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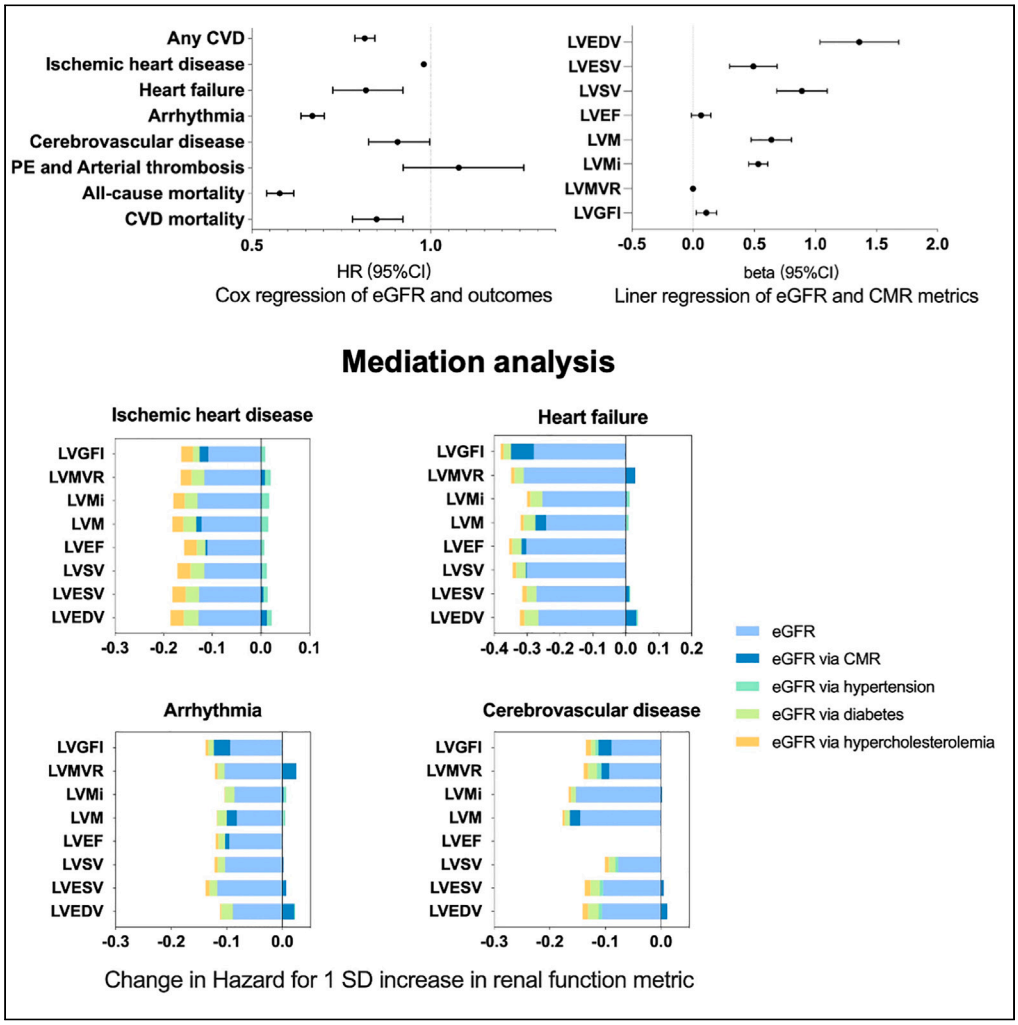

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Highlights

EGFR-cysC is an independent risk factor for multiple CVD events and deaths

EGFR-cysC significantly correlates with poor cardiovascular structure and function

Renal function-related cardiovascular remodeling could drive major CVD events

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The role of cardiac remodeling associated with renal function in mediating cardiovascular event outcomes

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SUMMARY

The potential impact of renal function-related cardiovascular remodeling on associated cardiovascular risk has not been previously investigated. Hence, we conducted multiple mediation analyses in the UK Biobank study to evaluate this association. Using multiple Cox models, we found lower renal function (estimated glomerular filtration rate based on cystatin C, eGFR-cysC) was independently related to increased risks of various cardiovascular events and mortalities. Multivariable linear regression revealed a progressive relationship between declining eGFR-cysC and adverse left ventricular (LV) remodeling and impaired systolic function. In Cox models, larger LV volume, mass, as well as decreased systolic function, were significantly correlated with adverse events, particularly in heart failure. Mediation analyses showed that undesirable LV remodeling and cardiometabolic diseases were independent mediators. Our study explores the connections between reduced renal function and poor cardiovascular phenotypes, as well as their significant independent role in mediating renal function–cardiovascular outcome relationships.

INTRODUCTION

Cardiovascular disease (CVD) continues to be a leading cause of premature death, disability, and significant economic burden worldwide.[1] Chronic kidney disease (CKD) is prevalent in the general population, characterized by decreased glomerular filtration rate (GFR) and increased albuminuria, often remaining undetected until later stages.[2] In this high-risk population, it is important to note that CVD, rather than end-stage renal disease, is the primary cause of mortality.[3] Therefore, CKD is regarded as a potent independent risk factor for CVD.

The prognostic relationship between impaired renal function and adverse CVD outcomes may be mediated by cardiac structural and functional abnormalities. Autopsy-based community studies have revealed connections between reduced estimated glomerular filtration rate (eGFR), left ventricular hypertrophy (LVH), and myocardial fibrosis.[4] Similarly, another community-based study demonstrated that lower eGFR and higher albuminuria were independently related to left ventricular mass (LVM), size, and systolic and diastolic function.[5] However, these investigations were limited to cross-sectional designs and did not establish a connection between renal function, cardiac changes, and subsequent adverse CVD events.

Cystatin C (cysC) has emerged as a more sensitive blood marker for renal function than creatinine. Studies have shown that eGFR based on cysC (eGFR-cysC) identifies a higher proportion of patients with CKD, reinforcing the relationship between eGFR categories and the risk of mortality and CVD events in both the general and CKD populations.[6]

Cardiovascular magnetic resonance (CMR) serves as the gold standard for assessing cardiac structure and function, surpassing ultrasound in terms of accuracy and precision. Prior studies have indicated that patients with CKD exhibit unhealthy patterns of cardiac remodeling, but most of these investigations relied on echocardiography.[5,7]

The UK Biobank is a very large population-based cohort study, including detailed participant characterization, linked longitudinally tracked health outcome data, and detailed standardized CMR data. The study hypotheses an association between reduced renal function and adverse CVD events during follow-up in the UK Biobank cohort, which may be mediated by changes in cardiac structure and function as well as cardiometabolic disorders including hypertension, diabetes, and hypercholesterolemia.

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Table 1. Participant characteristics

Characteristics	Total	eGFR-cysC (mL/min/1.73 m^2)			p
		≥90	60–89	<60	
N	35847	21041	14227	579	
Age, years	54.9 (7.5)	52.4 (7.1)	58.1 (6.5)	61.7 (5.4)	<0.001
Sex (male%)	17045 (47.5%)	9225 (43.8%)	7510 (52.8%)	310 (53.5%)	<0.001
Ethnicity (white%)	34744 (96.9%)	20330 (96.6%)	13852 (97.4%)	562 (97.1%)	<0.001
Body mass index, kg/m^2	26.5 (4.3)	25.8 (4.0)	27.4 (4.6)	28.9 (5.4)	<0.001
Townsend Deprivation Index	−2.62 (3.35)	−2.60 (3.36)	−2.66 (3.28)	−2.48 (3.77)	0.018
Smoking	13299 (37.1%)	7328 (34.8%)	5713 (40.2%)	258 (44.6%)	<0.001
Alcohol	34448 (96.1%)	20355 (96.6%)	13580 (95.5%)	533 (92.1%)	<0.001
Systolic blood pressure, mmHg	140 (19)	138 (18)	144 (19)	144 (18)	<0.001
Diastolic blood pressure, mmHg	79 (10)	78 (10)	79 (10)	77 (10)	<0.001
Hypertension status	16001 (44.6%)	8386 (39.9%)	7291 (51.2%)	324 (56.0%)	<0.001
Diabetes status	3434 (9.6%)	1470 (7.0%)	1831 (12.9%)	133 (23.0%)	<0.001
Hypercholesterolemia status	7066 (19.7%)	3404 (16.2%)	3477 (24.4%)	185 (32.0%)	<0.001
Any CVD status	3151 (8.8%)	1435 (6.8%)	1601 (11.3%)	115 (19.9%)	<0.001
Hemoglobin, g/dL	14.17 (1.22)	14.02 (1.22)	14.38 (1.18)	14.31 (1.35)	<0.001
Cholesterol, mmol/L	5.73 (1.08)	5.68 (1.05)	5.80 (1.12)	5.41 (1.22)	<0.001
Triglyceride, mmol/L	1.39 (1.02)	1.27 (0.93)	1.57 (1.09)	1.75 (1.08)	<0.001
Low-Density Lipoprotein, mmol/L	3.58 (0.83)	3.53 (0.81)	3.67 (0.85)	3.41 (0.93)	<0.001
High-Density Lipoprotein, mmol/L	1.48 (0.38)	1.52 (0.38)	1.42 (0.36)	1.29 (0.35)	<0.001
Glucose, mmol/L	4.88 (0.63)	4.87 (0.63)	4.89(0.63)	4.91 (0.67)	0.019
Glycated hemoglobin, mmol/mol	34.60 (4.70)	34.10 (4.50)	35.30 (4.60)	36.40 (4.90)	<0.001
C-Reactive Protein, mg/L	1.07 (1.59)	0.89 (1.32)	1.37 (1.92)	2.21 (3.35)	<0.001
Creatinine, µmol/L	72.15 (13.95)	68.60 (12.26)	76.56 (13.62)	94.52 (24.61)	<0.001
Cystatin C, mg/L	0.87 (0.13)	0.79 (0.07)	0.97 (0.07)	1.30 (0.20)	<0.001
eGFR-cysC, mL/min/1.73 m^2	92.46 (14.21)	102.27 (7.50)	79.56 (7.37)	53.74 (6.46)	<0.001
Adverse events					
Any CVD	4177 (11.7%)	1867 (8.9%)	2143 (15.1%)	167 (28.8%)	<0.001
IHD	2211 (6.2%)	927 (4.4%)	1180 (8.3%)	104 (18.0%)	<0.001
HF	324 (0.9%)	120 (0.6%)	176 (1.2%)	28 (4.8%)	<0.001
Arrhythmia	1911 (5.3%)	836 (4.0%)	997 (7.0%)	78 (13.5%)	<0.001
Cerebrovascular disease	570 (1.6%)	245 (1.2%)	300 (2.1%)	25 (4.3%)	<0.001
PE and Arterial thrombosis	250 (0.7%)	155 (0.7%)	93 (0.7%)	2 (0.3%)	0.456
All-cause mortality	304 (0.8%)	134 (0.6%)	153 (1.0%)	17 (2.9%)	<0.001
CVD mortality	55 (0.2%)	22 (0.1%)	29 (0.2%)	4 (0.7%)	<0.001

CVD, cardiovascular disease; eGFR-cysC, estimated glomerular filtration rate based on Cystatin C; IHD, ischemic heart disease; HF, heart failure; PE, pulmonary embolism.

Townsend Deprivation Index, glucose, glycated hemoglobin, triglyceride, C-Reactive Protein are expressed as the median and interquartile range. Data are presented as mean ± standard deviation (SD) for the remaining continuous variables and n (%) for categorical variables.

The p-value determines the significance of the difference between the three groups.

RESULTS

Baseline characteristics and cardiovascular magnetic resonance metrics description

A total of 35,847 participants were included in the study, and their baseline characteristics are presented in Table 1. The average age of the participants was 54.9 years, with 47.5% being male, and 96.9% being of white ethnicity. Individuals with lower eGFR levels were found to be older, have higher BMI, a higher proportion of males, a higher prevalence of smoking, and a higher likelihood of comorbid conditions such as hypertension, diabetes, hypercholesterolemia, and CVD. Additionally, they exhibited elevated levels of blood glucose, glycated

Table 2. Associations of renal function metrics with adverse CVDs and mortality outcomes

		Model1		Model2		Model3	
Outcomes	Exposure	HR (95%CI)	p	HR (95%CI)	P	HR (95%CI)	p
Any CVD	eGFR (continuous)	**0.76 (0.73, 0.78)** [a]	**<0.001**	**0.76 (0.73, 0.79)** [a]	**<0.001**	**0.82 (0.79, 0.84)** [a]	**<0.001**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	**1.38 (1.29, 1.47)** [b]	**<0.001**	**1.37 (1.28, 1.46)** [b]	**<0.001**	**1.27 (1.19, 1.36)** [b]	**<0.001**
	eGFR<60	**2.73 (2.31, 3.23)** [b]	**<0.001**	**2.66 (2.25, 3.15)** [b]	**<0.001**	**2.00 (1.69, 2.37)** [b]	**<0.001**
IHD	eGFR (continuous)	**0.97 (0.96, 0.97)** [a]	**<0.001**	**0.97 (0.96, 0.97)** [a]	**<0.001**	**0.98 (0.98, 0.99)** [a]	**<0.001**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	**1.47 (1.33, 1.61)** [b]	**<0.001**	**1.45 (1.32, 1.60)** [b]	**<0.001**	**1.46 (1.33, 1.61)** [b]	**<0.001**
	eGFR<60	**3.16 (2.56, 3.92)** [b]	**<0.001**	**3.06 (2.47, 3.79)** [b]	**<0.001**	**1.40 (1.12, 1.75)** [b]	**<0.001**
HF	eGFR (continuous)	**0.77 (0.69, 0.87)** [a]	**<0.001**	**0.78 (0.69, 0.88)** [a]	**<0.001**	**0.82 (0.73, 0.92)** [a]	**0.001**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	1.05 (0.82, 1.35)	0.716	1.04 (0.81, 1.341)	0.749	1.00 (0.78, 1.29)	0.989
	eGFR<60	**2.75 (1.77, 4.30)** [b]	**<0.001**	**2.67 (1.71, 4.16)** [b]	**<0.001**	**2.24 (1.43, 3.51)** [b]	**<0.001**
Arrhythmia	eGFR (continuous)	**0.65 (0.62, 0.68)** [a]	**<0.001**	**0.65 (0.62, 0.68)** [a]	**<0.001**	**0.67 (0.64, 0.70)** [a]	**<0.001**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	**1.79 (1.62, 1.98)** [b]	**<0.001**	**1.79 (1.61, 1.98)** [b]	**<0.001**	**1.75 (1.58, 1.94)** [b]	**<0.001**
	eGFR<60	**3.52 (2.73, 4.53)** [b]	**<0.001**	**3.48 (2.70, 4.48)** [b]	**<0.001**	**2.99 (2.32, 3.86)** [b]	**<0.001**
Cerebrovascular disease	eGFR (continuous)	**0.89 (0.81, 0.98)** [a]	**0.015**	**0.90 (0.82, 0.98)** [a]	**0.021**	**0.91 (0.83, 0.99)** [a]	**0.043**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	1.07 (0.89, 1.29)	0.461	1.07 (0.89, 1.28)	0.493	1.06 (0.88, 1.28)	0.510
	eGFR<60	**1.61 (1.03, 2.50)** [b]	**0.036**	1.57 (1.00, 2.44)	0.048	1.43 (0.91, 2.23)	0.120
pE and Arterial thrombosis	eGFR (continuous)	1.07 (0.92, 1.25)	0.391	1.07 (0.92, 1.25)	0.388	1.08 (0.92, 1.26)	0.339
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	0.93 (0.70, 1.25)	0.645	0.93 (0.70, 1.25)	0.645	0.92 (0.69, 1.24)	0.591
	eGFR<60	0.52 (0.13, 2.13)	0.364	0.52 (0.13, 2.13)	0.363	0.51 (0.12, 2.10)	0.355
All-cause mortality	eGFR (continuous)	**0.54 (0.50, 0.58)** [a]	**<0.001**	**0.54 (0.51, 0.58)** [a]	**<0.001**	**0.58 (0.54, 0.62)** [a]	**<0.001**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	**2.37 (2.05, 2.75)** [b]	**<0.001**	**2.36 (2.04, 2.73)** [b]	**<0.001**	**2.28 (1.96, 2.64)** [b]	**<0.001**
	eGFR<60	**7.64 (5.52, 10.58)** [b]	**<0.001**	**7.40 (5.34, 10.26)** [b]	**<0.001**	**5.51 (3.96, 7.67)** [b]	**<0.001**
CVD mortality	eGFR (continuous)	**0.82 (0.75, 0.89)** [a]	**<0.001**	**0.82 (0.76, 0.89)** [b]	**<0.001**	**0.85 (0.78, 0.92)** [a]	**<0.001**
	eGFR≥90	Ref.	p	Ref.	p	Ref.	p
	eGFR60-89	**1.22 (1.03, 1.44)** [b]	**0.023**	**1.21 (1.02, 1.44)** [b]	**0.026**	**1.20 (1.01, 1.42)** [b]	**0.041**
	eGFR<60	**2.35 (1.62, 3.39)** [b]	**<0.001**	**2.29 (1.58, 3.30)** [b]	**<0.001**	**1.93 (1.33, 2.80)** [b]	**0.001**

When eGFR was used as a continuous variable, the results were hazard ratios (HRs), 95% confidence intervals (CIs) and P-values associated with per 1 SD increase in eGFR. eGFR for 1 SD = 14.21 mL/min/1.73 m^2 eGFR as a categorical variable, with the eGFR≥90 mL/min/1.73 m^2 group as the reference, the results were HRs, 95% CIs and p-values for the remaining two groups compared to the reference group.

Model 1: Adjusted for age, sex, ethnicity, and body mass index.

Model 2: Additionally adjusted for smoking, alcohol consumption, and the Townsend Deprivation Index.

Model 3: Further adjusted for C-Reactive Protein, Hemoglobin, status of hypertension, diabetes, hypercholesterolemia and any CVD.

Bold values that are statistically significant.

[a]Indicates statistically significant when eGFR was used as a continuous variable.

[b]Indicates statistically significant when eGFR was used as a categorical variable compared to the reference group.

hemoglobin, and CRP. CMR metrics were summarized for all participants and categorized into three groups based on eGFR levels, as shown in Table S1.

Adverse events

The review of death data and results from the HES encompassed data up until May 19, 2021. At a mean follow-up duration of 11.5 (±0.5) years, a total of 11.7% of participants experienced new CVD events. The most common CVD events were IHD, which occurred in 6.2% of participants,

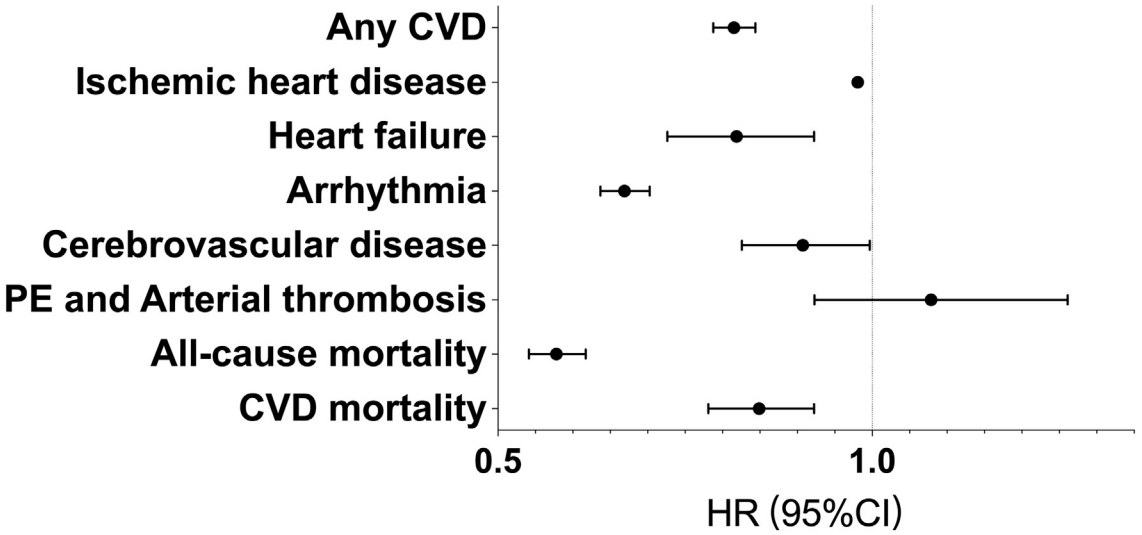

Figure 1. Fully adjusted Cox regression forest plot of eGFR (as a continuous variable) versus outcomes

Cox regression results were HRs and 95% CIs associated with per 1 SD increase in eGFR. eGFR for 1 SD = 14.21 mL/min/1.73 m^2.

and arrhythmias, which occurred in 5.3% of participants. With the exception of pulmonary embolism and arterial thrombosis, the incidence of other adverse events showed a gradual increase as eGFR levels decreased. Moreover, among the participants, 0.8% experienced death, and within this group, 18.1% of deaths were attributed to cardiovascular causes.

Association between renal function and adverse cardiovascular events

In a fully adjusted Cox regression model, lower eGFR demonstrated a significant relation with increased risks of various adverse event outcomes, with the exception of pulmonary embolism and arterial thrombosis (see Table 2; Figure 1). After adjusting for confounding factors, each SD decrease in eGFR (equivalent to a decrease of 14.21 mL/min/1.73 m^2) was linked to an 18% increased risk of any CVD, a 2% elevated risk of IHD, an 18% higher risk of HF, a 33% enhanced risk of arrhythmias, a 9% improved risk of cerebrovascular disease, a 42% excess risk of all-cause mortality, and a 15% greater risk of CVD mortality. Comparing participants with eGFR<60 mL/min/1.73 m^2 to those with eGFR≥90 mL/min/1.73 m^2 (reference group), the former had a higher risk of adverse events. Specifically, the risk of any CVD, IHD, HF, arrhythmias, and cerebrovascular disease was elevated by factors of 1.00, 0.40, 1.24, 1.99, and 0.43, respectively. In addition, the risk of all-cause mortality and CVD mortality increased by factors of 4.41 and 0.93. Conversely, participants with eGFR between 60 and 89 mL/min/1.73 m^2 had enhanced risks for these adverse events, with risk reduction factors of 0.27, 0.46, 0.75, 0.06, 1.28, and 0.20 for any CVD, IHD, arrhythmias, cerebrovascular disease, all-cause mortality, and CVD mortality, respectively. Although adjustments were made for comorbidities (such as hypertension, diabetes, hypercholesterolemia, and CVD), the observed links remained robust and independent. However, no significant correlation was found between eGFR and the occurrence of pulmonary embolism and arterial thrombosis, regardless of adjustment.

Association between renal function and cardiovascular magnetic resonance metrics

In a fully adjusted linear regression model, a decline in eGFR exhibited a significant connection with adverse cardiac remodeling. Specifically, as eGFR declined, there were notable reductions in left ventricular volume (LVEDV, LVESV), diminished left ejection volume (LVSV), decreased left ventricular mass (LVM, LVMi), increased concentric remodeling of the left ventricle (LVMVR), and impaired left ventricular function (LVGFI) (refer to Figure 2; Table S2).

Association between cardiovascular magnetic resonance metrics and adverse cardiovascular events

To explore the potential influence of cardiac alterations on the association between renal function and adverse outcomes, we investigated the relationship between CMR metrics and adverse events. In fully adjusted Cox regression models, we found that larger LVEDV, LVESV, LVM, and LVMi, as well as smaller LVEF and LVGFI, were significantly related to adverse events (refer to Table S3). Additionally, LVSV showed a positive correlation with any CVD and IHD, while demonstrating a negative correlation with HF, arrhythmias, and all-cause mortality. LVMVR displayed a positive relation between any CVD, IHD, and cerebrovascular disease, but exhibited a negative relation with HF and CVD mortality. Notably, these results were most pronounced for HF. However, there was no significant link between CMR metrics and the occurrence of pulmonary thrombosis and arterial thrombosis as outcome events.

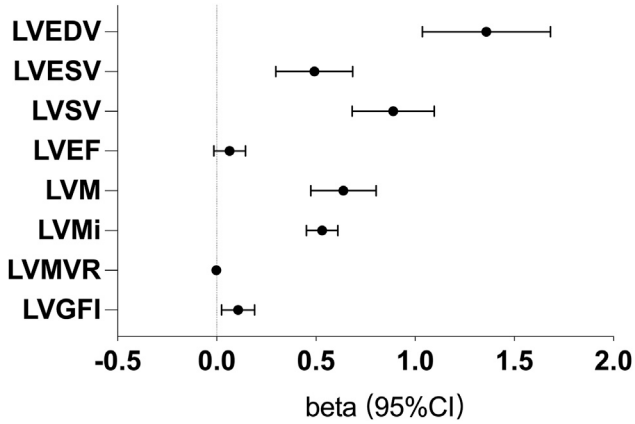

Figure 2. Forest plot of multiple linear regression of eGFR and CMR metrics

The results were beta coefficients and 95% CIs associated with per 1 SD increase in eGFR. eGFR for 1 SD = 14.21 mL/min/1.73 m^2.

Mediation analysis

Multiple mediation analyses were conducted to investigate the underlying mechanisms that drive the correlation between renal function and adverse CVD outcomes, taking into account changes in cardiac structure and function as suggested by CMR and cardiometabolic diseases including hypertension, diabetes, and hypercholesterolemia (refer to Figure 3; Table S4). The mediation analysis focused on the four primary outcome events: IHD, HF, arrhythmias, and cerebrovascular disease. Overall, the direct effect of eGFR on these outcome events was primarily influenced by eGFR itself, independent of mediators and confounding factors. However, adverse cardiac remodeling, hypertension, diabetes, and hypercholesterolemia partially mediated the relationship, with varying roles in different diseases.

Among the CMR metrics, LVEF, LVM, and LVGFI were identified as potential mediators for all outcome events, with LVGFI playing the most prominent mediating role. These effects were not linked to cardiometabolic diseases. In comparison with other outcomes, CMR metrics showed the largest mediating role in the models with HF and arrhythmias as outcomes. For the model with IHD as the outcome, diabetes, and hypercholesterolemia played the largest mediating role compared to other outcomes. LVEDV and LVESV demonstrated some mediating effect in the model, but the relationship was opposite to that of renal function. This suggested that a decline in eGFR was connected to decreased LVEDV and LVESV, while an increase in these CMR metrics was related to the occurrence of adverse outcomes. Similarly, a reduced eGFR was linked to the absence of hypertension (albeit with a small effect size), but the presence of hypertension was correlated with an improved risk of adverse outcomes. The opposite effect was observed for LVMVR, indicating that a decreased eGFR was related to an increased LVMVR, but a depressed LVMVR was associated with adverse outcomes.

DISCUSSION

In this large population-based cohort, we considered the role of renal function-related cardiovascular remodeling in potentially driving key incident cardiovascular outcomes. Our findings revealed several important insights. Firstly, we established that even a mild decline in renal function independently predicted adverse cardiovascular events. Secondly, lower eGFR-cysC levels were linked to poor LV remodeling and impaired LV function. Thirdly, we identified significant associations between increased LVESV, elevated LVMi, reduced LVGFI, decreased LVEF, as well as LVH, and a raised risk of various adverse cardiovascular events (except pulmonary embolism and arterial thrombosis). These connections were particularly prominent for HF. Lastly, multiple mediation analyses indicated that altered cardiac structure and function, and cardiometabolic disorders (including hypertension, diabetes and hypercholesterolemia) were independent mediators of the correlation between decreased renal function and adverse CVD events.

Our findings align with previous studies that have reported an association between renal function and poor cardiac remodeling, as well as impaired function.[5] For instance, in patients with CKD without HF, lower eGFR levels were related to a higher prevalence of LVH and abnormal LV geometry but not with diastolic or systolic dysfunction.[8] Similarly, CKD, as determined by eGFR and albuminuria, was linked to cardiac remodeling and subtle systolic dysfunction in individuals with HF with reduced ejection fraction (HFpEF).[9] Furthermore, studies in population cohorts have demonstrated an association between mild to moderate decline in renal function and increased LVMi and LVH.[10]

Our results shed light on the connection between eGFR and LV volume and mass. While a weak positive linear relationship was observed between eGFR and these CMR metrics in our study population, it is important to note that the majority of participants (98%) had normal or mildly declining renal function, as reported in a previous community study.[5] This suggests that the positive association between eGFR and LV volume/mass might be weak and that the negative linear relationship had not yet to be revealed. Notably, LVMVR, reflecting concentric remodeling or hypertrophy,[11] demonstrated a significant and independent correlation with eGFR. As eGFR reduced, LVMVR raised, sensitively indicating the presence of adverse changes in LV structure connected to concentric remodeling.

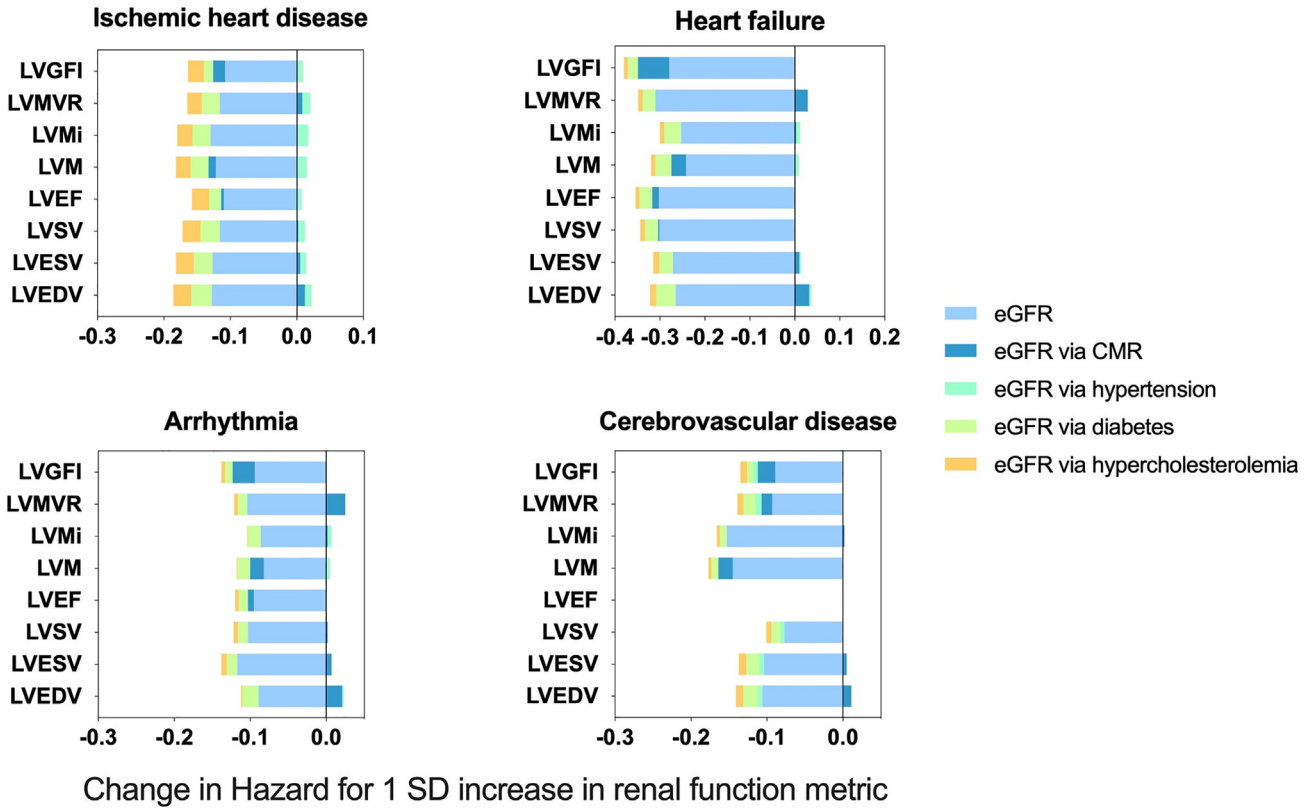

Figure 3. Visualization of Multiple Mediator Analysis

Results of fully adjusted multiple mediation models between eGFR and CVD events, mediated by the one raw CMR metric and the three cardiometabolic disease conditions in each iteration. The overall size of the bars corresponds to the strength of the total effect between eGFR and disease occurrence. Each individual area of the bar reflects the magnitude of the effect mediated by each mediator.

Increased left ventricular volumes and degree of concentric remodeling are generally associated with poor outcomes.[11] A correlation was found between lower eGFR and reduced LV volumes, as well as an elevated LVMVR in the sample. However, our multiple mediation analysis revealed that larger LV volumes and lower LVMVR were linked to a higher risk of adverse outcomes. This suggests that different stages of CKD-related heart disease may be involved. CKD-related factors, such as abnormal arterial stiffness, enhanced systemic arterial resistance, and systolic hypertension, initially lead to concentric LVH.[12] Subsequent sustained LV overload leads to maladaptive cardiac changes, cardiomyocyte death, eccentric hypertrophy, LV dilation, systolic dysfunction, and reduced ejection fraction[13] As CKD progresses, myocardial fibrosis and maladaptive ventricular hypertrophy occur, further contributing to cardiac dilation.[14]

LVGFI, an emerging measure of LV function encompassing ventricular structure, has been shown to be more reliably associated with disease in population cohorts than LVEF.[15] In our study, we observed a significant correlation between eGFR and LVGFI. Moreover, our findings revealed that LVGFI displayed a substantial mediating role as a CMR phenotype in several diseases. We are the first to report this connection in a large cohort. Our findings indicated that while eGFR was not related to LVEF, it was independently associated with LVGFI. The decrease in LVGFI with declining eGFR suggests impaired LV function sensitively, ultimately increasing the risk of adverse outcomes.

Cardiometabolic diseases, well-established risk factors for CKD and CVD,[3] had a significant impact on our study. However, the direct impact of renal function on outcomes cannot be disregarded. Meta-analyses have highlighted the independent correlation between eGFR (based on creatinine) and albuminuria with CVD events, and enhanced outcome prediction beyond traditional risk factors,[6] suggesting the contribution of non-traditional kidney-specific mechanisms to CVD risk. Mechanisms underlying this link include the dysregulation of mineral metabolism, vascular calcification, atherosclerosis,[16] renal anemia-induced LVH,[17] inflammation,[18,19] sodium and volume overload,[20] activation of the renin-angiotensin-aldosterone system and sympathetic overactivity,[21] retention of uremic solutes,[22] and coronary microvascular dysfunction.[23]

In conclusion, our study, conducted in a large population-based cohort, identifies a significant and independent association between renal function decline (measured by eGFR-cysC) and adverse CVD events, even with mild renal function impairment. More importantly, our findings suggest that cardiac remodeling and cardiometabolic diseases play mediating roles in this connection. Kidney-specific mechanisms may significantly contribute to the development of CVD and warrant further exploration. This highlights the need for research focused on identifying direct pathways to inform therapeutic interventions and lifestyle modifications.

Limitations of the study

The event outcomes were based on data from the HES, which may only capture incident diseases recorded in the hospital setting. The protocol used in the UK Biobank Imaging Study did not include more comprehensive tissue characterization sequences, such as gadolinium contrast-enhanced images. The available information did not provide details on the severity, duration, and specific drug treatments for hypertension, which limited the clarification of the relationship between renal function and hypertension. Furthermore, changes in renal function and cardiac alterations during the period between recruitment and CMR could not be determined, as blood samples were obtained at the time of recruitment and CMR was performed later. Despite efforts to include other ethnic groups, the majority of participants were of Caucasian European descent. Thus, it is necessary to interpret our results with caution. It is important to note that the mediation analysis conducted in our study was exploratory and does not establish causality. Therefore, further longitudinal or interventional studies are warranted to clarify causal relationships. Finally, future investigations should consider the bidirectional relationship between CKD and CVD, as described in the cardiorenal syndrome,[24] although it could not be definitively determined in our study.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109143.

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AUTHOR CONTRIBUTIONS

DG conceptualized the idea. ZL and YF devised the study and conducted the statistical analyses. ZL wrote the first version of the article, which was critically refereed by the other authors. All authors made contributions to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
UK Biobank	UK Biobank	https://www.ukbiobank.ac.uk/
Software and algorithms		
SPSS (R26.0.0.0)	IBM SPSS (Statistical Product and Service Solutions) Statistics	https://www.ibm.com/products/spss-statistics
R 4.3.0	The R Foundation for Statistical Computing	https://www.r-project.org/
mma (R)	Open source	https://cran.r-project.org/web/packages/mma/index.html

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Dengfeng Gao (gaomedic@mail.xjtu.edu.cn).

Materials availability

This study did not generate new material or reagent.

Data and code availability

- The study utilised data from public databases. Data support the main findings in this study are accessible via the UK Biobank under application number 68722. Therefore, data used in this study cannot be directly shared with other researchers.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Ethics approval for UK Biobank was obtained from the North West Multi-Centre Research Ethics Committee, which covers the UK (approval number: 11/NW/0382). Informed consent was obtained from all participants.

UK Biobank is a large-scale prospective cohort study comprising over 500,000 individuals aged 40–69 years (around 54% of female and 94% of self-reported European ancestry) from various regions across the United Kingdom, identified through the National Health Service (NHS). Baseline assessments encompassed comprehensive information on sociodemographics, lifestyle factors, medical history, physical measurements, and biological samples including blood and urine. Prospective tracking of health outcomes was enabled through linkage to national electronic health records, including HES and death registries.[25] Notably, the UK Biobank initiated the world's largest multimodal imaging study, inviting 100,000 participants to undergo multiple imaging examinations, including CMR imaging.[26]

METHOD DETAILS

Study design

This cohort observational study based on the UK Biobank participants aimed to examine the relationship between renal function, cardiovascular outcomes, and CMR phenotypes. We included all participants who underwent CMR, ensuring a comprehensive analysis. Participants with missing baseline cysC, body surface area, or CMR data were excluded from the study. Figure S1 illustrated a comprehensive flowchart detailing the exclusion criteria and the resulting study sample. Missing variables were estimated using multiple interpolation. Baseline characteristics encompassed essential demographic information, clinical data, and subsequent CMR measurements. Ethnicity was categorized as either white or other ethnicities. Smoking and drinking history were self-reported and classified as current/former smokers or never smokers, and current/former alcohol drinkers or never drinkers, respectively. Socioeconomic status was determined using the Townsend Deprivation Index (TDI). Diabetes was identified based on self-report, reported use of insulin, and blood biomarkers collected at baseline (serum glucose >11.1 mmol/L or serum glycated hemoglobin >48 mmol/mol). Hypertension was ascertained using self-report, self-reported use of antihypertensive medication, and baseline blood pressure measurements (≥140/90 mmHg). Hypercholesterolemia was determined based on self-reported use of cholesterol-lowering medication and total serum cholesterol levels >7 mmol/L. A status of CVD was defined as a diagnosis of ischemic heart disease (IHD), heart failure (HF), arrhythmia, cerebrovascular disease, pulmonary embolism and arterial thrombosis, identified using International Classification of Diseases, 10th Revision (ICD-10) codes at baseline.

Renal function indicators

During the baseline visit, blood samples were collected from participants and sent to a central laboratory for analysis. Renal function indicators, including cysC, creatinine, and lipid profile (including high density, low density, and total cholesterol), among other parameters, were measured. Specifically, serum levels of cysC and creatinine were determined. The eGFR based on cysC (eGFR-cysC) was calculated using the 2012 CKD Epidemiology Collaboration equation,[27] which takes into account the measured cysC levels. Serum cysC levels were quantified using a latex-enhanced immunoturbidimetric assay conducted on a Siemens Advia 1800 analyzer from Siemens (Erlangen, Germany), with an inter-assay coefficient of variation of 1.1%.[28]

CMR measures

Native CMR scans were conducted following a predetermined acquisition protocol17 using 1.5 Tesla scanners (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare).[29] The protocol consisted of acquiring standard long-axis images and a short-axis stack encompassing both ventricles from the base to the apex, employing balanced steady-state free precession sequences. The CMR images were subject to analysis using a fully automated quality-controlled pipeline.[30] Various measures pertaining to the structure and function of the left ventricle (LV) were incorporated, including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular stroke volume (LVSV), left ventricular mass (LVM), left ventricular mass index (LVMi) (calculated based on BSA), left ventricular ejection fraction (LVEF), left ventricular mass-to-volume ratio (LVMVR), left ventricular global function index (LVGFI), and left ventricular hypertrophy (LVH). LVMVR denoted the ratio of LVM to LVEDV, providing insight into the degree of concentric remodeling of the left ventricle.[11] LVGFI was defined as LVSV divided by LV global volume, multiplied by 100, where LV global volume was determined as the mean lumen volume of the LV [(LVEDV + LVESV)/2] combined with myocardial volume (LVM/density).[31] The density of the LV was specified as 1.05 g/mL. LVH was identified as LVMi exceeding 72 g/m^2 in men and 55 g/m^2 in women.[32]

Ascertainment of outcomes

The ascertainment of CVD outcomes involved the inclusion of the following new events: ischemic heart disease (IHD), heart failure (HF), arrhythmia, cerebrovascular disease, pulmonary embolism, and arterial thrombosis. The composite outcome encompassed any CVD event as defined by the aforementioned events. The identification and recording of CVD events were carried out in accordance with the ICD-10 codes. Specifically, IHD was represented by codes I20-I25, HF by codes I110, I130, I132, I500, I501, I509, arrhythmia by codes I44-I49, cerebrovascular disease by codes I60-I69, and pulmonary embolism and arterial thrombosis by codes I26 and I74, respectively. Additionally, all-cause mortality and CVD mortality (where any CVD event was recorded as the primary cause of death, including algorithmically-defined myocardial infarction outcomes 42000 and stroke outcomes 42006) were included by extracting data from record links to death registration records.

Definition of covariates

The selection of covariates was based on biological plausibility, taking into account factors that could potentially confound the analysis. To determine the relation between exposure and outcome, we accounted for several potential confounders, namely age, sex, ethnicity, body mass index (BMI), TDI, smoking status, alcohol consumption, C-reactive protein (CRP), hemoglobin (Hb), status of hypertension, diabetes, hypercholesterolemia and CVD. Additionally, we considered hypertension, diabetes, and hypercholesterolemia as cardiometabolic diseases with possible causal relationships to the outcomes under investigation. By including these covariates, we aimed to control for their influence on the exposure-outcome association and obtain more accurate estimates.

QUANTIFICATION AND STATISTICAL ANALYSIS

Baseline characteristics and CMR data are reported based on eGFR categorized into three groups: $\geq$90, 60–89, and <60 mL/min/1.73m^2. In examining the connection between renal function and event outcomes, we employed the eGFR as a measure of renal function at baseline, along with subsequent event outcomes during follow-up. Cox proportional hazards regression models were utilized to assess the relationship between eGFR and CVD events, including IHD, HF, arrhythmias, cerebrovascular disease, pulmonary embolism and arterial embolism, and any CVD, as well as mortality outcomes encompassing all-cause death and CVD-related death. When eGFR was treated as a continuous variable, the results were reported as hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for each standard deviation (SD) increase in eGFR. Alternatively, when eGFR was categorized into three groups ($\geq$90 mL/min/1.73m^2, 60–89 mL/min/1.73m^2, <60 mL/min/1.73m^2), with eGFR $\geq$90 mL/min/1.73m^2 as the reference group, the HRs and 95% CIs for the other two groups were presented. Hierarchical models were constructed in a stepwise manner, progressively adjusting for covariates to evaluate their impact on the primary association between renal function and outcomes. Model 1 accounted for demographic characteristics, including age, sex, ethnicity, and BMI. Model 2 further adjusted for lifestyle factors, such as smoking, alcohol consumption, and the TDI. The fully adjusted model, model 3, incorporated additional potential mediators, namely CRP, Hb, status of hypertension, diabetes hypercholesterolemia and CVD.

To investigate the correlation between eGFR (as a continuous variable) and the CMR phenotypes, multivariable linear regression was employed. The effect sizes of CMR metrics were reported as beta coefficients and their corresponding 95% CIs, standardized beta coefficients, and P-values for comparison of magnitude.

Additional analyses were conducted to examine the role of the CMR cardiovascular phenotypes and cardiometabolic diseases as potential mediators in the relationship between renal function and event outcomes. Cox regression models were utilized to describe the correlation between CMR metrics and CVD event outcomes. The main stages of the statistical methods were shown in the flowchart in Figure S2. Subsequently, the multiple mediation analysis package (mma[33]) was employed to quantify the proportion of the effects of renal function on outcomes that were mediated by cardiac remodeling (CMR metrics), hypertension, diabetes, and hypercholesterolemia. Confidence intervals for coefficients in the mediation models were estimated based on 500 bootstrapped replicates. Statistical analyses were performed using SPSS (R26.0.0.0), R (version 4.3.0) and Rstudio. For all tests, $p < 0.05$ was defined as statistically significant and marked with symbols in this analysis.