117.49)	98.90 (92.89, 104.49)	89.08 (81.13, 96.22)	74.35 (67.48, 81.93)	<0.001
eGFR in 2010, median (IQR), mL/min/1.73 m^2	110.25 (104.38, 116.79)	100.37 (94.75, 106.45)	89.10 (81.92, 95.94)	76.78 (69.91, 84.30)	<0.001
BMI, median (IQR), kg/m^{2b}	24.29 (22.14, 26.66)	24.74 (22.66, 26.89)	24.63 (22.69, 26.75)	25.01 (23.03, 27.13)	<0.001
SBP, median (IQR), mm Hg[b]	121.65 (113.50, 131.11)	125.78 (116.23, 137.57)	127.11 (117.33, 139.77)	131.50 (120.65, 144.56)	<0.001
DBP, median (IQR), mm Hg[b]	80.35 (75.33, 86.66)	82.23 (76.65, 88.83)	82.89 (77.33, 89.77)	84.32 (79.00, 90.50)	<0.001
Heart rate, median (IQR), beats/min[b]	74.67 (70.00, 80.00)	72.67 (68.00, 78.00)	73.33 (68.67, 78.33)	73.00 (68.50, 77.67)	<0.001
FBG, median (IQR), mmol/L[b]	5.22 (4.86, 5.66)	5.20 (4.85, 5.66)	5.25 (4.87, 5.73)	5.21 (4.87, 5.70)	<0.001
TG, median (IQR), mmol/L[b]	1.32 (0.94, 2.01)	1.31 (0.94, 1.93)	1.32 (0.97, 1.90)	1.30 (0.96, 1.86)	0.003
TC, median (IQR), mmol/L[b]	4.87 (4.34, 5.46)	4.98 (4.43, 5.58)	4.91 (4.39, 5.49)	4.90 (4.39, 5.48)	<0.001
CRP, median (IQR), mg/L[b]	1.25 (0.69, 2.34)	1.30 (0.69, 2.64)	1.58 (0.81, 3.82)	1.55 (0.79, 3.11)	<0.001

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; IQR, interquartile range; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride. [a]*p* value <0.05 indicates the overall difference among 4 trajectory groups was statistically significant. [b]Average levels based on measurements in 2006, 2008, and 2010.

those who maintained optimal levels of eGFR during the 4-year assessment period, participants with a moderate-increasing trajectory or high-decreasing trajectory showed a higher risk of AF; those with a low-stable trajectory had the highest risk of developing AF. The results remained consistent after adjusting for other cardiovascular risk factors and single measurement of eGFR at baseline. These findings have important public health implications because they link the changing pattern of eGFR in populations without significant renal insufficiency with the risk of AF.

Several studies have investigated the association between risk of AF and eGFR within the normal to mildly impaired range, but these studies have failed to generate consistent results [5, 7–10]. In a cohort study including over one million participants, lower eGFR was independently associated with a higher risk of incident AF in populations with normal or mildly impaired renal function [7]. Data from the Atherosclerosis Risk in Communities cohort similarly showed that CKD stage 2 based on cystatin C was associated with a higher AF risk than CKD stage 1, but the same result was not found using CKD classification based on creatinine [5]. In the Women's Health Study, participants with eGFR 75–89 mL/min/1.73 m^2 or 60–74 mL/min/1.73 m^2 did not show a higher risk of AF than those with eGFR ≥90 mL/min/1.73 m^2 [8]. In several other studies, CKD stage 1 and stage 2 were also found to have a comparable risk of AF [9, 10]. The above studies mainly focused on single measurement of eGFR. However, given that the atrial fibrosis and conduction disturbances that trigger AF develop over time, we believe that exploring the time-varying and cumulative effect of eGFR could be more clinically relevant and informative in the prediction of AF than single measurement. Thus, unlike previous studies, we examined the predictive value of eGFR trajectories based on repeated measurements. We observed that participants with a high-decreasing eGFR trajectory had a higher risk of AF than participants with a high-stable eGFR trajectory, although they had an optimal eGFR at baseline. Similar findings were generated in a previous study by Kwon et al. [19] in a population with elevated eGFR variability. We also observed that participants who started with mildly impaired renal function but had an improved eGFR over time exhibited a lower risk of AF than those who consistently had mildly impaired renal function. This observation may indicate that improvement in mild renal impairment may dilute

Table 2. Hazard ratios (95% CI) for incident atrial fibrillation according to eGFR trajectories

Atrial fibrillation	eGFR trajectories, HR (95% CI)			
	high-stable	moderate-increasing	high-decreasing	low-stable
Cases, *n*	24	156	64	241
Incidence rate, per 1,000 person-years	0.20	0.71	0.84	1.27
Model 1	1 (Reference)	3.46 (2.25–5.32)	4.09 (2.56–6.55)	6.18 (4.06–9.40)
Model 2	1 (Reference)	1.72 (1.11–2.68)	1.92 (1.19–3.11)	2.48 (1.60–3.85)
Model 3	1 (Reference)	1.70 (1.09–2.66)	1.92 (1.18–3.13)	2.28 (1.46–3.56)
Sensitivity analysis 1	1 (Reference)	1.95 (1.18–3.22)	1.99 (1.22–3.24)	2.74 (1.59–4.71)
Sensitivity analysis 2	1 (Reference)	1.79 (1.14–2.82)	2.13 (1.27–3.59)	2.68 (1.58–4.54)
Sensitivity analysis 3	1 (Reference)	1.60 (1.02–2.52)	1.80 (1.10–2.95)	2.01 (1.28–3.16)
Sensitivity analysis 4	1 (Reference)	1.72 (1.09–2.71)	1.93 (1.17–3.17)	2.30 (1.46–3.63)
Sensitivity analysis 5	1 (Reference)	1.69 (1.08–2.64)	1.95 (1.20–3.18)	2.22 (1.42–3.48)
Sensitivity analysis 6	1 (Reference)	1.70 (1.10–2.64)	1.92 (1.18–3.13)	2.22 (1.43–3.44)

Model 1 was non-adjusted model. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, smoking status, drinking status, antihypertensive medication use, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, triglycerides, total cholesterol, C-reactive protein, and proteinuria; sensitivity analysis 1 was further adjusted for eGFR in 2006; sensitivity analysis 2 was further adjusted for eGFR in 2010; sensitivity analysis 3 was further adjusted for the slope of body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, triglycerides, total cholesterol, and C-reactive protein during 2006–2010; sensitivity analysis 4 excluded participants who had other arrhythmia at baseline; sensitivity analysis 5 excluded participants who had AF within the first year of follow-up; sensitivity analysis 6 was the model taking into account the competing risk of death. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

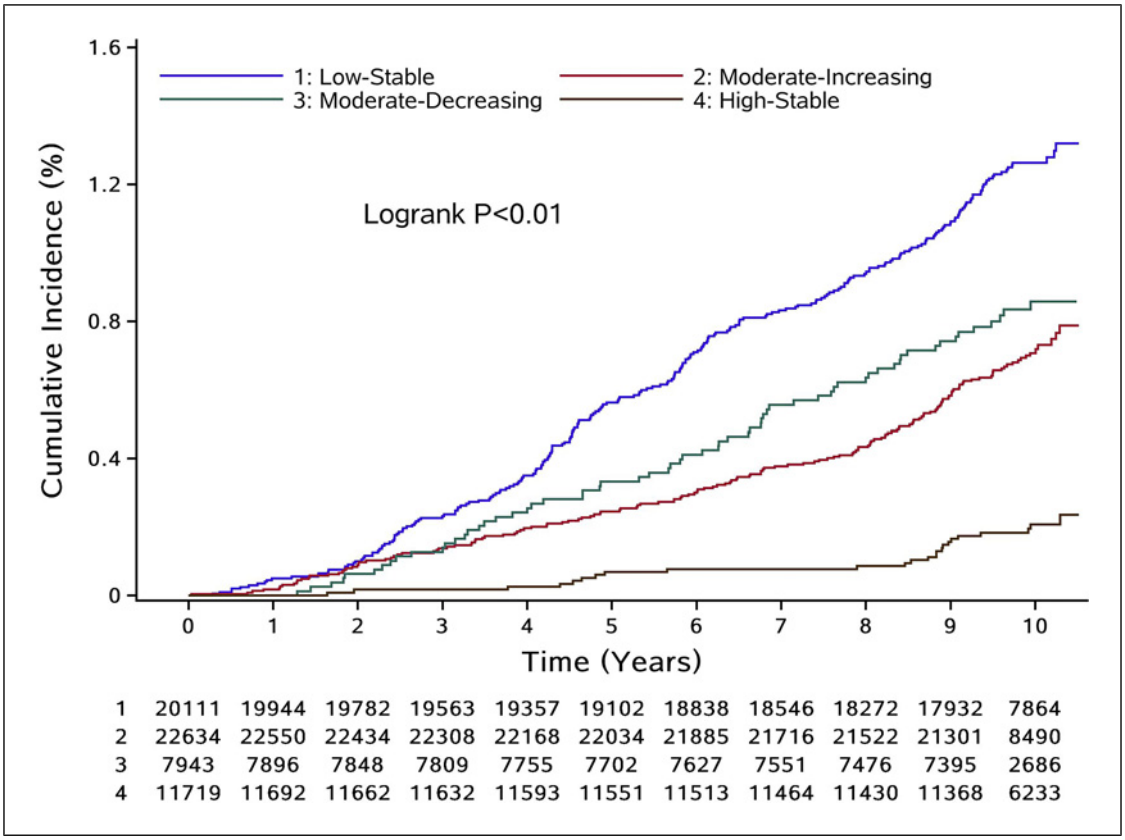

Fig. 3. Kaplan-Meier estimates of cumulative incidence of atrial fibrillation according to four eGFR trajectories. The average duration of follow-up was 9.63 years. eGFR, estimated glomerular filtration rate.

Kidney Dis 2024;10:274–283
DOI: 10.1159/000539289

Table 3. Stratified analyses for the association between eGFR trajectories and incident atrial fibrillation

	eGFR trajectories, HR (95% CI)				
	high-stable	moderate-increasing	high-decreasing	low-stable	*p* value for interaction[a]
Age					
<50 years (*n* = 32,520)	1 (Reference)	1.10 (0.57–2.13)	2.47 (1.19–5.12)	2.41 (1.29–4.51)	0.021
≥50 years (*n* = 29,887)	1 (Reference)	2.34 (1.15–4.79)	2.26 (1.07–4.78)	2.99 (1.47–6.08)	
Sex					
Women (*n* = 13,177)	1 (Reference)	0.91 (0.33–2.51)	1.19 (0.37–3.76)	1.41 (0.51–3.89)	0.489
Men (*n* = 49,230)	1 (Reference)	1.93 (1.17–3.17)	2.11 (1.23–3.61)	2.49 (1.51–4.09)	
Antihypertensive medication use					
No (*n* = 52,107)	1 (Reference)	1.56 (0.98–2.50)	1.63 (0.97–2.76)	1.74 (1.08–2.81)	0.401
Yes (*n* = 10,300)	1 (Reference)	3.54 (0.85–14.82)	5.41 (1.25–23.45)	4.59 (1.09–19.35)	
Proteinuria					
No (*n* = 54,223)	1 (Reference)	1.74 (1.04–2.91)	1.92 (1.09–3.36)	2.49 (1.49–4.15)	0.302
Yes (*n* = 8,184)	1 (Reference)	1.64 (0.66–4.07)	2.06 (0.77–5.50)	1.69 (0.68–4.22)	
Diabetes mellitus					
No (*n* = 55,899)	1 (Reference)	1.55 (0.98–2.47)	1.70 (1.02–2.85)	1.85 (1.16–2.97)	0.184
Yes (*n* = 6,508)	1 (Reference)	3.05 (0.70–13.26)	4.94 (1.09–22.33)	3.07 (0.69–13.72)	
CRP					
<1 mg/L (*n* = 22,633)	1 (Reference)	1.96 (0.82–4.68)	2.57 (0.99–6.62)	2.59 (1.07–6.25)	0.574
≥1 mg/L (*n* = 39,774)	1 (Reference)	1.63 (0.98–2.72)	1.80 (1.03–3.14)	1.79 (1.06–3.02)	

All models were adjusted for age (as appropriate), sex (as appropriate), smoking status, drinking status, antihypertensive medication use (as appropriate), body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose (as appropriate), triglycerides, total cholesterol, C-reactive protein (as appropriate), and proteinuria (as appropriate). CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio. [a]*p* value for interaction <0.05 indicates that the statistical interaction between eGFR trajectories and the stratified variable to atrial fibrillation risk was significant.

subsequent risk of AF. Taken together, these observations suggested a novel perspective that longitudinal trajectories of eGFR could provide greater insight into risk estimation and early prevention of AF in populations with normal or mildly impaired renal function.

The potential mechanisms underlying the association between eGFR trajectories without significant renal insufficiency and incident AF are as follows. The decline of renal function poses activation of renin-angiotensin-aldosterone system and sympathetic system, resulting in cardiac fibrosis and cardiac hypertrophy [20]. An experimental study in rats indicated that even mild renal impairment can result in early cardiac fibrosis and impaired ventricular filling [21], which contribute to AF development [1, 22]. Additionally, systematic inflammation is considered a key process in renal impairment and is involved in the development of cardiovascular damage [1, 23]. Agharazii et al. [24] found that increased inflammatory cytokines expression activate reactive oxygen species generation and downstream intracellular signaling pathways and therefore cause arterial calcification in rats with renal mass ablation. Population studies also observed that mild renal impairment is associated with endothelial dysfunction and atherosclerosis [25–27]. Myocardial ischemia caused by vascular calcification and atherosclerosis could result in release of norepinephrine and generation of cardiac arrhythmias [20]. Moreover, several traditional cardiovascular risk factors, including hypertension and insulin resistance, have also been found to be more prevalent in mild renal impairment [28, 29], which contribute to the occurrence of AF [1, 30]. In consistent with above-mentioned studies, we observed higher baseline blood pressure and higher serum concentrations of CRP in participants with the high-decreasing trajectory and low-stable trajectory. However, further adjustment for blood pressure, CRP, and their annual change during 2006–2010 did not substantially change the results.

Our findings have several clinical and public health implications. First, these heterogeneous eGFR trajectories may provide more accurate information for distinguishing

Table 4. HRs (95% CI) for incident atrial fibrillation according to secondary exposures

	Secondary exposures				*p* trend
eGFR in 2010[a]					
Range, mL/min/1.73 m^2	≥105	90–104	75–89	60–74	
Cases/Total, *n*	38/15,192	174/21,817	156/15,212	117/10,186	
Incidence rate, per 1,000 person-years	0.25	0.83	1.09	1.22	
HR (95% CI)	1 (Reference)	1.35 (0.92–1.96)	1.59 (1.08–2.35)	1.63 (1.09–2.44)	0.030
Cumulative average of eGFR during 2006–2010[a]					
Range, mL/min/1.73 m^2	≥105	90–104	75–89	60–74	
Cases/total, *n*	24/10,116	142/22,783	213/20,505	106/9,003	
Incidence rate, per 1,000 person-years	0.24	0.64	1.09	1.24	
HR (95% CI)	1 (Reference)	1.23 (0.78–1.93)	1.48 (0.94–2.34)	1.60 (0.99–2.58)	0.001
Change of proteinuria during 2006–2010[a,b]					
Range	Absence to absence	Presence to absence	Absence to presence	Presence to presence	
Cases/total, *n*	385/54,435	16/1,416	45/3,389	7/510	
Incidence rate, per 1,000 person-years	0.73	1.21	1.42	1.48	
HR (95% CI)	1 (Reference)	1.33 (0.81–2.21)	1.61 (1.18–2.20)	1.31 (0.61–2.79)	N/A

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; N/A, not applicable. [a]Models were adjusted for age, sex, smoking status, drinking status, antihypertensive medication use, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, triglycerides, total cholesterol, C-reactive protein, and proteinuria. [b]Model was further adjusted for the average of eGFR during 2006–2010.

individuals at risk of AF than single or cumulative measurements. In the current analysis, the association between eGFR trajectories and incident AF remained consistent after adjusting for baseline measurement of eGFR, indicating that the changing pattern of eGFR may have additional contributions to the development of AF. Our findings suggest the need to include longitudinal patterns of eGFR in the risk assessment of AF. Second, because declines in renal function within early stages are commonly asymptomatic and therefore frequently undetected, our study reinforces the importance of long-term monitoring of renal function in populations with normal or mildly impaired renal function, especially those with renal risk factors (for instance, hypertension, diabetes, and high levels of systemic inflammation) or genetic susceptibility for AF. Monitoring eGFR may contribute to early identification and timely intervention of individuals at high risk of AF, which may further promote cardiac health and reduce the health burden of AF-related ischemic stroke. Furthermore, our data support efforts to explore targeted intervention for mild renal impairment. These findings can serve as a basis for future randomized controlled trails.

Strengths and Limitations

The longitudinal trajectory is a combination of cumulative exposure, long-term variability, and changing direction [31]. Thus, the main strength of our study is that we provided a more precise estimate of the association between eGFR and subsequent AF risk in populations with normal or mildly impaired renal function by repeatedly collecting data on eGFR. Additionally, we conducted this prospective study using a large community-based cohort, with biennial examinations and surveys, and all AF events were confirmed by ECG or review of the medical records. These features enabled us to collect detailed baseline characteristics and track outcome events in all participants. However, the current study had several limitations. First, our cohort only included participants from the Kailuan community; therefore, the results may not be completely generalizable to other populations. Given the higher prevalence of AF in people with White race and ethnicity [32], the eGFR trajectory-AF relationship in White populations merits further investigation. Second, the populations of Kailuan cohort are employees of coal mining companies. Therefore, there were more men than women in the study population, which may limit the generalizability of our results. Third, biennial physical

examinations did not include ambulatory ECG monitoring and echocardiography. Several patients with asymptomatic paroxysmal AF or abnormal cardiac structure (e.g., left ventricular hypertrophy, atrial enlargement, and valvular heart disease) might have gone undetected. However, the prevalence of asymptomatic paroxysmal AF is low [33], and we excluded patients with history of cardiovascular events and a detected murmur on cardiac auscultation. Thus, the bias could be small. Fourth, we did not distinguish between valvular AF and non-valvular AF. Most previous studies have focused on non-valvular AF, but renal impairment is also associated with valve thickening and calcification [34], which may further trigger incident valvular AF. Additionally, data on paroxysmal, persistent, and permanent AF were not documented during outcome collection. The association between eGFR within the normal to mildly impaired range and subtypes of AF still needs to be further explored.

In conclusion, we identified four distinct trajectories of eGFR in populations with normal or mildly impaired renal function over a 4-year period, and these trajectories were found to be associated with differential risk of AF development. These findings provide further evidence supporting the association between AF risk and eGFR within the normal to mildly impaired range, and they highlight the importance of monitoring eGFR trajectories for early risk prediction of AF in populations with normal or mildly impaired renal function. Further clinical trials are needed to assess the beneficial effect of intervention in people with mild renal impairment for the prevention of AF.

Acknowledgments

We sincerely thank all the survey teams of the Kailuan Study Group for their contribution and the study participants who contributed their information.

Statement of Ethics

The study protocol complied with the Declaration of Helsinki. The study was approved by the Ethics Committee of Kailuan General Hospital (Reference No.: 2006-5) and was under annual review since 2006. All participants provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Chi Wang: conceptualization, data curation, formal analysis, methodology, and writing – original draft. Qian Xin: conceptualization, formal analysis, methodology, and writing – original draft. Junjuan Li: data curation, formal analysis, and methodology. Jianli Wang: data curation and formal analysis. Siyu Yao, Miao Wang, and Maoxiang Zhao: data curation. Shuohua Chen: data curation and project administration. Shouling Wu and Hao Xue: conceptualization, formal analysis, methodology, supervision, and writing – original draft.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author upon reasonable request.

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