Excess risk of cardiovascular events in patients in the United States vs. Japan with chronic kidney disease is mediated mainly by left ventricular structure and function

Subtitle: Excess CVD Risk and LV Structure and Function

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Definition of echocardiographic parameters

LV mass (LVM) was calculated using 2-dimensional images of the LV short-axis muscle area and the apical LV length with Devereux's formula using LV internal end-diastolic diameter (LVEDD), interventricular septum thickness at end-diastole (IVSd), and posterior wall thickness in diastolic phase (PWd) as follows.[S1,S2]

$$LVM\ (g) = 0.8 \times \{1.04 \times [([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6.$$

LVMI was calculated as LVM divided by height (m) to the power of 2.7, written as $m^{2.7}$. This indexation was originally proposed by de Simone et al.[S3] and was utilized in a multiethnic comparison of LVMI.[S4] We defined LVH as LVMI >50 $g/m^{2.7}$ in males and >47 $g/m^{2.7}$ in females based on previous research.[S2] Relative wall thickness (RWT) was calculated as IVSd plus PWd divided by the LVEDD, and we defined high RWT as ≥0.45. LV geometry was categorized by LVMI and RWT as (1) normal (normal LVMI and RWT), (2) concentric remodeling (normal LVMI and high RWT), (3) eccentric hypertrophy (high LVMI and normal RWT), or (4) concentric hypertrophy (high LVMI and RWT). To assess the symmetry between IVSd and PWd, we also examined the septal-to-posterior wall thickness ratio. We defined asymmetric septal hypertrophy (ASH) as a septal-to-posterior wall thickness ratio of more than 1.3, which is a common feature in patients with advanced CKD.[S5] LV systolic function was assessed as EF {([end-diastolic volume] - [end-systolic volume])/[end-systolic volume]} × 100%.

Definition of outcome events in both cohorts

In the CRIC study, the following process was repeated every six months to confirm events. CRIC participants were asked about the occurrence of an outcome event and possible hospitalization, and then, inpatient medical records were selectively reviewed. For records where the hospital billing codes suggested a cardiovascular CRIC event of interest,

records were then collected at the clinical sites and stored centrally. Deidentified copies of the medical records were distributed to members of the CRIC Event Adjudication Committee, which ultimately provided the final determination regarding the occurrence of a CRIC clinical outcome event. Peripheral arterial disease data were abstracted by a nurse and not reviewed by two physicians. CVD outcome events were defined as follows.

1) Acute Myocardial Infarction (MI): MI occurring in the inpatient setting was defined by a combination of abnormalities of the electrocardiogram (ECG), elevations of cardiac enzymes and the presence of symptoms.
2) Hospitalization for CHF: CHF was recorded as an outcome event when hospitalization occurred for clinical symptoms of CHF in the setting of objective confirmatory evidence, including radiographs, evidence of pulmonary congestion/edema, physical examination, invasive hemodynamic monitoring or the use of inotropic support.
3) Peripheral Vascular Disease (PVD): A peripheral vascular event was documented when one of the following was present
   · PVD with resultant amputation
   · Peripheral surgical or percutaneous revascularization procedures such as arterial angioplasty and artery-artery bypass grafting.
4) Cerebrovascular event: Cerebrovascular events were categorized as follows:
   · Intraparenchymal hemorrhage
   · Subarachnoid hemorrhage
   · Large-vessel cerebral infarction
   · Cardioembolic cerebral infarction
   · Small-vessel cerebral infarction
   · Cerebral infarction not otherwise specified

5) Sudden Cardiac Death: Sudden cardiac death was ascertained via questionnaires that were administered to next of kin addressing the timing and location of death as well as the circumstances and symptoms just prior to death. Interviews took place as soon as possible upon the confirmation of participant death. Two physicians reviewed the questionnaire information and adjudicated the final determination of a sudden cardiac death event.

In the CKD-JAC study, on the other hand, once local investigators recognized a possible event occurrence, they submitted the report of a potential CVD event to the data center. The CVD event adjudication committee, which comprised three physicians, reviewed the anonymized event reports and provided the final decision on the events. CVD events were defined as follows.

1) Myocardial infarction: The diagnosis was based on specific changes in electrocardiograms, elevations in myocardial desensitization enzymes, and angiographic findings.
2) Sudden death: All of the following were met:

   (1) Death within 1 hour after the onset of serious symptoms, or death confirmed by the last person seeing the patient as asymptomatic at the time of death.

   (2) No evidence of any disease other than acute or chronic coronary artery disease that could have resulted in death.

   (3) "Unexpected" death occurring in a person who was not resting at home, admitted to a hospital, or otherwise institutionalized because of illness within 24 hours before death.
3) Congestive heart failure: At least one of the following criteria was met.

   (1) Heart failure not due to an acute event (due to a chronic event)

   (2) Marked dyspnea

(3) Marked pulmonary edema on frontal chest X-ray

(4) Marked elevated BNP level (if measured)

(5) Strict in-out balance control was required.

4) Fatal arrhythmia: Deaths due to the following arrhythmia.

5) Cerebrovascular events were classified into the following three categories:

(1) Cerebral infarction

(2) Cerebral hemorrhage

(3) Subarachnoid hemorrhage

All of the following conditions had to be met as the basis for diagnosis.

(1) Recent onset with clear and objective findings of focal neurologic deficits.

(2) The finding has persisted for at least 24 hours.

(3) Neurological findings were not due to extracranial damage.

(4) CT or MRI or autopsy records within 3 weeks of onset of the disease showed that the cerebrovascular disease could be classified as cerebral hemorrhage, cerebral infarction, or subarachnoid hemorrhage.

6) Peripheral vascular disease: defined as any of the following

(1) Vascular intermittent claudication

(2) Unilateral loss or weakness of femoral arterial pulsation

(3) Unilateral loss or weakness of the dorsal foot artery and posterior carotid artery pulsation

(4) Bilateral loss or weakness of the dorsal foot artery and/or posterior carotid artery pulsation

(5) Ankle–brachial index (ABI) < 0.8

(6) Angiographic evidence of stenosis (>75% stenosis or collateral vessels)

(7) Leg gangrene or ulcer

7) Other fatal CVD event: Included aortic dissection and following arrhythmia
   (1) Ventricular fibrillation
   (2) Sustained ventricular tachycardia
   (3) Torsades de pointes
   (4) Cardiac arrest (due to atrioventricular block, sinus dysfunction syndrome, etc.)

Overall, the definitions of CVD events were similar between the two cohorts, with the exception of PVD and sudden death. Although the methods of collecting reports of possible events differed, both cohorts shared the adjudication of events by a third-party organization irrelevant to the study and analysis.

Definition of covariates

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of any antihypertensive drugs, including diuretics. DM was defined as fasting blood glucose ≥126 mg/dL, random blood glucose ≥200 mg/dL, or the use of antidiabetic drugs. Regarding body mass index, we set different classifications for Asian people and other ethnic groups to account for racial diversity: for Asian participants, BMI <18.5 was underweight, 18.5–22.9 was normal weight, 23–24.9 was overweight, 25–29.9 was obese I, and BMI ≥30 was obese II or higher. For the other ethnic groups, BMI <18.5 was defined as underweight; 18.5–24.9, normal weight; 25–29.9, overweight; 30–34.9, obese I; and ≥35, obese II or higher. A prior history of CVD consisted of four subcategories: coronary artery disease, CHF, PAD, and stroke. Those with any CVD had at least one CVD subcategory.

Biomarker harmonization between the CRIC and CKD-JAC studies

In our collaboration project, we examined the differences in the medical history and

harmonized several biomarkers.[S6] Since LV measures are considered one of the major components of CKD mineral bone disease (CKD-MBD),[S7] we standardized MBD-related biomarkers, namely, phosphate and parathyroid hormone (PTH), by measuring the same values in different assays (Japanese and American) or using an equation for 25(OH) vitamin D. Serum phosphate was measured by a phosphomolybdate assay in the CRIC study and an enzymatic assay in the CKD-JAC study. Total PTH was measured by immunoradiometric assay (Scantibodies Laboratories, Santee, CA, USA) in the CRIC study, while intact PTH was measured by electrochemiluminescence immunoassay (Roche® Elecsys 2010 System, Roche Diagnostics). Intact fibroblast growth factor-23 (FGF23) was measured by a sandwich-antibody method that detects only the biologically active form of FGF23 (Kyowa Medex Inc, Tokyo, Japan). We randomly selected 897 samples from the CRIC study and securely transferred them to the same Japanese laboratory that measured intact FGF23. In the CRIC study, 25(OH) vitamin D was measured by liquid chromatography and mass spectrometry, while a conventional radioimmunoassay (DiaSorin® LIAISON 25OH Vitamin D Total Assay, Stillwater, MN) was used in the CKD-JAC study. In a previous study, we developed the conversion equations for serum phosphate and PTH into those measured in the CRIC study using Deming regression. Regarding 25(OH) vitamin D, we used the conversion equation for standardization.[S8] Detailed information on harmonization of the laboratory assays for these biomarkers is described elsewhere.[S9]

Mediation analysis

The percentage mediation was estimated as follows: 100%× (hazard ratio [HR] – HRc)/(HR – 1), where “HRc” is the HR of CRIC vs. CKD-JAC after adding potential mediators to the model, and “HR” is the HR in a model without the mediators.[S10] The 95% confidence

intervals for the estimated percentage mediation were obtained using a 1000-iteration bootstrap resampling procedure.[S11] We adjusted for factors in Model 3 except for LVMI, EF, phosphate, iFGF23, and CRP. The combined potential mediating effect of multiple mediators was quantified using the same equation.

We also performed a secondary analysis using a method under the counterfactual framework approach, namely, we used the R package “CMAverse”, which accommodated multiple sequential mediators, adjusting for confounders preceding mediators (https://bs1125.github.io/CMAverse/). Multiple imputations for missing values were also available. The 95% confidence intervals for the estimated percentage mediation were obtained using a 1000-iteration bootstrap resampling procedure. In Model 3, we adjusted for all factors except for LVMI, EF, phosphate, iFGF23, and CRP.

In the original method proposed by Hafeman[S10], the proportion mediated was estimated in the presence of only one mediator. However, we found that essentially the same formula was used in the R package CMAverse for multiple mediators under the rare disease assumption.[S12] Specifically, in CMAverse, the proportion mediated was estimated using the following formula:

$$HR^{NDE}(HR^{NIE} - 1)/(HR^{TE} - 1)$$

where HR^{NDE}, HR^{NIE}, and HR^{TE} are the natural direct, natural indirect, and total effects in the hazard ratio scale, respectively. Because HRNDE × HRNIE = HRTE, we can rewrite the formula above as:

$$(HR^{TE} - HR^{NDE})/(HR^{TE} - 1).$$

This is the same as the formula proposed by Hafeman[S10] when there is no treatment-mediator interaction in the Cox model.

In the causal mediation framework, these mediators must conform to the following assumptions[S12]:

(1) There are no unmeasured confounders of the association between the exposure and the outcome.

(2) There are no unmeasured confounders of the association between the mediator and the outcome.

(3) There are no unmeasured confounders of the association between the exposure and the mediator.

(4) The confounders of the association between the mediator and the outcome are not affected by the exposure.

Here, we quantified unmeasured confounders by their E-value, defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure–outcome association, conditional on the measured covariates.[S13] For the fourth assumption, the best we could do was to make multivariable adjustments for measured confounders that would affect both the mediators and the outcomes (i.e., obesity and CVD history).

[References]

S1. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. Am J Cardiol. 1986;57(6):450–458.

S2. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's guidelines and standards committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiograph. J Am Soc Echocardiogr. 2005;18(12):1440–1463.

S3. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: Assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol. 1995;25(5):1056–1062.

S4. Akintoye E, Mahmoud K, Shokr M, et al. Racial/ethnic differences in the prognostic utility of left ventricular mass index for incident cardiovascular disease. Clin Cardiol. 2018;41(4):502–509.

S5. Straumann E, Bertel O, Meyer B, et al. Symmetric and asymmetric left ventricular hypertrophy in patients with end-stage renal failure on long-term hemodialysis. Clin Cardiol. 1998;21(9):672–678.

S6. Imaizumi T, Hamano T, Fujii N, et al. Cardiovascular disease history and β-blocker prescription patterns among Japanese and American patients with CKD: a cross-sectional study of the CRIC and CKD-JAC studies. Hypertens Res. 2021;44(6):700–710.

S7. Hamano T, Sakaguchi Y, Fujii N, Isaka Y. Clinical features of CKD-MBD in Japan: cohort studies and registry. Clin Exp Nephrol. 2017;21(Suppl 1):9–20.

S8. Janssen MJW, Wielders JPM, Bekker CC, et al. Multicenter comparison study of current methods to measure 25-hydroxyvitamin D in serum. Steroids. 2012;77(13):1366–1372.

S9. Fujii N, Hamano T, Hsu JY, et al. A Comparative Study of Serum Phosphate and Related Parameters in CKD between the US and Japan. Am J Nephrol. 2022; 53(2–3): 226–239

S10. Hafeman DM. “proportion explained”: A causal interpretation for standard measures of indirect effect? Am J Epidemiol. 2009;170(11):1443–1448.

S11. Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. Stat Med. 2018;37(14):2252–2266.

S12. Van Der weele T, Vansteelandt S. Mediation analysis with multiple mediators. Epidemiol Method. 2014;2(1):95–115.

S13. Van Der Weele TJ, Ding P. Sensitivity analysis in observational research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268–274.

Supplementary Table S1. Baseline characteristics of those with or without echocardiography in the Chronic Kidney Disease Japan Cohort (CKD-JAC) study

	Total (N = 2813)	Echo data available (n = 1171)	Echo data not available (n = 1642)	P value
Age, years	60 (12)	61 (11)	60 (12)	<0.001*
Sex (male)	1,753 (62)	748 (64)	1,005 (61)	0.15
eGFR, mL/min/1.73m^2	29.0 (12.3)	28.8 (12.6)	29.2 (12.1)	0.44
UACR, mg/g	490 (112–1316)	523 (139–1386)	466 (97–1233)	0.017*
Diabetes	1,057 (38)	494 (42)	563 (34)	<0.001*
Atrial fibrillation	60 (2)	29 (2)	31 (2)	0.29
BMI (kg/m^2)	24 (4)	24 (4)	23 (4)	0.19
Smoking status (current smoker)	407 (17)	181 (17)	226 (17)	0.74
Alcohol consumption (yes)	464 (20)	213 (21)	251 (19)	0.34
Obesity category				0.20
Underweight	187 (7)	72 (6)	115 (8)	
Normal	1,023 (40)	453 (40)	570 (41)	
Overweight	523 (21)	243 (22)	280 (20)	
Obese I	655 (26)	285 (25)	370 (26)	
Obese II or more	140 (6)	71 (6)	69 (5)	
Systolic BP (mmHg)	132 (19)	132 (18)	131 (19)	0.41
Diastolic BP (mmHg)	76 (12)	76 (12)	76 (12)	0.40
Medication				
Number of antihypertensive agents	3 (2–4)	3 (2–4)	3 (2–4)	0.089
ACEi/ARB	2,292 (81)	974 (83)	1,318 (80)	0.050*
Beta Blockers	573 (20)	237 (20)	336 (20)	0.88
Alpha blockers	380 (14)	135 (12)	245 (15)	0.009*
Calcium channel blockers	1,561 (55)	672 (57)	889 (54)	0.088
Diuretics	892 (32)	409 (35)	483 (29)	0.002*
Active vitamin D	243 (9)	85 (7)	158 (10)	0.028*
Phosphate binders	589 (21)	266 (23)	323 (20)	0.050
Antiplatelets	1,116 (40)	511 (44)	605 (37)	<0.001*
Statins	379 (13)	159 (14)	220 (13)	0.89
Any CVD history	727 (26)	331 (28)	396 (24)	0.013*
CAD history	329 (12)	178 (15)	151 (9)	<0.001*
CHF history	151 (5)	69 (6)	82 (5)	0.30
Stroke history	295 (10)	131 (11)	164 (10)	0.31
PAD history	96 (3)	49 (4)	47 (3)	0.057
Locally measured laboratory data				
Alb, g/dL	4.0 (0.4)	4.0 (0.5)	4.0 (0.4)	0.014*
Hb, g/dL	12.1 (1.8)	12.2 (1.9)	12.0 (1.8)	0.095
Total cholesterol, mg/dL	195 (44)	193 (44)	196 (43)	0.091
HbA1c (NGSP), %	5.9 (0.9)	6.0 (0.9)	5.9 (0.9)	0.004*
Corrected calcium, mg/dL	9.0 (0.5)	9.0 (0.5)	9.1 (0.5)	0.010*
Phosphate, mg/dL	3.5 (0.7)	3.5 (0.7)	3.5 (0.7)	0.53
Total PTH, pg/mL	78 (53–125)	78 (53–124)	78 (54–125)	0.95
Intact FGF23, pg/mL	57 (40–91)	58 (42–93)	55 (39–90)	0.024*
25(OH)D, ng/mL	15 (10–22)	15 (10–22)	15 (9–21)	0.11

Data are expressed as N (%) for categorical values and mean (S.D.) or median (interquartile range) for continuous values. *P <0.05. Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio; BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; CAD, coronary artery disease; CHF, congestive heart failure; PAD, peripheral artery disease; NGSP, National Glycohemoglobin Standardization Program; PTH, parathyroid hormone; FGF, fibroblast growth factor.

Supplementary Table S2. Factors associated with left ventricular mass index (LVMI) in the combined cohort

	Model 1	Model 2	Model 3	Model 4
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
CRIC (vs. CKD-JAC)	**10.2 (8.85–11.5)**	**7.61 (6.32–8.89)**	**7.68 (6.26–9.10)**	**6.55 (5.08–8.02)**
Age (/10 years)	**1.00 (0.50–1.51)**	**1.43 (0.95–1.90)**	**1.59 (1.11–2.07)**	**1.34 (0.87–1.82)**
Male (vs. female)	**3.13 (2.08–4.19)**	**3.97 (2.97–4.97)**	**3.91 (2.89–4.93)**	**3.82 (2.81–4.84)**
Smoking status	0.33 (-1.12–1.78)	**1.78 (0.42–3.14)**	**1.96 (0.60–3.31)**	**1.86 (0.51–3.21)**
eGFR (/10 ml/min/1.73 m²)	**-0.63 (-1.02–-0.25)**	**-0.48 (-0.84–-0.12)**	-0.02 (-0.44–0.39)	0.16 (-0.26–0.58)
ln(UACR)	**0.91 (0.61–1.20)**	**0.98 (0.71–1.26)**	**0.85 (0.57–1.12)**	**0.84 (0.56–1.11)**
Diabetes mellitus	**3.52 (2.47–4.58)**	0.27 (-0.75–1.29)	0.20 (-0.83–1.22)	-0.14 (-1.18–0.89)
CAD history	**3.62 (2.29–4.95)**	**3.08 (1.84–4.33)**	**3.21 (1.97–4.45)**	**2.63 (1.38–3.88)**
CHF history	**9.00 (7.15–10.8)**	**8.84 (7.11–10.6)**	**8.47 (6.74–10.2)**	**7.88 (6.15–9.61)**
Stroke history	-1.93 (-4.03–0.17)	-0.88 (-2.84–1.09)	-1.16 (-3.12–0.81)	-1.34 (-3.30–0.61)
PAD history	**2.59 (0.98–4.19)**	**2.86 (1.36–4.36)**	**2.86 (1.37–4.36)**	**2.42 (0.94–3.91)**
Atrial fibrillation	**4.83 (3.36–6.31)**	**4.20 (2.82–5.58)**	**4.08 (2.71–5.46)**	**3.68 (2.31–5.04)**
Hemoglobin, g/dL	**-0.88 (-1.20–-0.56)**	**-1.30 (-1.60–-1.00)**	**-1.09 (-1.41–-0.78)**	**-1.11 (-1.42–-0.80)**
Systolic blood pressure, mmHg	**0.15 (0.13–0.18)**	**0.13 (0.11–0.15)**	**0.12 (0.10–0.15)**	**0.11 (0.09–0.13)**
ln(CRP)	**1.70 (1.30–2.10)**	**0.40 (0.01–0.79)**	**0.46 (0.07–0.85)**	**0.44 (0.06–0.83)**
Obesity category				
Underweight		**-5.68 (-8.85–-2.51)**	**-5.68 (-8.83–-2.52)**	**-5.56 (-8.70–-2.43)**
Normal				
Overweight		**4.91 (3.56–6.26)**	**4.85 (3.50–6.20)**	**4.59 (3.25–5.93)**
Obese I		**10.6 (9.17–12.0)**	**10.3 (8.88–11.7)**	**9.76 (8.37–11.1)**
Obese II or more		**17.7 (16.2–19.3)**	**17.3 (15.7–18.8)**	**16.5 (14.9–18.0)**
Corrected calcium, mg/dL			-0.62 (-1.66–0.43)	-0.69 (-1.73–0.34)
Phosphate, mg/dL			**1.09 (0.51–1.66)**	**0.99 (0.42–1.56)**
ln(total PTH)			**1.56 (0.73–2.38)**	**1.36 (0.53–2.18)**
ln(intact FGF23)			0.86 (-0.10–1.83)	0.74 (-0.21–1.70)
Active vitamin D supplementation			**-2.75 (-4.63–-0.86)**	**-2.90 (-4.77–-1.03)**
ln(25(OH) vitamin D)			-0.64 (-1.41–0.13)	-0.60 (-1.37–0.16)
Antihypertensive medication				
β-blockers				**2.86 (1.84–3.88)**
Calcium channel blockers				**1.95 (0.98–2.92)**
ACEi/ARB				-0.70 (-1.76–0.36)
Diuretics				**1.67 (0.65–2.70)**

Emboldened values were statistically significant ($P < 0.05$)

CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; CRP, C-reactive protein; PTH, parathyroid hormone; FGF, fibroblast growth factor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Supplementary Table S3. Factors associated with left ventricular ejection fraction (LVEF) in the combined cohort

	Model 1	Model 2	Model 3	Model 4
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
CRIC (vs. CKD-JAC)	**-10.4 (-11.1–-9.69)**	**-10.5 (-11.2–-9.73)**	**-10.9 (-11.7–-10.1)**	**-10.4 (-11.3–-9.60)**
Age (/10 years)	**0.74 (0.47–1.01)**	**0.74 (0.47–1.01)**	**0.74 (0.46–1.01)**	**0.65 (0.37–0.92)**
Male (vs. female)	**-2.38 (-2.94–-1.82)**	**-2.41 (-2.98–-1.85)**	**-2.27 (-2.85–-1.69)**	**-2.41 (-2.99–-1.83)**
Smoking status	0.49 (-0.29–1.27)	0.56 (-0.22–1.34)	0.56 (-0.23–1.35)	0.60 (-0.19–1.39)
eGFR (/10 ml/min/1.73 m²)	0.06 (-0.14–0.26)	0.06 (-0.15–0.26)	0.09 (-0.14–0.33)	0.12 (-0.12–0.36)
ln(UACR)	-0.10 (-0.26–0.05)	-0.11 (-0.26–0.05)	-0.08 (-0.23–0.08)	-0.15 (-0.31–0.00)
Diabetes mellitus	0.01 (-0.54–0.57)	-0.10 (-0.67–0.47)	-0.12 (-0.70–0.46)	-0.12 (-0.70–0.46)
CAD history	**-3.35 (-4.05–-2.64)**	**-3.37 (-4.07–-2.66)**	**-3.39 (-4.09–-2.68)**	**-3.48 (-4.19–-2.76)**
CHF history	**-6.74 (-7.71–-5.77)**	**-6.74 (-7.71–-5.77)**	**-6.75 (-7.73–-5.78)**	**-6.51 (-7.49–-5.53)**
Stroke history	-0.15 (-1.25–0.96)	-0.11 (-1.21–1.00)	-0.15 (-1.26–0.97)	-0.16 (-1.27–0.95)
PAD history	0.25 (-0.60–1.09)	0.23 (-0.61–1.08)	0.23 (-0.62–1.07)	0.10 (-0.75–0.94)
Atrial fibrillation	**-1.32 (-2.09–-0.55)**	**-1.34 (-2.11–-0.57)**	**-1.31 (-2.08–-0.54)**	**-1.38 (-2.14–-0.61)**
Hemoglobin, g/dL	-0.02 (-0.19–0.14)	-0.05 (-0.22–0.12)	-0.08 (-0.26–0.10)	-0.08 (-0.26–0.10)
Systolic blood pressure, mmHg	-0.01 (-0.02–0.01)	-0.01 (-0.02–0.01)	-0.01 (-0.02–0.01)	-0.01 (-0.02–0.00)
ln(CRP)	**-0.47 (-0.68–-0.25)**	**-0.50 (-0.72–-0.28)**	**-0.49 (-0.72–-0.27)**	**-0.48 (-0.71–-0.26)**
Obesity category				
Underweight		-0.45 (-2.30–1.40)	-0.48 (-2.32–1.37)	-0.27 (-2.11–1.57)
Normal				
Overweight		0.22 (-0.55–0.98)	0.23 (-0.54–0.99)	0.16 (-0.60–0.92)
Obese I		0.90 (0.12–1.68)	0.97 (0.18–1.75)	0.76 (-0.02–1.55)
Obese II or more		0.36 (-0.51–1.23)	0.51 (-0.37–1.38)	0.23 (-0.66–1.11)
Corrected calcium, mg/dL			0.57 (-0.02–1.17)	0.50 (-0.09–1.08)
Phosphate, mg/dL			0.06 (-0.26–0.38)	0.08 (-0.24–0.40)
ln(total PTH)			-0.30 (-0.77–0.17)	-0.27 (-0.74–0.19)
ln(intact FGF23)			0.30 (-0.30–0.91)	0.25 (-0.34–0.84)
Active vitamin D supplementation			**1.12 (0.07–2.18)**	1.05 (-0.01–2.10)
ln(25(OH) vitamin D)			0.23 (-0.21–0.66)	0.18 (-0.25–0.61)
Antihypertensive medication				
β-blockers				0.21 (-0.36–0.78)
Calcium channel blockers				**1.80 (1.25–2.36)**
ACEi/ARB				**1.03 (0.43–1.62)**
Diuretics				**-0.77 (-1.36–-0.18)**

Emboldened values were statistically significant ($P < 0.05$)

CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; CRP, C-reactive protein; PTH, parathyroid hormone; FGF, fibroblast growth factor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Supplementary Table S4. Description of outcome events

Left ventricular measurements	Events	Subjects	Incidence rate (/1000 person-years)				
			CVD	ASCVD	CHF	All-cause death	Kidney failure
All	832	4222	35.3	15.5	18.3	18.2	49.8
CRIC	599	3125	38.5	17.6	19.5	20.3	45.2
CKD-JAC	233	1097	23.5	7.9	13.8	10.2	67.6
LVH							
All							
without LVH	264	1976	15.9	8.7	6.2	9.5	32.5
with LVH	568	2246	54.6	22.2	30.1	26.5	66.3
CRIC							
without LVH	148	1275	16.3	9.9	5.5	10.7	25.5
with LVH	451	1850	56.8	23.7	30.7	27.8	60.6
CKD-JAC							
without LVH	116	701	14.9	5.7	7.8	6.5	50
with LVH	117	396	41.4	12.6	26.3	17.8	103.9
P for interaction							
Geometry							
All							
Normal	106	790	15.6	7.4	6.7	7.8	34.6
Concentric remodeling	158	1186	16.1	9.4	5.9	10.5	31.2
Eccentric LVH	89	379	63.7	19.7	39.9	29.1	64.8
Concentric LVH	479	1867	52.9	22.6	28.3	26	66.6
CRIC							
Normal	35	340	17	9.5	6.7	9	22.5
Concentric remodeling	113	935	16	10	5.1	11.3	26.6
Eccentric LVH	54	236	72.3	24.2	42.1	30.1	56.1
Concentric LVH	397	1614	54.5	23.6	29.1	27.5	61.3
CKD-JAC							
Normal	71	450	14.2	5.4	6.7	6.6	47
Concentric remodeling	45	251	16.3	6.2	9.9	6.2	55.6
Eccentric LVH	35	143	45.5	9.8	35.1	26.7	84.9
Concentric LVH	82	253	39.1	14.2	21.3	12.6	114.8

CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CRIC, Chronic Renal Insufficiency Cohort; CKD-JAC, Chronic Kidney Disease Japan Cohort; LVH, left ventricular hypertrophy.

Supplementary Table S5. Factors associated with the incidence of cardiovascular disease (CVD) events

	Model 1	Model 2	Model 3
	HR (95% CI)	HR (96% CI)	HR (97% CI)
LVMI (per 10 g/m$^{2.7}$)	**1.19 (1.14–1.24)**	**1.21 (1.15–1.26)**	**1.19 (1.14–1.24)**
LVEF (per 10%)	**0.72 (0.66–0.78)**	**0.72 (0.67–0.79)**	**0.72 (0.66–0.78)**
CRIC (vs. CKD-JAC)	**1.61 (1.22–2.12)**	**1.79 (1.34–2.38)**	**1.88 (1.38–2.56)**
Age (/10 years)	**1.40 (1.26–1.55)**	**1.35 (1.21–1.50)**	**1.40 (1.26–1.56)**
Male (vs. female)	1.18 (0.99–1.42)	1.19 (0.98–1.45)	1.18 (0.97–1.44)
Smoking status	**1.43 (1.14–1.80)**	**1.39 (1.10–1.76)**	**1.39 (1.10–1.77)**
eGFR (/10 ml/min/1.73 m^2)	**0.78 (0.72–0.84)**	**0.79 (0.73–0.86)**	**0.82 (0.75–0.90)**
ln(UACR)	**1.12 (1.07–1.17)**	**1.10 (1.05–1.16)**	**1.10 (1.04–1.15)**
Diabetes mellitus	**1.56 (1.29–1.88)**	**1.58 (1.29–1.93)**	**1.51 (1.23–1.85)**
Any CVD history	**2.18 (1.80–2.63)**	**2.13 (1.76–2.58)**	**2.10 (1.74–2.55)**
ln(CRP)	1.04 (0.97–1.11)	1.06 (0.99–1.14)	1.07 (1.00–1.15)
Systolic blood pressure, mmHg		1.00 (1.00–1.01)	1.00 (1.00–1.01)
Obesity category			
Underweight		1.62 (0.83–3.14)	1.50 (0.77–2.94)
Normal		1.00 (Reference)	1.00 (Reference)
Overweight		0.78 (0.59–1.03)	0.79 (0.60–1.05)
Obese I		0.85 (0.64–1.13)	0.83 (0.63–1.11)
Obese II or more		**0.59 (0.43–0.81)**	**0.58 (0.43–0.80)**
Number of antihypertensive agents		1.05 (0.97–1.13)	1.05 (0.97–1.13)
Hemoglobin, g/dL		0.96 (0.91–1.01)	0.98 (0.93–1.04)
Corrected calcium, mg/dL			0.86 (0.71–1.03)
Phosphate, mg/dL			**1.12 (1.04–1.21)**
ln(total PTH)			1.00 (0.85–1.16)
ln(intact FGF23)			1.18 (1.00–1.38)
Active vitamin D supplementation			0.77 (0.54–1.09)
ln(25(OH) vitamin D)			**0.83 (0.70–0.97)**

Multivariable models were adjusted as follows: **Model 1**: age, sex, baseline smoking status, eGFR, ln(UACR), diabetes, history of any CVD and CRP; **Model 2**: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin; **Model 3**: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D). CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; CRIC, chronic renal insufficiency cohort; CKD-JAC, chronic kidney disease Japan cohort; UACR, urinary albumin-creatinine ratio.

Emboldened values were statistically significant ($P < 0.05$)

Supplementary Table S6. Association of left ventricular indices with the incidence of atherosclerotic cardiovascular disease (ASCVD) events

Left ventricular indices	Events	Subjects	Incidence rate*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
LVEF (per 10%)						
All (CRIC+CKD-JAC)	248	4222	15.5	0.88 (0.77–1.00)	0.88 (0.77–1.01)	0.88 (0.77–1.01)
CRIC	221	3125	17.6	**0.85 (0.74–0.98)**	**0.86 (0.74–1.00)**	**0.86 (0.74–0.99)**
CKD-JAC	27	1097	7.9	1.04 (0.72–1.52)	1.07 (0.72–1.59)	1.07 (0.71–1.59)
P for interaction				0.43	0.39	0.39
LVMI (continuous, per 10 g/m$^{2.7}$)						
All (CRIC+CKD-JAC)	248	4222	15.5	1.04 (0.97–1.12)	1.06 (0.99–1.15)	1.07 (0.99–1.15)
CRIC	221	3125	17.6	1.04 (0.97–1.12)	1.06 (0.98–1.15)	1.07 (0.99–1.16)
CKD-JAC	27	1097	7.9	1.14 (0.88–1.46)	1.14 (0.85–1.51)	1.12 (0.84–1.50)
P for interaction				0.82	0.77	0.79
LVH						
All (CRIC+CKD-JAC)						
without LVH	68	1976	8.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	180	2246	22.2	1.27 (0.93–1.73)	1.37 (0.99–1.91)	1.39 (1.00–1.93)
CRIC						
without LVH	55	1275	9.9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	166	1850	23.7	1.21 (0.86–1.69)	1.34 (0.93–1.91)	1.35 (0.94–1.94)
CKD-JAC						
without LVH	13	701	5.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	14	396	12.6	1.77 (0.81–3.88)	1.68 (0.71–3.97)	1.65 (0.70–3.92)
P for interaction				0.59	0.61	0.63
Geometry						
All (CRIC+CKD-JAC)						
Normal	22	790	7.4	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	46	1186	9.4	1.09 (0.64–1.86)	1.10 (0.64–1.87)	1.15 (0.67–1.95)
Eccentric LVH	26	379	19.7	1.11 (0.62–1.99)	1.24 (0.68–2.25)	1.29 (0.71–2.34)
Concentric LVH	154	1867	22.6	1.40 (0.86–2.28)	1.51 (0.92–2.50)	1.57 (0.95–2.61)
CRIC						
Normal	14	340	9.5	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	41	935	10	1.10 (0.59–2.04)	1.11 (0.59–2.06)	1.17 (0.63–2.19)
Eccentric LVH	22	236	24.2	1.08 (0.55–2.12)	1.24 (0.62–2.47)	1.30 (0.65–2.61)
Concentric LVH	144	1614	23.6	1.33 (0.75–2.36)	1.47 (0.82–2.65)	1.56 (0.86–2.81)
CKD-JAC						
Normal	8	450	5.4	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	5	251	6.2	0.88 (0.28–2.75)	0.88 (0.27–2.80)	0.90 (0.28–2.88)
Eccentric LVH	4	143	9.8	1.22 (0.35–4.28)	1.14 (0.31–4.15)	1.16 (0.31–4.26)
Concentric LVH	10	253	14.2	1.95 (0.74–5.12)	1.89 (0.66–5.35)	1.86 (0.65–5.33)
P for interaction				0.82	0.80	0.83

Multivariable models adjusted for **Model 1**: age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, CRP, CRIC (vs. CKD-JAC), and EF (or LVMI); **Model 2**: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin; **Model 3**: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D). CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; PTH, parathyroid hormone; FGF, fibroblast growth factor.

*Number of events per 1000 person-years

Emboldened values were statistically significant ($P < 0.05$).

Supplementary Table S7. Association of left ventricular indices with the incidence of congestive heart failure (CHF)

Left ventricular indices	Events	Subjects	Incidence rate*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
LVEF (per 10%)						
All (CRIC+CKD-JAC)	292	4222	18.3	**0.62 (0.56–0.69)**	**0.61 (0.55–0.68)**	**0.61 (0.55–0.68)**
CRIC	245	3125	19.5	**0.61 (0.55–0.69)**	**0.60 (0.53–0.67)**	**0.60 (0.53–0.68)**
CKD-JAC	47	1097	13.8	**0.66 (0.51–0.84)**	**0.66 (0.51–0.85)**	**0.64 (0.49–0.84)**
P for interaction				0.55	0.6	0.75
LVMI (continuous, per 10 g/m$^{2.7}$)						
All (CRIC+CKD-JAC)	292	4222	18.3	**1.28 (1.21–1.34)**	**1.28 (1.21–1.36)**	**1.26 (1.19–1.33)**
CRIC	245	3125	19.5	**1.30 (1.23–1.37)**	**1.29 (1.22–1.37)**	**1.27 (1.20–1.35)**
CKD-JAC	47	1097	13.8	1.13 (0.95–1.35)	1.20 (0.99–1.46)	1.17 (0.95–1.44)
P for interaction				0.18	0.28	0.2
LVH						
All (CRIC+CKD-JAC)						
without LVH	49	1976	6.2	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	243	2246	30.1	**2.04 (1.46–2.85)**	**1.97 (1.39–2.80)**	**1.85 (1.30–2.63)**
CRIC						
without LVH	31	1275	5.5	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	214	1850	30.7	**2.21 (1.49–3.29)**	**2.05 (1.35–3.10)**	**1.94 (1.28–2.94)**
CKD-JAC						
without LVH	18	701	7.8	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	29	396	26.3	1.71 (0.90–3.24)	**2.01 (1.01–4.00)**	1.94 (0.95–3.96)
P for interaction				0.68	0.69	0.64
Geometry						
All (CRIC+CKD-JAC)						
Normal	20	790	6.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	29	1186	5.9	0.75 (0.42–1.33)	0.75 (0.42–1.34)	0.71 (0.40–1.27)
Eccentric LVH	51	379	39.9	**1.78 (1.08–2.93)**	**1.76 (1.06–2.94)**	1.58 (0.94–2.66)
Concentric LVH	192	1867	28.3	**1.72 (1.09–2.73)**	**1.66 (1.03–2.67)**	1.51 (0.94–2.43)
CRIC						
Normal	10	340	6.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	21	935	5.1	0.76 (0.37–1.58)	0.78 (0.38–1.62)	0.74 (0.35–1.54)
Eccentric LVH	37	236	42.1	**1.94 (1.01–3.73)**	1.88 (0.97–3.67)	1.66 (0.85–3.26)
Concentric LVH	177	1614	29.1	**1.84 (1.01–3.36)**	1.72 (0.93–3.19)	1.58 (0.85–2.92)
CKD-JAC						
Normal	10	450	6.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	8	251	9.9	0.65 (0.22–1.88)	0.72 (0.24–2.13)	0.74 (0.25–2.20)
Eccentric LVH	14	143	35.1	1.47 (0.63–3.43)	1.69 (0.69–4.16)	1.63 (0.65–4.11)
Concentric LVH	15	253	21.3	1.49 (0.68–3.27)	1.88 (0.79–4.46)	1.86 (0.76–4.54)
P for interaction				0.94	0.94	>0.99

Multivariable models adjusted for **Model 1**: age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, CRP, CRIC (vs. CKD-JAC), and EF (or LVMI); **Model 2**: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin; **Model 3**: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D). CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; PTH, parathyroid hormone; FGF, fibroblast growth factor.

*Number of events per 1000 person-years

Emboldened values were statistically significant ($P < 0.05$).

Supplementary Table S8. Association of left ventricular indices with the incidence of all-cause death

Left ventricular indices	Events	Subjects	Incidence rate*	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
LVEF (per 10%)						
All (CRIC+CKD-JAC)	304	4222	18.2	**0.81 (0.73–0.91)**	**0.86 (0.77–0.97)**	**0.86 (0.77–0.97)**
CRIC	269	3125	20.3	**0.80 (0.71–0.91)**	**0.86 (0.76–0.98)**	**0.87 (0.76–0.99)**
CKD-JAC	35	1097	10.2	0.86 (0.65–1.16)	0.88 (0.65–1.18)	0.86 (0.63–1.16)
P for interaction				0.94	0.95	0.93
LVMI (continuous, per 10 g/m$^{2.7}$)						
All (CRIC+CKD-JAC)	304	4222	18.2	**1.15 (1.08–1.22)**	**1.22 (1.14–1.29)**	**1.20 (1.13–1.28)**
CRIC	269	3125	20.3	**1.14 (1.08–1.21)**	**1.22 (1.14–1.30)**	**1.21 (1.13–1.29)**
CKD-JAC	35	1097	10.2	1.19 (0.97–1.46)	1.22 (0.97–1.52)	1.18 (0.93–1.50)
P for interaction				0.94	0.84	0.82
LVH						
All (CRIC+CKD-JAC)						
without LVH	77	1976	9.5	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	227	2246	26.5	**1.42 (1.07–1.89)**	**1.74 (1.29–2.34)**	**1.64 (1.21–2.21)**
CRIC						
without LVH	62	1275	10.7	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	207	1850	27.8	**1.31 (0.97–1.78)**	**1.63 (1.18–2.26)**	**1.53 (1.10–2.12)**
CKD-JAC						
without LVH	15	701	6.5	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
with LVH	20	396	17.8	**2.11 (1.04–4.29)**	**2.29 (1.06–4.94)**	2.07 (0.94–4.56)
P for interaction				0.4	0.41	0.38
Geometry						
All (CRIC+CKD-JAC)						
Normal	24	790	7.8	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	53	1186	10.5	1.25 (0.77–2.05)	1.31 (0.80–2.15)	1.23 (0.75–2.01)
Eccentric LVH	40	379	29.1	1.56 (0.94–2.61)	**1.94 (1.15–3.28)**	**1.76 (1.04–2.99)**
Concentric LVH	187	1867	26	**1.68 (1.07–2.64)**	**2.12 (1.33–3.38)**	**1.91 (1.20–3.04)**
CRIC						
Normal	14	340	9	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	48	935	11.3	1.19 (0.67–2.11)	1.24 (0.70–2.20)	1.12 (0.63–2.00)
Eccentric LVH	29	236	30.1	1.29 (0.70–2.37)	1.63 (0.88–3.04)	1.42 (0.76–2.66)
Concentric LVH	178	1614	27.5	1.52 (0.90–2.59)	**1.96 (1.14–3.38)**	1.71 (0.99–2.95)
CKD-JAC						
Normal	10	450	6.6	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	5	251	6.2	1.12 (0.39–3.21)	1.24 (0.42–3.62)	1.22 (0.41–3.61)
Eccentric LVH	11	143	26.7	**2.68 (1.02–7.01)**	**2.86 (1.01–8.06)**	2.60 (0.90–7.51)
Concentric LVH	9	253	12.6	1.88 (0.72–4.88)	2.24 (0.83–6.03)	2.02 (0.74–5.54)
P for interaction				0.73	0.76	0.64

Multivariable models adjusted for **Model 1**: age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, CRP, CRIC (vs. CKD-JAC), and EF (or LVMI); **Model 2**: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin; **Model 3**: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D). CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; PTH, parathyroid hormone; FGF, fibroblast growth factor.

*Number of events per 1000 person-years

Emboldened values were statistically significant ($P < 0.05$).

Supplementary Table S9. Association of left ventricular indices with the incidence of kidney failure

Left ventricular measurements	Events	Subjects	Incidence rate*	Model 1	Model 2	Model 3
LVEF (per 10%)						
All (CRIC+CKD-JAC)	832	4222	49.8	0.92 (0.85–1.00)	0.95 (0.87–1.03)	0.94 (0.87–1.02)
CRIC	599	3125	45.2	**0.88 (0.80–0.97)**	**0.89 (0.81–0.99)**	**0.89 (0.80–0.98)**
CKD-JAC	233	1097	67.6	1.03 (0.90–1.19)	1.04 (0.90–1.20)	1.02 (0.88–1.19)
P for interaction				0.23	0.25	0.29
LVMI (continuous, per 10g/m$^{2.7}$)						
All (CRIC+CKD-JAC)	832	4222	49.8	**1.08 (1.04–1.12)**	**1.07 (1.03–1.12)**	**1.06 (1.01–1.10)**
CRIC	599	3125	45.2	**1.07 (1.02–1.11)**	**1.07 (1.02–1.12)**	**1.06 (1.01–1.11)**
CKD-JAC	233	1097	67.6	**1.12 (1.03–1.21)**	**1.09 (1.00–1.19)**	**1.09 (1.00–1.19)**
P for interaction				0.06	0.03	0.01
LVH						
All (CRIC+CKD-JAC)						
without LVH	264	1976	32.5	Reference	Reference	Reference
with LVH	568	2246	66.3	**1.23 (1.05–1.46)**	**1.24 (1.04–1.48)**	1.18 (0.99–1.41)
CRIC						
without LVH	148	1275	25.5	Reference	Reference	Reference
with LVH	451	1850	60.6	1.16 (0.94–1.43)	1.22 (0.98–1.52)	1.17 (0.93–1.46)
CKD-JAC						
without LVH	116	701	50	Reference	Reference	Reference
with LVH	117	396	103.9	**1.40 (1.07–1.84)**	1.24 (0.92–1.67)	1.24 (0.91–1.67)
P for interaction				0.07	0.07	0.04
Geometry						
All (CRIC+CKD-JAC)						
Normal	106	790	34.6	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	158	1186	31.2	1.13 (0.87–1.45)	1.15 (0.89–1.49)	1.12 (0.87–1.45)
Eccentric LVH	89	379	64.8	**1.31 (1.00–1.72)**	**1.39 (1.05–1.83)**	**1.33 (1.00–1.76)**
Concentric LVH	479	1867	66.6	**1.32 (1.05–1.67)**	**1.32 (1.04–1.68)**	1.24 (0.97–1.58)
CRIC						
Normal	35	340	22.5	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	113	935	26.6	1.05 (0.73–1.50)	1.05 (0.72–1.51)	1.02 (0.70–1.47)
Eccentric LVH	54	236	56.1	1.15 (0.78–1.69)	1.30 (0.88–1.93)	1.25 (0.84–1.85)
Concentric LVH	397	1614	61.3	1.20 (0.86–1.68)	1.23 (0.87–1.72)	1.14 (0.81–1.60)
CKD-JAC						
Normal	71	450	47	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Concentric remodeling	45	251	55.6	0.95 (0.64–1.41)	0.95 (0.63–1.42)	0.95 (0.63–1.44)
Eccentric LVH	35	143	84.9	1.40 (0.94–2.10)	1.20 (0.79–1.84)	1.28 (0.83–1.98)
Concentric LVH	82	253	114.8	**1.39 (1.00–1.95)**	1.28 (0.89–1.85)	1.21 (0.84–1.76)
P for interaction				0.38	0.44	0.27

Multivariable models adjusted for **Model 1**: age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, CRP, CRIC (vs. CKD-JAC), and EF (or LVMI); **Model 2**: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin; **Model 3**: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D). CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; PTH, parathyroid hormone; FGF, fibroblast growth factor.

*Number of events per 1000 person-years

Emboldened values were statistically significant ($P < 0.05$).

Supplementary Table S10. Association of left atrial dimension (LAD: /10 mm) with subsequent cardiovascular disease (CVD) events

	Model1	Model2	Model3
CVD event			
LAD (per 10 mm)	**1.17 (1.01–1.35)**	**1.21 (1.05–1.40)**	**1.22 (1.06–1.42)**
LVMI (per 10g/$m^{2.7}$)	**1.18 (1.13–1.23)**	**1.19 (1.14–1.25)**	**1.18 (1.12–1.23)**
LVEF (per 10%)	**0.73 (0.67–0.79)**	**0.74 (0.68–0.80)**	**0.73 (0.67–0.80)**
ASCVD			
LAD (per 10 mm)	0.95 (0.75–1.19)	0.97 (0.77–1.22)	0.97 (0.77–1.22)
LVMI (per 10g/$m^{2.7}$)	1.06 (0.98–1.14)	1.06 (0.98–1.15)	1.07 (0.99–1.16)
LVEF (per 10%)	0.89 (0.77–1.02)	0.89 (0.77–1.03)	0.89 (0.77–1.02)
CHF			
LAD (per 10 mm)	**1.44 (1.19–1.74)**	**1.47 (1.21–1.78)**	**1.48 (1.22–1.80)**
LVMI (per 10g/$m^{2.7}$)	**1.24 (1.18–1.31)**	**1.25 (1.18–1.32)**	**1.23 (1.16–1.30)**
LVEF (per 10%)	**0.64 (0.58–0.71)**	**0.63 (0.57–0.71)**	**0.63 (0.57–0.71)**
All-cause death			
LAD (per 10 mm)	1.10 (0.91–1.33)	**1.22 (1.00–1.48)**	**1.26 (1.03–1.53)**
LVMI (per 10g/$m^{2.7}$)	**1.14 (1.08–1.22)**	**1.20 (1.13–1.28)**	**1.19 (1.11–1.27)**
LVEF (per 10%)	**0.83 (0.74–0.93)**	**0.89 (0.79–1.00)**	**0.89 (0.79–1.00)**
Kidney failure			
LAD (per 10 mm)	1.02 (0.90–1.15)	1.00 (0.88–1.14)	1.00 (0.88–1.14)
LVMI (per 10g/$m^{2.7}$)	**1.07 (1.02–1.11)**	**1.06 (1.02–1.11)**	**1.05 (1.00–1.10)**
LVEF (per 10%)	0.93 (0.86–1.01)	0.95 (0.87–1.03)	0.94 (0.87–1.03)

Emboldened values were statistically significant ($P < 0.05$)
Model 1: CRIC (vs. CKD-JAC), age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, CRP
Model 2: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin
Model 3: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D).
CVD, cardiovascular disease;

Supplementary Table S11. Subgroup analyses of the association between region and outcomes (no cardiovascular disease [CVD] history and estimated glomerular filtration rate [eGFR] 20–60 mL/min/173 m^2)

Event and subgroup	Model1	Model2	Model3
CVD event			
All (N=4222)	1.61 (1.22–2.12)	1.79 (1.34–2.38)	1.88 (1.38–2.56)
No CVD history (N = 2851)	2.09 (1.28–3.41)	2.34 (1.41–3.91)	2.32 (1.32–4.09)
eGFR 20-60 (N = 3142)	1.66 (1.18–2.34)	1.87 (1.31–2.67)	1.85 (1.27–2.69)
ASCVD			
All (N=4222)	2.75 (1.73–4.39)	3.01 (1.87–4.86)	3.23 (1.92–5.43)
No CVD history (N = 2851)	2.87 (1.35–6.12)	3.08 (1.42–6.67)	3.53 (1.49–8.36)
eGFR 20-60 (N = 3142)	2.62 (1.53–4.49)	2.85 (1.64–4.95)	3.02 (1.67–5.48)
CHF			
All (N=4222)	1.31 (0.91–1.88)	1.44 (0.99–2.11)	1.70 (1.13–2.58)
No CVD history (N = 2851)	1.62 (0.80–3.26)	1.80 (0.85–3.81)	2.02 (0.87–4.65)
eGFR 20-60 (N = 3142)	1.53 (0.95–2.47)	1.68 (1.01–2.78)	1.77 (1.04–3.01)
Death			
All (N=4222)	1.77 (1.18–2.67)	2.27 (1.49–3.47)	2.38 (1.51–3.75)
No CVD history (N = 2851)	2.05 (1.08–3.90)	2.65 (1.36–5.16)	2.11 (1.02–4.36)
eGFR 20-60 (N = 3142)	1.60 (1.00–2.55)	2.19 (1.34–3.58)	2.35 (1.39–3.98)
Kidney failure			
All (N=4222)	2.38 (1.96–2.90)	2.53 (2.06–3.11)	2.35 (1.86–2.96)
No CVD history (N = 2851)	2.52 (1.92–3.31)	2.90 (2.17–3.88)	2.51 (1.82–3.46)
eGFR 20-60 (N = 3142)	3.07 (2.26–4.17)	3.26 (2.37–4.49)	3.08 (2.20–4.32)

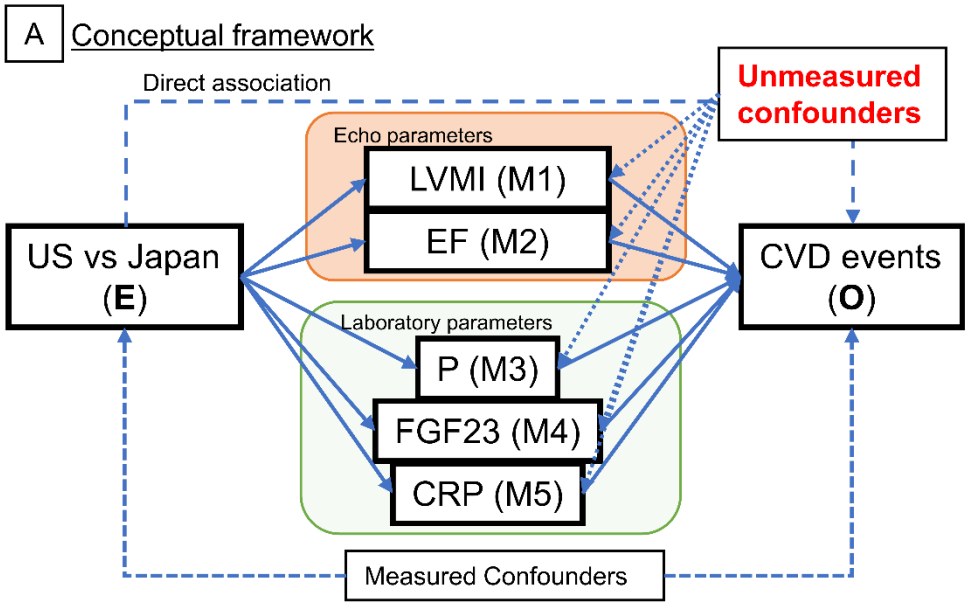
Multivariable models adjusted for **Model 1**: age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, CRP, CRIC (vs. CKD-JAC), and EF (or LVMI); **Model 2**: model 1 + systolic blood pressure, obesity category, number of classes of antihypertensive agents, and hemoglobin; **Model 3**: model 2 + corrected calcium, phosphate, ln(total PTH), ln(intact FGF23), active vitamin D supplementation, and ln(25(OH) vitamin D). CVD, cardiovascular disease; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; UACR, urinary albumin-creatinine ratio; PTH, parathyroid hormone; FGF, fibroblast growth factor.

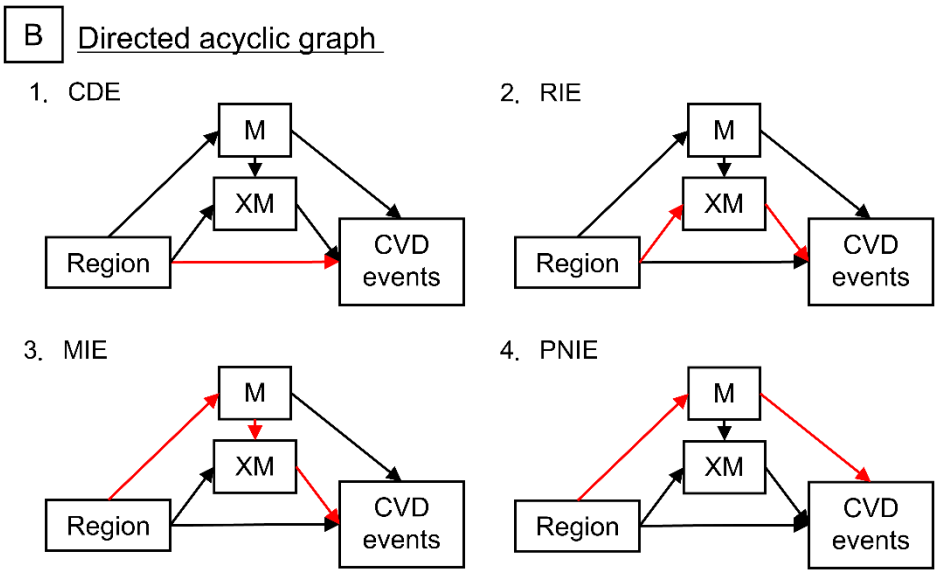
Supplementary Table S12. Proportion mediated of parameters associated with outcomes using mediation analysis

Outcome	(%)	LVMI	EF	LVMI+EF	P	iFGF23	CRP	P+FGF+CRP
		Proportion	Proportion	Proportion	Proportion	Proportion	Proportion	Proportion
CVD								
	CDE	71.2 (62.1-78.4)	66.5 (53.8-75.6)	53.8 (38.3-61.2)	93.4 (86.9-99.5)	86.4 (68.5-132)	93.9 (86.9-99.0)	73.1 (55.9-121)
	RI	2.77 (-1.28-7.70)	-10.6 (-16.5--3.70)	-6.21 (-13.2-0.00)	-4.44 (-9.02--0.70)	1.44 (-4.08-34.7)	-3.30 (-7.36--0.30)	-6.15 (-14.2-24.3)
	MI	16.0 (7.35-23.2)	31.7 (21.2-44.0)	33.3 (19.7-45.2)	11.4 (1.07-20.3)	3.01 (-60.9-15.3)	7.55 (-1.05-15.2)	22.7 (-42.6-38.7)
	PNIE	10.1 (4.44-18.8)	12.5 (3.45-25.2)	19.1 (8.47-38.6)	-0.36 (-8.20-9.00)	9.16 (-4.51-24.5)	1.85 (-3.10-7.10)	10.3 (-7.27-35.7)
	OPM	26.0 (20.9-32.5)	44.1 (32.3-57.8)	52.4 (44.1-66.0)	11.1 (5.45-16.6)	12.2 (-53.8-25.3)	9.40 (3.22-17.2)	33.1 (-32.3-44.6)
ASCVD								
	CDE	91.1 (80.3-99.9)	90.2 (77.4-99.7)	86.3 (72.0-97.7)	108 (98.4-133)	93.7 (68.8-150)	99.4 (90.8-112)	102 (71.2-177)
	RI	-0.39 (-5.61-1.70)	-10.4 (-21.2-1.40)	-9.93 (-26.6-1.90)	-1.10 (-21.3-13.4)	0.16 (-5.06-92.8)	-5.38 (-16.7-3.30)	-6.86 (-33.8-93.8)
	MI	5.05 (-7.89-16.2)	21.4 (-0.73-42.4)	21.8 (-1.16-44.0)	-0.062 (-23.1-19.5)	5.85 (-133-25.3)	9.07 (-5.66-23.8)	13.9 (-148.0-46.4)
	PNIE	4.28 (-2.78-18.0)	-1.17 (-12.0-8.70)	1.85 (-11.9-15.8)	-7.04 (-22.5-6.80)	0.30 (-25.3-27.1)	-3.14 (-14.7-5.40)	-8.90 (-49.9-32.2)
	OPM	9.33 (0.79-19.9)	20.2 (2.02-38.9)	23.7 (8.62-44.2)	-7.10 (-23.5-3.8)	6.16 (-141.3-27.3)	5.93 (-7.24-17.3)	5.10 (-160.0-29.7)
CHF								
	CDE	58.6 (46.1-67.4)	49.5 (37.3-61.9)	34.5 (18.6-43.5)	95.6 (89.7-104)	79.3 (66.8-127)	93.8 (84.3-101)	69.3 (51.6-117)
	RI	8.22 (1.65-15.3)	-9.63 (-15.1--1.70)	-0.49 (-8.52-7.10)	-4.25 (-10.0-0.70)	3.02 (-7.46-34.1)	-3.51 (-8.33-2.60)	-4.75 (-18.1-24.6)
	MI	23.2 (10.5-32.9)	38.3 (19.8-50.5)	40.9 (25.6-57.4)	11.0 (-4.45-21.8)	5.13 (-61.4-19.0)	8.06 (-4.27-18.9)	24.2 (-50.4-41.5)
	PNIE	10.0 (1.91-21.9)	21.9 (5.65-38.9)	25.1 (9.34-51.7)	-2.36 (-10.7-11.4)	12.55 (-6.05-41.1)	1.66 (-4.91-8.10)	11.2 (-9.11-41.9)
	OPM	33.2 (27.1-42.8)	60.2 (45.8-71.6)	66.0 (57.0-80.5)	8.61 (1.12-14.2)	17.7 (-48.0-29.9)	9.73 (-3.21-20.6)	35.4 (-40.6-47.7)
Death								
	CDE	77.1 (67.8-86.1)	79.8 (67.0-89.2)	69.8 (56.1-80.9)	95.9 (85.1-123)	107.2 (67.6-180)	86.0 (76.0-92.0)	83.0 (52.4-142)
	RI	-1.61 (-6.03-3.00)	-10.7 (-17.1--4.40)	-8.38 (-20.1-0.20)	-11.3 (-43.5--2.00)	6.14 (-9.80-37.6)	-5.10 (-10.0--1.40)	-12.2 (-44.7-34.4)
	MI	14.9 (4.50-23.0)	23.6 (9.47-40.6)	25.6 (6.41-42.9)	22.0 (3.79-58.2)	-26.3 (-133-12.9)	13.7 (2.66-26.4)	19.6 (-64.6-56.1)
	PNIE	9.58 (2.17-21.2)	7.34 (-4.15-19.8)	13.0 (0.45-32.4)	-6.60 (-31.4-8.10)	12.9 (-4.57-57.9)	5.39 (-0.08-14.00)	9.54 (-19.7-53.7)
	OPM	24.5 (17.3-33.8)	31.0 (16.5-43.7)	38.6 (25.0-52.9)	15.5 (7.51-25.4)	-13.4 (-106-28.2)	19.1 (11.8-30.2)	29.1 (-39.9-55.1)
Kidney failure								
	CDE	94.8 (85.2-105)	92.4 (83.2-102)	91.2 (79.6-105)	93.2 (83.6-103)	106.4 (85.9-132)	102 (97.9-106)	98.2 (73.2-123)
	RI	-1.52 (-8.18-1.60)	-9.89 (-18.6-0.60)	-12.8 (-20.7--0.30)	-3.50 (-7.90-0.00)	-11.3 (-27.5-1.50)	3.64 (-0.52-14.0)	-10.3 (-25.4-6.50)
	MI	-1.59 (-16.4-6.50)	18.2 (-1.62-31.8)	16.8 (-9.90-30.4)	-13.8 (-32.1-1.10)	-29.5 (-116-11.0)	-6.30 (-20.4-1.10)	-61.8 (-140--6.20)
	PNIE	8.35 (2.20-20.3)	-0.72 (-6.86-3.90)	4.77 (-2.43-19.4)	24.2 (8.21-44.8)	34.4 (-6.62-117)	0.69 (-3.04-5.10)	73.8 (18.6-155)
	OPM	6.76 (0.16-14.4)	17.5 (0.63-30.4)	21.6 (4.54-34.8)	10.3 (-0.47-18.6)	4.87 (-15.3-20.7)	-5.61 (-19.5-2.1)	12.0 (-12.9-32.0)

Proportion mediated for each parameter was calculated using causal mediation analysis based on counterfactual approach. We adjusted for the same covariates in Figure 6. Overall proportion mediated represents the mediation effects of interest, which can be calculated as (MI+PNIE)/(CDE+RI+MI+PNIE). LVMI, left ventricular mass index; EF, ejection fraction; CKD-JAC, chronic kidney disease Japan cohort; CRIC, chronic renal insufficiency cohort; CVD, cardiovascular disease; CHF, congestive heart failure. CRE, controlled direct effect; RI, reference interaction; MI, mediated interaction; PNIE, pure natural indirect effect; OPM, overall proportion mediated.

Supplementary Figure S1. Causal diagram

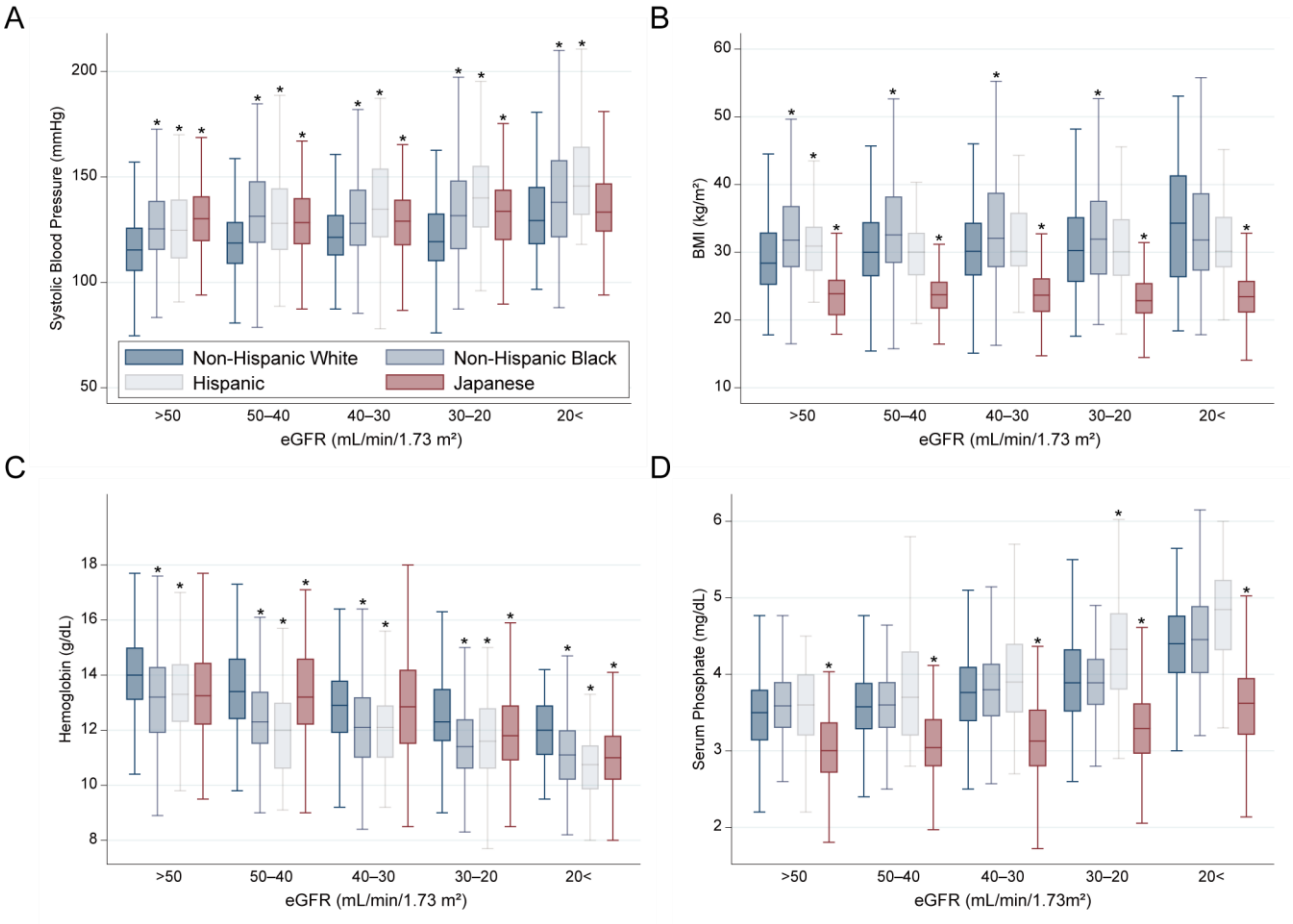




Effects (%)	Mediators	
	LVMI	EF
CDE	71.2 (62.1-78.4)	66.5 (53.8-75.6)
RIE	2.77 (-1.28-7.70)	-10.6 (-16.5--3.70)
MIE	16.0 (7.35-23.2)	31.7 (21.2-44.0)
PNIE	10.1 (4.44-18.8)	12.5 (3.45-25.2)

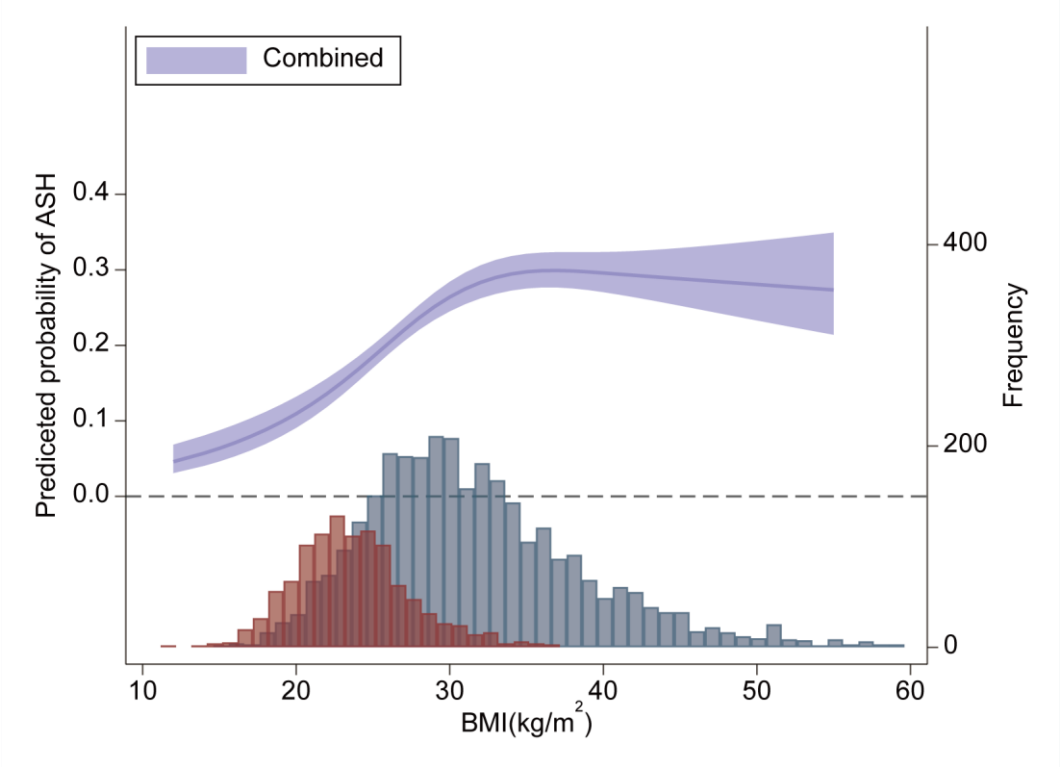
A. Conceptual framework. Associations between exposure (US vs. Japan), outcome (CVD events), and mediators. Measured confounders include age, sex, baseline smoking status, eGFR, ln(UACR), diabetes mellitus, history of any CVD, systolic blood pressure, obesity category, number of classes of antihypertensive agents, hemoglobin corrected calcium, ln(total PTH), active vitamin D supplementation, and ln(25(OH) vitamin D) **B. Directed acyclic graph.** M represents mediators and XM represents interaction between region and mediators. CDE, controlled direct effects; RIE, reference interaction effects; MIE, mediated interaction effects; PNIE, pure natural indirect effects.

Supplementary Figure S2. Distribution of factors associated with increased left ventricular mass index (LVMI) compared among ethnic groups across levels of estimated glomerular filtration rate (eGFR)



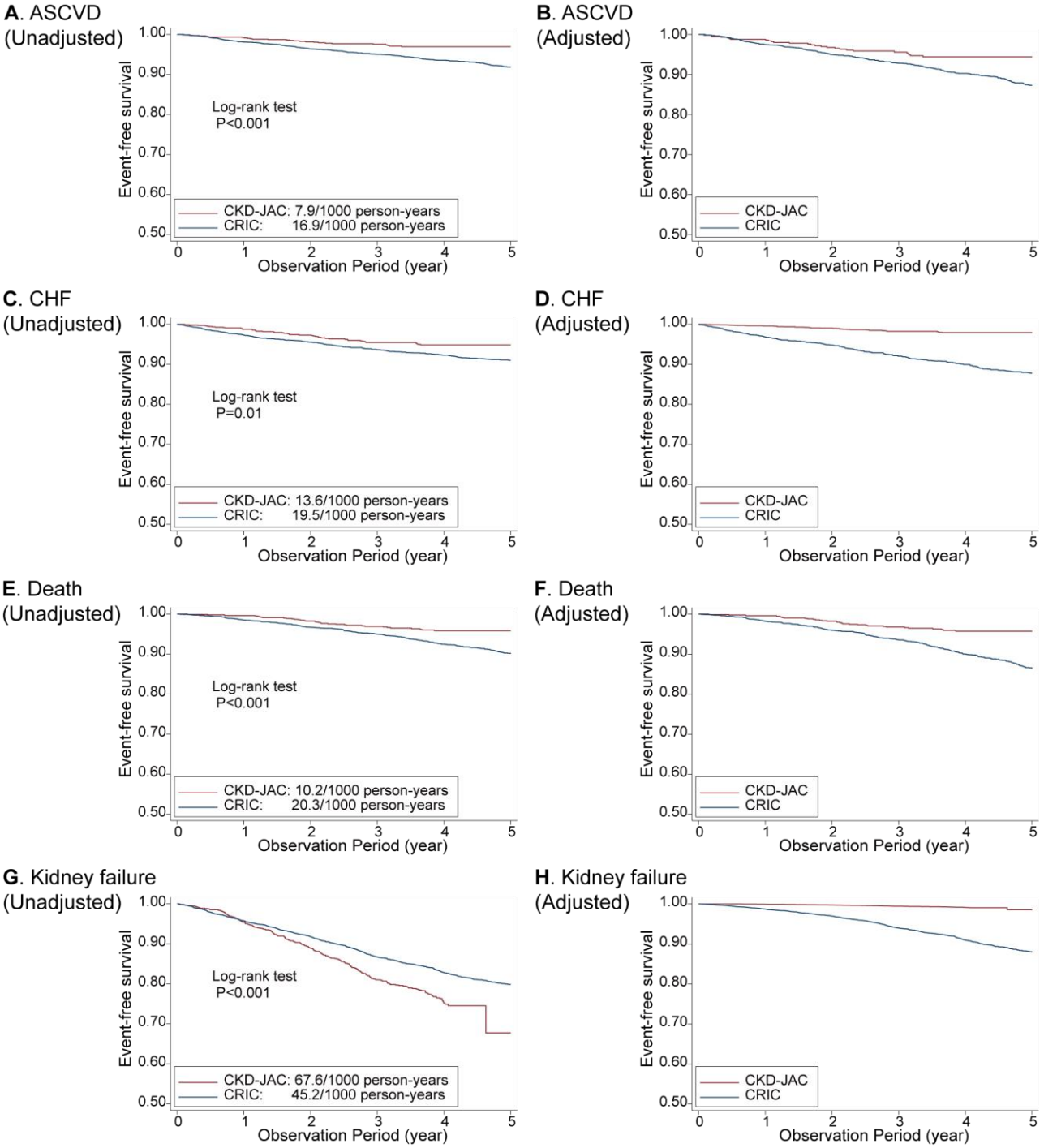
A. Systolic blood pressure. **B.** Body mass index. **C.** Hemoglobin. **D.** Serum phosphate in the CRIC and CKD-JAC studies. Comparisons among ethnic groups were performed with the Dunnett test using non-Hispanic White as a reference (*P <0.05). LVMI, left ventricular mass index; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Supplementary Figure S3. Association between BMI and asymmetric septal hypertrophy



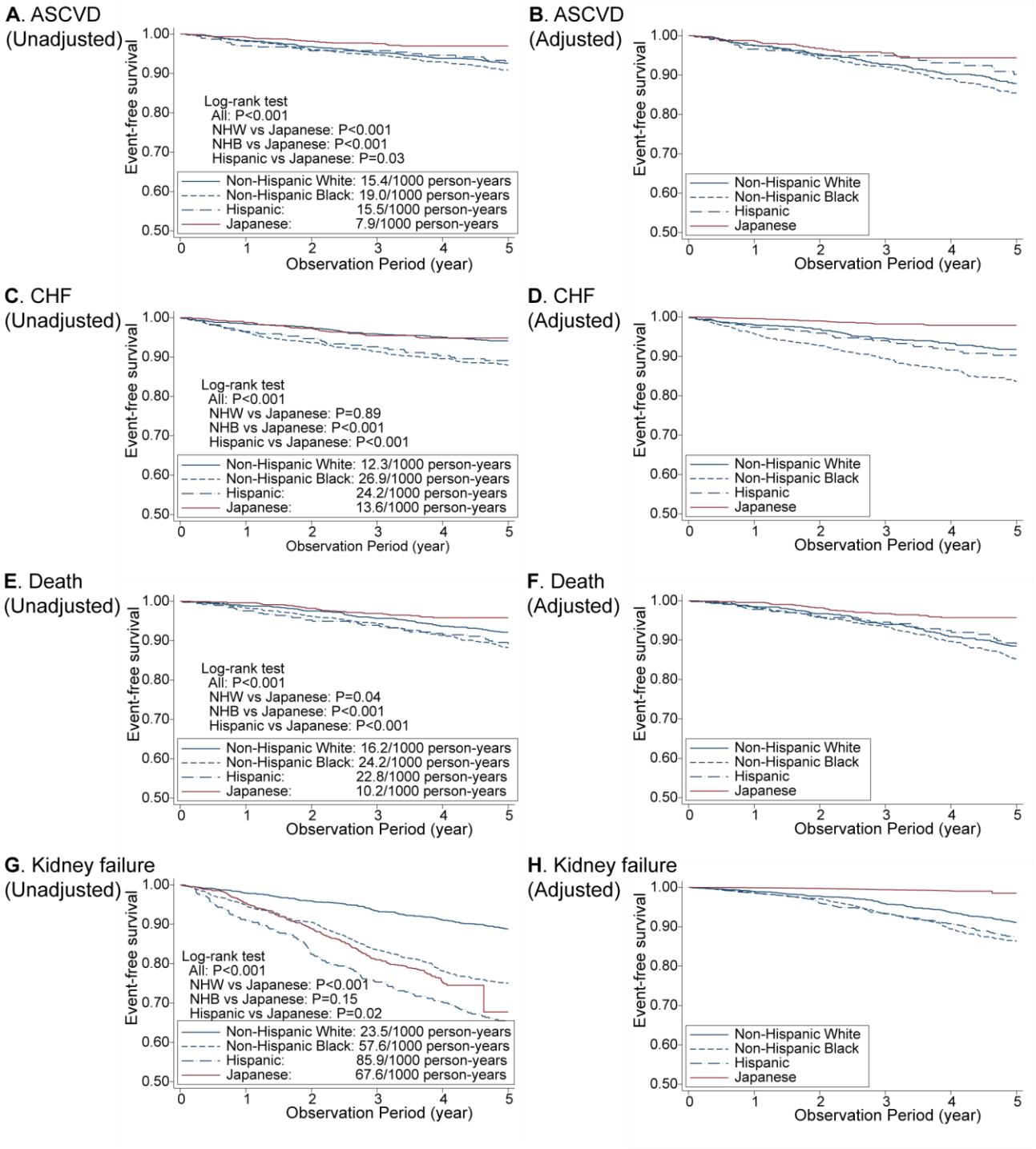
Restricted cubic spline analysis to examine the predicted probability of ASH across levels of BMI in the combined cohort. ASH was defined as a septal-to-posterior wall thickness ratio ≥1.3. BMI, body mass index; ASH, asymmetric septal hypertrophy

Supplementary Figure S4. Unadjusted and adjusted event-free survival of adverse events (Chronic Renal Insufficiency Cohort [CRIC] vs. Chronic Kidney Disease Japan Cohort [CKD-JAC])



Unadjusted and adjusted event-free survival for ASCVD event (**A, B**), CHF (**C, D**), all-cause death (**E, F**), and kidney failure (**G, H**). A multivariable adjustment was made for age, sex, DM, eGFR, and log-transformed UACR. CRIC, chronic renal insufficiency cohort; CKD-JAC, chronic kidney disease Japan cohort; CVD, cardiovascular disease. ASCVD, atherosclerotic cardiovascular disease; UACR, urinary albumin-creatinine ratio.

Supplementary Figure S5. Unadjusted and adjusted event-free survival of adverse events (4 different race-ethnic groups)



Unadjusted and adjusted event-free survival for ASCVD event (**A, B**), CHF (**C, D**), all-cause death (**E, F**), and kidney failure (**G, H**). A multivariable adjustment was made for age, sex, DM, eGFR, and log-transformed UACR. CVD, cardiovascular disease. ASCVD, atherosclerotic cardiovascular disease; NHW, non-Hispanic White; NHB, non-Hispanic Black; UACR, urinary albumin-creatinine ratio.