ORIGINAL RESEARCH

Electrocardiographic Strain Pattern Is Associated With Left Ventricular Concentric Remodeling, Scar, and Mortality Over 10 Years: The Multi-Ethnic Study of Atherosclerosis

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***Background*—**Both ECG strain pattern and QRS measured left ventricular (LV) hypertrophy criteria are associated with LV hypertrophy and have been used for risk stratification. However, the independent predictive value of ECG strain in apparently healthy individuals in predicting mortality and adverse cardiovascular events is unclear.

***Methods and Results*—**MESA (Multi-Ethnic Study of Atherosclerosis) is a multicenter, prospective cohort of 6441 participants (mean age, 62 years; 54% women). In 2847 of these participants, cardiac magnetic resonance imaging was repeated ≈10 years later (Year-10). At Year-10, 1759 participants underwent cardiac magnetic resonance imaging with gadolinium to detect myocardial scar. During a median follow-up of 11.7 years, ECG strain (n=168, 2.6%) was significantly associated with all-cause death (adjusted hazard ratio, 1.33; 95% confidence interval, 1.01–1.77; P=0.045), heart failure (2.62; 1.73–3.97; P<0.001), myocardial infarction (1.86; 1.09–3.18; P=0.024), and incident cardiovascular disease (1.45; 1.06–2.00; P=0.022). ECG strain was also associated with an increase in LV mass (β=9.29 g; P<0.001) and LV mass-to-volume ratio (β=0.07 g/mL; P=0.007) and a decline in LV ejection fraction (β=−3.30%; P<0.001). Moreover, ECG strain either at baseline and Year-10 was associated with LV scar (odds ratio, 4.93 and 5.22; P=0.002 and <0.001, respectively), whereas these associations were not observed in ECG LV hypertrophy.

***Conclusions*—**ECG strain is independently associated with all-cause mortality, adverse cardiovascular events, development of LV concentric remodeling and systolic dysfunction, and myocardial scar over 10 years in multiethnic participants without past cardiovascular disease. ECG strain may be an early marker of LV structural remodeling that contributes to development of adverse cardiovascular events.

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Key Words: cardiovascular magnetic resonance imaging • cardiovascular outcomes • ECG • remodeling • repolarization

The strain pattern in the 12-lead ECG, defined as ST-segment depression and T-wave inversion, represents ventricular repolarization abnormalities.[1] The mechanism underlying ECG strain is unclear, although it has been proposed as subendocardial ischemia.[2,3] ECG strain is associated with concentric left ventricular (LV) hypertrophy (LVH), rather than eccentric LVH, in individuals with hypertension[4] and aortic valve disease.[5] However, there is conflicting evidence regarding the association of ECG strain with LV function.[3,4,6] Moreover, the association of ECG strain

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Accompanying Data S1, Tables S1, S2, and Figure S1 are available at http://jaha.ahajournals.org/content/6/9/e006624/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- This multiethnic study of adults without past cardiovascular disease showed that ECG strain is associated with a higher risk for all-cause death, incident heart failure, myocardial infarction, and incident cardiovascular disease independent of ECG left ventricular (LV) hypertrophy measured by QRS.
- ECG strain is associated with development of LV concentric remodeling, decline in LV systolic function, and LV myocardial scar after 10 years of follow-up, although these associations were not observed in ECG LV hypertrophy.

What Are the Clinical Implications?

- Individuals with ECG strain may be treated aggressively for modifiable risk factors of LV hypertrophy regardless of the presence of ECG LV hypertrophy.
- Additional studies are needed to validate the present findings and examine whether aggressive treatment of modifiable risk factors in individuals with ECG strain leads to improved cardiovascular outcomes.

with temporal changes of LV structure and function has not been investigated.

ECG strain predicts heart failure (HF)[7] and death[8] in individuals with hypertension, likely reflecting the fact that LVH is a strong predictor of HF.[9,10] ECG-LVH criteria, determined by QRS voltage and duration, have also been used for risk stratification[11]; However, it remains unclear whether ECG strain has an additional prognostic value beyond ECG-LVH among individuals without a history of cardiovascular disease (CVD).

In this study, we examined the value of ECG strain in predicting adverse cardiovascular events compared to those of ECG-LVH in a multiethnic cohort without past CVD. We also aimed to establish the longitudinal association of ECG strain with parameters of LV structure and function using cardiac magnetic resonance imaging (CMR). Finally, we examined whether ECG strain is associated with LV myocardial scar detected by CMR late gadolinium enhancement (LGE) as a marker of subendocardial ischemia.

Methods

Study Design and Participants

The MESA (Multi-Ethnic Study of Atherosclerosis) is a multicenter, prospective cohort study to investigate the prevalence, correlation, and progression of subclinical CVD. Inclusion criteria and methods of the MESA were previously described.[12] In July 2000 to July 2002 (Year-0; first MESA field center examination), 6814 men and women aged 45 to

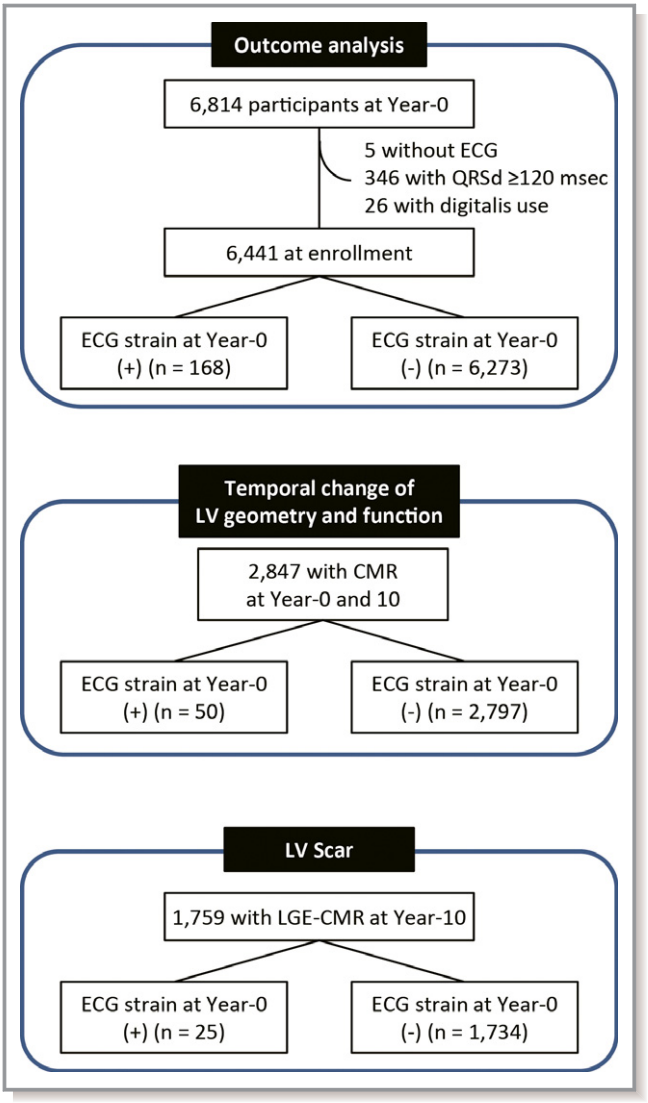

Figure 1. Participant enrollment. CMR indicates cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; LV, left ventricular; QRSd, QRS duration.

84 years who were free of clinical CVD were enrolled at 6 US field centers: Johns Hopkins University, Baltimore, Maryland; Wake Forest University, Winston-Salem, North Carolina; the University of Minnesota, Minnesota; Northwestern University, Illinois; and the University of California, Los Angeles, California. All participants underwent an extensive evaluation that consisted of clinical questionnaires and physical examinations. Participants with QRS duration ≥120 ms (n=346)[13] and digitalis use (n=26) were excluded, leaving 6441 subjects included in the current study; ECG strain (+) (n=168) and strain (−) (n=6273; Figure 1). Of 4735 individuals who underwent CMR at baseline, 2847 participants (60%) agreed to undergo a follow-up CMR at Year-10, the fifth follow-up examination between 2010 and 2012. We compared temporal changes of LV structure and function in 2847 participants with CMR between Year-0 and Year-10. Of the 2847

participants, 1759 (61.9%) consented to, and were eligible for, contrast-enhanced CMR with LGE to assess LV scar at Year-10. When assessing ECG strain at Year-10, we also excluded participants with QRS duration ≥120 ms (n=83) and digitalis use (n=2). Both Year-0 and Year-10 ECGs were used for assessing the association with LV scar defined by LGE-CMR at Year-10. The institutional review boards at each center approved the study protocol, and all participants gave written informed consent.

Outcomes

Full details of event ascertainment and definition are available in MESA's Manual of Procedures.[14] Clinical outcomes were assessed at MESA study examinations and by telephone interview every 9 to 12 months. Records were obtained for ≈99% of hospitalizations and 97% of outpatient cardiovascular diagnostic encounters through the end of calendar year 2014. Two physicians from the MESA study events committee who were blinded to the ECG and CMR results independently reviewed all the medical records for end point classification using prespecified criteria for all-cause death, HF, myocardial infarction (MI), angina, and stroke. An incident CVD event was defined as a composite of adjudicated MI, resuscitated cardiac arrest, coronary heart disease (CHD)-related death, stroke, or stroke-related death. CHD was defined as MI, angina, percutaneous coronary intervention, or bypass surgery.

Electrocardiography

ECGs were recorded digitally at 10 mm/mV calibration and a speed of 25 mm/s using MAC 1200 ECG machines (Marquette Electronics, Milwaukee, WI) in all clinical centers. The ECGs were transmitted to the ECG Reading Center. All ECGs were initially checked visually for quality, and ECG interpretation was performed automatically with the GE Marquette 12-SL program 2001 version (GE Marquette, Milwaukee, WI). Finally, trained staff manually confirmed computer-detected ECG abnormalities. The ECG strain was defined as coexistence, in any of leads I, II, aVL, or V3 to V6: ST-segment horizontal or downward sloping depression ≥0.05 mV, plus negative T-wave (Minnesota code 4-1 or 4-2 and 5-1 or 5-2).[15,16] The product of QRS duration times the Cornell voltage combination (R in lead aVL+S in lead V3, with 0.6 mV added in women)[17] >2400 mm×ms or Sokolow–Lyon voltage (S in lead V1+R in lead V5 or V6)[18] >38 mm was calculated to identify ECG-LVH.[7]

Cardiac Magnetic Resonance Imaging

The MESA CMR protocol, image analysis, and inter- and intrareader reproducibility have been reported elsewhere.[10,19,20] The identical CMR protocol was used to scan all the individuals both in Year-0 and Year-10. LV end-diastolic volume, end-systolic volume, and mass were indexed to the body surface area (end-diastolic volume index, end-systolic volume index, and mass index; Data S1). Concentric remodeling was defined using a parameter of mass-to-volume ratio (MVR) derived as ratio of LV mass to LV end-diastolic volume. Changes (Δ) in parameters of LV structure and function were quantified as a change from Year-0 to Year-10, and were calculated by subtracting the values at Year-0 from the corresponding values at Year-10. Calibration between the 2 CMR examinations was performed in participants who had both image sequences acquired at MESA follow-up examination as detailed in Data S1.

To identify LV scar, LGE images were acquired 15 minutes after an intravenous bolus injection of gadolinium contrast (0.15 mmol/kg, Magnevist; Bayer HealthCare Pharmaceuticals, Montville, NJ) in short-axis slices, 1 horizontal and 1 vertical long axis—all at the same positions as those of the cine images as previously described and are included in Data S1.[21]

Statistical Analysis

Baseline demographic characteristics and ECG and CMR parameters were compared using Student *t* tests, a Wilcoxon's rank-sum test, and chi-square tests between ECG strain (+) group and ECG strain (−) group, as appropriate. Participants were also divided into 4 groups defined by the presence or absence of both ECG strain and ECG-LVH. ANOVA was used to compare means across multiple groups. Kaplan–Meier cumulative incidence plots were generated to characterize risk over time, with 4 groups compared to the log-rank test and death treated as a competing event.

Uni- and multivariable Cox proportional hazards regression models were used to calculate hazard ratios (HRs) for all cardiac events and 95% confidence intervals (CIs). Covariates were assessed at the initial MESA exam, described in MESA's Manual of Procedures, and chosen a priori.[14] In adjusted models, we included demographics (age, ethnicity, and sex), traditional risk factors (body mass index, heart rate, systolic blood pressure, current smoking, diabetes mellitus, antihypertensive medication use, and estimated glomerular filtration rate), and N-terminal pro-B-type natriuretic peptide or ECG-LVH. We also examined the interaction of ECG strain with sex, age, ethnicity, and ECG-LVH in its association with outcome using multiplicative interaction terms as well as using stratified analyses by sex, age, ethnicity, and ECG-LVH.

We also investigated the longitudinal changes in LV structure and function derived from CMR parameters separately as dependent continuous variables in multivariable linear regression models. Results are presented as β-coefficients and standardized β-coefficients defined by

Table 1. Participant Characteristics

		ECG Strain at Year-0		
	Total	(−)	(+)	
	(n=6441)	(n=6273)	(n=168)	*P* Value
Demographic characteristics				
Age, y	61.9±10.2	61.7±10.2	68.0±8.8	<0.001
Sex women, n (%)	3468 (54)	3382 (54)	86 (51)	0.485
Ethnicity, n (%)				
White	2432 (38)	2386 (38)	46 (27)	0.005
Chinese	783 (12)	767 (12)	16 (10)	0.290
Black	1788 (28)	1716 (27)	72 (43)	<0.001
Hispanic	1438 (22)	1404 (22)	34 (20)	0.510
Heart rate, beats/min	63±10	63±10	63±10	0.507
Body mass index, kg/m^2	28.3±5.5	28.3±5.5	29.5±5.1	0.004
Systolic blood pressure, mm Hg	126±21	126±21	144±25	<0.001
Diastolic blood pressure, mm Hg	72±10	72±10	76±12	<0.001
Current smoker, n (%)	844 (13)	821 (13)	23 (14)	0.833
Diabetes mellitus, n (%)		755 (12)	40 (24)	<0.001
Total cholesterol, mg/dL	194±36	194±36	197±39	0.405
Estimated GFR, mL/min	82±17	81±18	75±20	0.004
NT-proBNP, pg/mL (n=5278)	52 (22, 102)	51 (23, 103)	138 (62, 359)	<0.001
ECG parameters				
PR interval, ms	165±25	165±25	169±30	0.038
QRS duration, ms	91±10	91±9	93±10	0.050
ECG-LVH*	398 (6)	341 (5)	57 (34)	<0.001
Pathological Q-waves, n (%)	123 (1.9)	117 (1.9)	6 (3.6)	0.111
Corrected QT interval, ms	418±21	417±20	427±25	<0.001
CMR measurements (n=4735)				
LV EDVi, mL/m^2	69±12	69±12	72±16	0.006
LV ESVi, mL/m^2	26±7	26±6	28±13	<0.001
LV Mi, g/m^2	64±12	64±11	77±16	<0.001
LV MVR, g/mL	0.95±0.18	0.94±0.18	1.09±0.22	<0.001
LV wall thickness, mm	9.3±1.8	9.2±1.8	10.9±2.2	<0.001
LV wall thickness ≥15 mm	36 (0.8)	31 (0.7)	5 (4.5)	<0.001
LV EF, %	62.5±6	63±6	62±10	0.2238

Values are mean±SD or n (%). CMR indicates cardiac magnetic resonance imaging; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; GFR, glomerular filtration rate; LV, left ventricular; LVH, left ventricular hypertrophy; Mi, mass index; MVR, mass-to-volume ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*ECG-LVH was defined by the product of QRS duration times Cornell voltage combination or Sokolow–Lyon voltage.

dividing the differences between the observed values and the means by the corresponding SDs. The following models were used in multivariable analyses: (1) Model 1 was adjusted for demographics and traditional risk factors; (2) model 2 was additionally adjusted for interim CHD. Furthermore, logistic regression analyses were performed to evaluate the association between ECG parameters (both Year-0 and Year-10) and LGE on CMR. Participants lost to follow-up were censored at the time of the last follow-up, and missing values were handled based on an a priori analytical plan, that is, only participants who had missing data on a variable needed for a particular model were excluded from that analysis. Data were

analyzed with Stata software (version 14.0; StataCorp LP, College Station, TX). A 2-sided $P<0.05$ was considered statistically significant.

Results

Participant Characteristics

Mean and median follow-up periods were 11.7 and 13.0 years, respectively. Of the 6441 participants, 168 (2.6%, women 51%) had ECG strain at Year-0 (Table 1). The ECG strain (+) group was older than the ECG strain (−) group, had fewer whites and a higher frequency of blacks, had larger body mass index, higher systolic and diastolic blood pressure, estimated glomerular filtration rate, and N-terminal pro-B-type natriuretic peptide, and more individuals with diabetes mellitus. The ECG strain (+) group also had longer PR and corrected QT interval and ECG-LVH. CMR measurements revealed more-severe LV remodeling in the ECG strain (+) group, as evidenced by higher LV end-diastolic volume index and end-systolic volume index, mass index, MVR, and wall thickness. However, there was no significant difference in LV ejection fraction (EF) between the 2 groups. To better understand the influence of ECG-LVH on ECG strain, we compared the baseline clinical characteristics of the 4 groups stratified by the presence or absence of both ECG strain and ECG-LVH (Table S1). Within both the ECG strain (+) and (−) stratum, the ECG-LVH (+) participants were significantly older, had fewer whites and a higher frequency of Chinese or blacks, had higher systolic and diastolic blood pressure, and N-terminal pro-B-type natriuretic peptide. Interestingly, the ECG-LVH (+) group had reduced EF as well as higher LV end-diastolic volume index and end-systolic volume index, mass index, MVR, and wall thickness.

ECG Strain and Adverse Cardiovascular Events

During the follow-up, there were 1045 all-cause deaths, 260 HF, 252 MI, 798 CVD events, and 532 CHD events (Table 2). ECG strain was significantly associated with all-cause death (adjusted HR, 1.33; 95% CI, 1.01–1.77; $P=0.045$), incident HF (HR, 2.78; 95% CI, 1.84–4.20; $P<0.001$), MI (HR, 1.86; 95% CI, 1.09–3.18; $P=0.024$), and CVD events (HR, 1.45; 95% CI, 1.06–2.00; $P=0.022$) independent of ECG-LVH. When we used the definition of ECG strain including only leads V5 and/or V6, not including lead I, II, or aVL (n=110), to exclude the potential of underlying subclinical coronary disease and myocardial ischemia, ECG strain was also significantly associated with HF, CVD, and MI ($P<0.05$ for all; Table S2). Kaplan–Meier analysis showed that ECG strain was associated with higher risk of all-cause mortality and HF within the both ECG-LVH (+) and (−) stratum (Figure 2A and 2B). Importantly, MI and CVD

Table 2. ECG Strain and Adverse Cardiovascular Events

	Unadjusted				Model 1*				Model 2			
	No. of Events/ No. at Risk	Hazard Ratio	95% CI	*P* Value	No. of Events/ No. at Risk	Hazard Ratio	95% CI	*P* Value	No. of Events/ No. at Risk	Hazard Ratio	95% CI	*P* Value
All-cause mortality	1045/6437	2.53	1.94 to 3.30	<0.001	862/5252	1.35	1.00 to 1.82	0.047	1039/6390	1.33	1.01 to 1.77	0.045
HF	260/6412	6.19	4.25 to 9.01	<0.001	260/6412	3.37	2.15 to 5.30	<0.001	260/6412	2.78	1.84 to 4.20	<0.001
CVD†	798/6414	2.68	1.98 to 3.62	<0.001	653/5235	1.71	1.22 to 2.39	0.002	793/6369	1.45	1.06 to 2.00	0.022
CHD	532/6414	2.54	1.74 to 3.69	<0.001	431/5235	1.72	1.13 to 2.61	0.011	531/6369	1.38	0.92 to 2.05	0.118
MI	252/6413	2.97	1.79 to 4.92	<0.001	205/5234	2.31	1.34 to 3.99	0.003	252/6368	1.86	1.09 to 3.18	0.024
Angina	302/6412	2.23	1.33 to 3.75	0.002	248/5233	1.89	1.08 to 3.30	0.026	302/6367	1.44	0.84 to 2.49	0.186
Stroke	243/6412	2.11	1.15 to 3.86	0.016	206/5233	1.12	0.57 to 2.21	0.747	240/6367	1.12	0.60 to 2.11	0.724

CHD indicates coronary heart disease; CI, confident interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
*Model 1 was adjusted for demographics (age, sex, and ethnicity), traditional risk factors (body mass index, heart rate, systolic blood pressure, smoking, diabetes mellitus, antihypertensive medication use, and eGFR), and N-terminal pro-B-type natriuretic peptide. Model 2 was adjusted for demographics, traditional risk factors, and ECG/left ventricular hypertrophy.
†CVD includes MI, resuscitated cardiac arrest, CHD death, stroke, and stroke death.

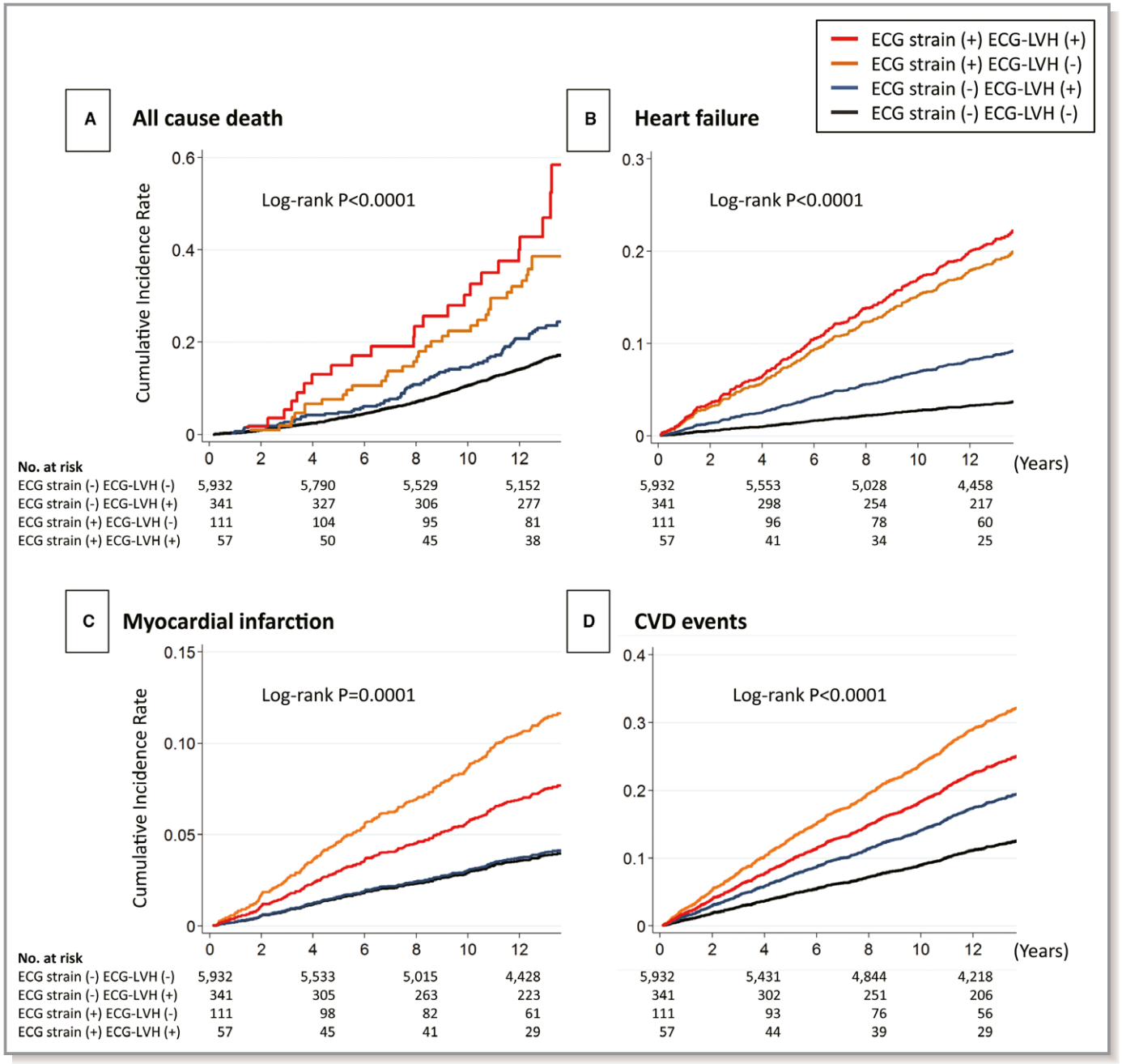

Figure 2. Kaplan–Meier cumulative incidence plots stratified by ECG strain and ECG-left ventricular hypertrophy (LVH). ECG-LVH was assessed by QRS voltage and duration. Note that the *y*-axis scales vary by outcome. A, All-cause death. B, Heart failure. C, Myocardial infarction. D, Composite cardiovascular disease (CVD).

event rate was highest in the ECG strain (+) without ECG-LVH group (Figure 2C and 2D).

When stratified by sex, age, ethnicity, and ECG-LVH, the association between ECG strain and adverse events was similar among the subgroups, with a few exceptions (Figure S1). For all-cause death, HF, and MI, the increased risk with ECG strain diminished with younger age<65, and for HF and CVD events, ECG strain was associated with increased risk only in participants without ECG-LVH. Subgroup analysis showed no significant interactions between ECG strain and subgroups (all *P*-values-for-interaction>0.05).

ECG Strain and Longitudinal Changes in LV Structure and Function

ECG strain was associated with increases in LV end-diastolic volume, end-systolic volume, mass, MVR (model 1, all $P<0.05$) and a decrease in LV EF ($P<0.001$) with highest standardized

Table 3. ECG Strain/LVH With Longitudinal Changes in LV Structure and Function

	Multivariate Linear Regression (n=2847)			
	Model 1‡		Model 2	
Variable	β (SE)	Standardized β	β (SE)	Standardized β
ECG strain				
LV EDV, mL	5.85 (2.95)	0.034†	6.39 (3.01)	0.037†
LV EDVi, mL/m^2	3.24 (1.29)	0.040†	3.58 (1.31)	0.043†
LV ESV, mL	7.13 (1.84)	0.069*	7.64 (1.87)	0.073*
LV ESVi, mL/m^2	3.13 (0.74)	0.069*	3.37 (0.76)	0.073*
LV mass, g	9.29 (2.47)	0.066*	8.77 (2.52)	0.061†
LV Mi, g/m^2	6.31 (1.34)	0.084*	6.13 (1.36)	0.080*
LV MVR, g/mL	0.07 (0.03)	0.046†	0.06 (0.03)	0.037*
LV EF, %	−3.30 (0.94)	−0.058*	−3.31 (0.96)	−0.057†
ECG-LVH				
LV EDV, mL	5.18 (1.86)	0.049†	5.07 (1.85)	0.048†
LV EDVi, mL/m^2	2.88 (0.81)	0.057*	2.82 (0.81)	0.056*
LV ESV, mL	2.64 (1.16)	0.042†	2.55 (1.15)	0.040†
LV ESVi, mL/m^2	1.33 (0.47)	0.047†	1.30 (0.47)	0.046†
LV mass, g	2.36 (1.55)	0.027	2.37 (1.55)	0.027
LV Mi, g/m^2	2.15 (0.84)	0.047†	2.16 (0.84)	0.047†
LV MVR, g/mL	−0.02 (0.02)	−0.021	−0.02 (0.02)	−0.020
LV EF, %	−1.11 (0.59)	−0.031	−1.09 (0.59)	−0.031

The β-coefficient represents the mean difference of the change in the parameters of LV structure and function derived from CMR from Year-0 to Year-10 in the ECG strain (+) group vs the ECG strain (−) group and the ECG-LVH (+) group vs the ECG-LVH (−) group after adjustment for the covariates. BMI indicates body mass index; BP, blood pressure; CHD, coronary heart disease; EDV, end-diastolic volume; EDVi, end-diastolic volume index; EF, ejection fraction; ESV, end-systolic volume; ESVi, end-systolic volume index; GFR, glomerular filtration rate; LV, left ventricular; LVH, left ventricular hypertrophy; Mi, mass index; MVR, mass-to-volume ratio.

*P<0.001.

†P<0.05.

‡Model 1 was adjusted for demographics (age, ethnicity, and sex), traditional HF risk factors (BMI, heart rate, systolic BP, smoking, diabetes mellitus, antihypertensive medication use, and estimated glomerular filtration rate), and each CMR parameter (LV EDVi, ESVi, Mi, MVR, and EF) at Year-0. Model 2 included interim CHD in addition to Model 1.

β-coefficients for LV Δmass index (standardized β-coefficient=0.084; Table 3). In contrast, ECG-LVH was associated with longitudinal increases in LV end-diastolic volume and end-systolic volume (all P<0.05), but was not associated with longitudinal changes in LV mass, MVR, and EF (P=0.13, 0.23 and 0.06, respectively). After additional adjustment for interim CHD events, the association between ECG strain and longitudinal changes in the parameters of LV structure and function remained significant.

ECG Strain and LV Scar Defined by LGE

LGE was identified in 137 (7.8%) of 1759 participants with gadolinium-enhanced CMR at Year-10. ECG strain at both Year-0 and Year-10 was significantly associated with an increased prevalence of LV scar (32.0 versus 7.4% at Year-0 and 25.9 versus 7.3% at Year-10; P<0.001 for both), whereas ECG-LVH was not (11.8 versus 7.6% at Year-0 and 11.9 versus 7.6% at Year-10; P=0.16 and P=0.15, respectively; Figure 3). The majority of LGE scar types were classified as nonischemic in all categories except ECG strain (+) group at Year-10. On the other hand, the extent of LV scar was not significantly different between ECG strain (+) and ECG strain (−) groups at both Year-0 and Year-10 (7.1±11.2 versus 6.0±7.4% of LV mass at Year-0 and 7.6±6.7 versus 5.7±7.2% at Year-10; P=0.73 and P=0.36, respectively).

In logistic regression analyses, ECG strain at Year-0 was significantly associated with LV scar at Year-10 (odds ratio, 5.81; P<0.001; Table 4). This association remained significant after adjustment for interim CHD (odds ratio, 5.33; P=0.001). In addition, cross-sectional analysis revealed that ECG strain at Year-10 was significantly associated with LV scar independent of interim CHD (odds ratio, 4.67; P<0.001). On the other hand, ECG-LVH at neither Year-0 nor Year-10 was associated with LV scar.

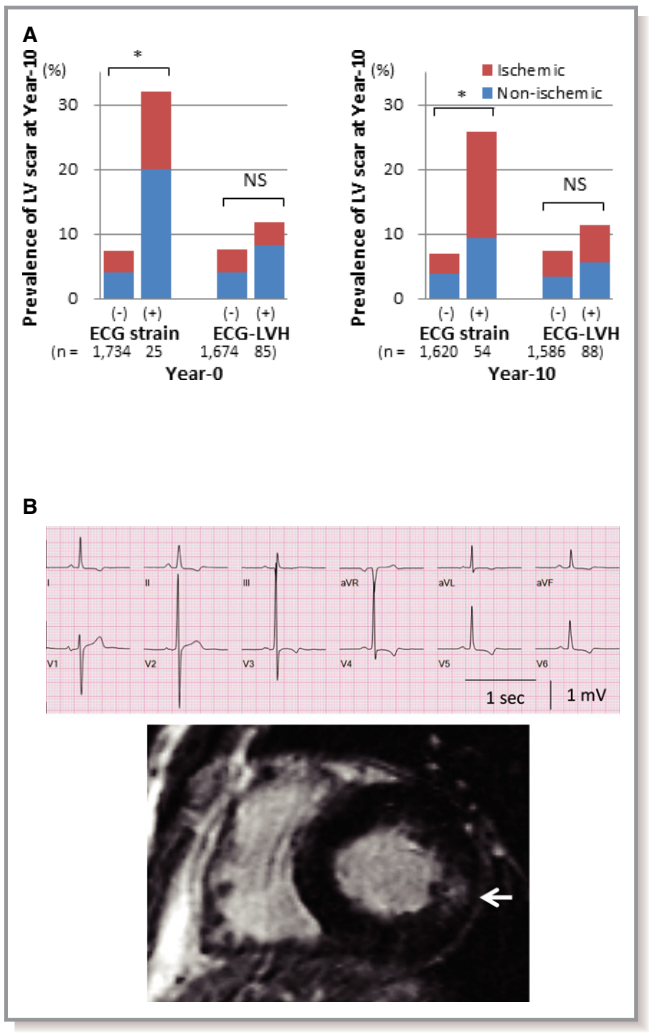

Figure 3. A, Frequency and subtype of left ventricular scar, by ECG strain and ECG-LVH at Year-0 (left) and at Year-10 (right). *P<0.001 between participants with and without ECG strain. B, ECG and corresponding late gadolinium enhancement (LGE) image. Late gadolinium enhancement image of a participant with the ECG strain and without ECG-LVH demonstrated evidence of focal myocardial scar in the lateral mid-myocardium (white arrow). LVH indicates left ventricular hypertrophy.

Discussion

Main Findings

We found that ECG strain is an independent predictor of all-cause death, incident HF, MI, and CVD over 10 years in multiethnic participants without past CVD. In addition, we found that ECG strain is associated with development of LV concentric remodeling, decline in LV systolic function, and LV myocardial scar after 10 years of follow-up, whereas these associations were not observed in ECG-LVH. Based on these findings, it is possible that ECG strain is an early marker of LV structural remodeling that contributes to development of adverse cardiovascular events. To our knowledge, this is the first study to demonstrate the prognostic value of ECG strain in predicting adverse cardiovascular events over 10 years in apparently healthy individuals in multiethnic populations.

ECG Strain Predicts Adverse Cardiovascular Events Over 10 Years

Our results demonstrate that ECG strain provides a robust, independent predictive value for adverse cardiovascular events over 10 years in an ethnically diverse population free of symptomatic CVD at baseline. This finding is consistent with previous reports. For example, in the Framingham Heart Study,[22,23] ECG LVH with ST depression and T-wave flattening or inversion was associated with a >3-fold increased risk of CHD development. ECG strain is an independent predictor of increased cardiovascular mortality, MI, and incident HF in hypertensive patients.[7,8] ECG strain is also an independent predictor of incident HF in individuals with aortic stenosis[24] and in Native Americans.[25] However, none of these previous studies have evaluated the predictive value of ECG strain in apparently healthy men and women in multiethnic populations.

The precise mechanism linking ECG strain to the adverse cardiovascular events is not clear. A classic explanation is that LVH mediates the development of HF in the presence of ECG strain. This explanation is supported by the facts that ECG strain is frequently associated with LVH[26–28] and LVH is typically associated with elevated LV systolic wall stress, impaired subendocardial coronary blood flow reserve, subsequent LV systolic dysfunction,[29,30] and incident HF.[10] However, we found that ECG strain predicts an increase in both LV mass and MVR, reflecting concentric remodeling, whereas ECG-LVH is associated with eccentric remodeling. Our findings from CMR provide a mechanistic implication that LV concentric remodeling may play a major role. Another possible contributor is a decline in LV systolic function. Cross-sectional studies have demonstrated that ECG strain identifies patients with lower myocardial contractility in hypertensive patients[4] and in those with aortic regurgitation.[6] However, the relation of ECG strain to longitudinal change in LV function has not been previously examined. Our findings —showing the participants with ECG strain have a normal range of EF at baseline and a decline in LV EF over 10 years— strongly suggest that ECG strain is an early manifestation of LV dysfunction. Drazner et al reported that increased LV mass is an independent predictor of a decline in LV EF.[29] A cross-sectional study found that the worse mid-wall fractional shortening despite normal LV EF in patients with aortic stenosis who had both ECG-LVH and ECG strain.[3] A recent study also showed that a reduction in LV EF is associated with reduced survival in HF patients with preserved EF.[31] Taken together, ECG strain may be an early marker of LV structural

Table 4. ECG Strain/LVH With LV Scar Defined by LGE

	Logistic Regression for LV Scar at Year-10								
	Unadjusted			Model 1*			Model 2		
	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Year 0 (n=1759)									
ECG strain at Year-0	5.81	(2.46–13.73)	<0.001	4.93	(1.83–13.30)	0.002	5.33	(1.98–14.32)	0.001
ECG-LVH at Year-0	1.61	(0.81–3.20)	0.172	1.42	(0.65–3.06)	0.377	1.30	(0.59–2.90)	0.515
Year-10 (n=1650)									
ECG strain at Year-10	4.85	(2.56–9.21)	<0.001	5.22	(2.53–10.78)	<0.001	4.67	(2.17–10.06)	<0.001
ECG-LVH at Year-10	1.67	(0.84–3.32)	0.141	1.98	(0.95–4.15)	0.069	1.81	(0.84–3.91)	0.131

*Model 1 was adjusted for demographics (age, ethnicity, and sex) and traditional HF risk factors (body mass index, heart rate, systolic blood pressure, smoking, diabetes mellitus, antihypertensive medication use, and estimated glomerular filtration rate). Model 2 included interim CHD in addition to Model 1. CI indicates confidence interval; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; OR, odds ratio.

remodeling that contributes to development of adverse cardiovascular events. It remains unclear whether aggressive treatment of modifiable risk factors in individuals with ECG strain leads to improved cardiovascular outcomes. Further studies are needed to investigate the underlying mechanism of ECG strain.

Abnormal Repolarization and LV Scar

To date, there has been limited literature concerning ECG strain and myocardial scar detected by CMR-LGE. Palmieri et al assessed the prevalence of echocardiographic global and segmental LV wall motion in 942 hypertensive patients with LVH.[2] Those with wall motion abnormalities had a higher prevalence of the ECG strain than subjects with normal wall motion. A recent study found that 100% of patients with aortic stenosis and ECG strain had focal mid-wall LV scar defined by LGE,[3] although our results showed that around 30% of apparently healthy individuals with ECG strain had LV scar. We also found that MI and CVD event rate was highest in the ECG strain (+) without ECG-LVH group. These findings demonstrate both the pathological and prognostic significance of ECG strain. Because the majority of scar pattern was nonischemic, the mechanism underlying the ECG strain is likely not related to epicardial coronary artery disease, but to silent subendocardial and mid-wall ischemia not manifest in ECG-LVH. For example, ischemia could induce the heterogeneity of the action potential duration that results in ST-segment depression and T-wave inversion typically observed in ECG strain. This may explain our finding that individuals with ECG strain have a higher prevalence of LV scar, leading subsequently to adverse cardiovascular events.

Strengths and Limitations

MESA study participants were free of any CVD at baseline and represent an apparently healthy sample of the population at large; hence, the general applicability of our results may be limited by selection and survivor biases. Although we have excluded individuals with a medical history of CVD, there is a possibility that our cohort included individuals with undiagnosed, but preexisting, underlying diseases, such as hypertrophic cardiomyopathy. In addition, the number of participants with both ECG strain and ECG-LVH at baseline was relatively small. However, the inclusion of 4 different ethnicities and both women and men in the MESA cohort are significant strengths that improve the applicability of the data. Finally, although all the computer-detected ECG interpretations were manually confirmed by trained staff, the high prevalence of T-wave inversions in leads V1 to V4 as a normal variant in black Caribbean individuals could have led to overdetection of the ECG strain in blacks in our study.[32] However, the inclusion of high-quality digital ECG phenotyping and CMR—collected by standardized protocols and automatically measured at central reading centers—strengthens the internal validity of the findings.

Conclusions

In middle-aged individuals without past CVD, ECG strain is associated with a higher risk for death, incident HF, MI, and CVD as well as development of LV concentric remodeling, systolic dysfunction, and scar. The ECG strain has an independent prognostic value to ECG-LVH in community-dwelling adults, and it cautions against overconfidence in risk stratification based on ECG-LVH assessment alone.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Cardiac magnetic resonance imaging

The LV mass was adjusted for body size by dividing 100 × LV mass by the predicted LV mass based on height, weight, and sex, as: 100 × LV mass/(a × height$^{0.54}$ × weight$^{0.61}$), where a = 6.82 for women and 8.25 = men with mass in grams, height in meters, weight in kilograms. Similarly, the body size-adjusted LV volume was computed as: 100 × LV × volume/(b × height$^{1.25}$ × weight$^{0.43}$), where b = 10.0 for women and 10.5 for men and LV volume is in milliliters.

Cine images were obtained with a temporal resolution of approximately 50 ms or less using a segmented k-space and an ECG gated, fast spoiled gradient-recalled echo (FGRE) pulse sequence during MESA examination 1 at Year-0. On the other hand, ECG gated long- and short-axis cine images were acquired using a steady-state free precession (SSFP) sequence at MESA examination 5 at Year-10. Reader and pulse sequence calibration equations were algebraically combined to obtain overall equations[1, 2]. All calibration curves were found to be linear and were fitted with ordinary regression methods. This equation was used to correct Year-0 readings to be comparable to Year-10 readings.

For the identification of a regional scar, the LGE images were manually analyzed offline. The myocardial scar area was manually defined as the area with increased signal intensity by using a full-width at half-maximum criterion[3] and was quantified as a percentage of LV mass by using QMass. An ischemic pattern scar was defined as a myocardial scar that involved the subendocardium in a coronary artery distribution. A non-ischemic pattern scar was defined as a myocardial scar that predominantly affected the midwall or subepicardium without subendocardial involvement in a non–coronary artery distribution.

Table S1. Differences in baseline characteristics among ECG strain/LVH groups

	ECG strain (-)		ECG strain (+)		
	ECG-LVH (-) (n = 5,932)	ECG-LVH (+) (n = 341)	ECG-LVH (-) (n = 111)	ECG-LVH (+) (n = 57)	p Value
Demographic characteristics					
Age (years)	61.5 ± 10.2	64.4 ± 9.6	67.5 ± 8.6	69.0 ± 9.2	0.047
Sex women, n (%)	3,192 (54)	190 (56)	55 (50)	31 (54)	0.999
Ethnicity, n (%)					0.002
White	2,314 (39)	72 (21)	36 (32)	10 (18)	
Chinese	712 (12)	55 (16)	9 (8)	7 (12)	
African	1,577 (27)	139 (41)	45 (41)	27 (47)	
Hispanic	1,329 (22)	75 (22)	21 (19)	13 (23)	
Heart rate (beats/min)	63 ± 10	62 ± 10	63 ± 10	62 ± 10	0.903
Body mass index (kg/m2)	28.2 ± 5.5	29.1 ± 5.5	30.1 ± 5.3	28.4 ± 4.5	0.279
Systolic blood pressure (mmHg)	125 ± 21	139 ± 25	140 ± 24	150 ± 26	<0.001
Diastolic blood pressure (mmHg)	72 ± 10	75 ± 11	75 ± 12	78 ± 14	<0.001
Current smoker, n (%)	791 (13)	31 (9)	13 (12)	10 (18)	<0.001
Diabetes, n (%)	688 (12)	67 (20)	29 (26)	11 (19)	<0.001
Total cholesterol (mg/dl)	194 ± 36	196 ± 37	197 ± 40	196 ± 38	0.162
Estimated GFR (mL/min)	81 ± 18	84 ± 18	75 ± 20	74 ± 20	0.636
NT-proBNP (pg/mL) (n = 5,278)	57 (24, 113)	75 (31, 151)	147 (64, 306)	261 (84, 476)	<0.001
CMR measurements (n = 4,735)					
LV EDVi (ml/m^2)	69 ± 12	75 ± 15	71 ± 16	75 ± 17	<0.001
LV ESVi (ml/m^2)	26 ± 6	29 ± 9	27 ± 11	31 ± 15	<0.001
LV Mi (g/m^2)	64 ± 11	73 ± 14	73 ± 14	83 ± 18	<0.001
LV MVR (g/ml)	0.94 ± 0.18	0.99 ± 0.20	1.06 ± 0.23	1.13 ± 0.20	0.001
LV wall thickness ≥15mm	25 (0.6)	6 (2.5)	2 (3.1)	3 (6.7)	<0.001
LV wall thickness (mm)	9.2 ± 1.8	10.1 ± 2.0	10.5 ± 2.1	11.4 ± 2.2	0.002
LV EF (%)	63 ± 6	62 ± 7	63 ± 8	60 ± 11	<0.001

Table S2. ECG strain and adverse cardiovascular events in participants with ECG strain in only lead V5/V6

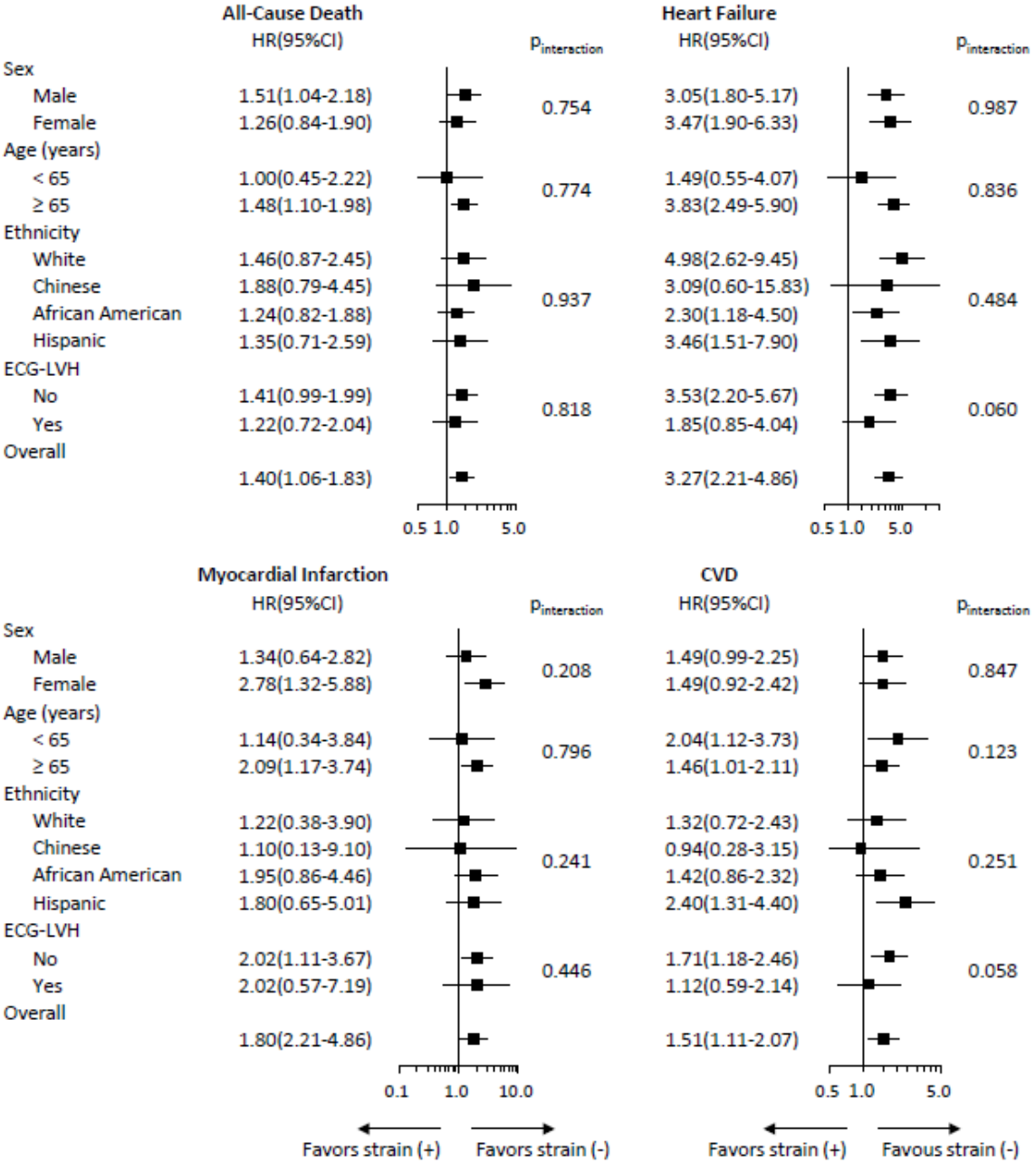
	Unadjusted				Model 1*				Model 2			
	No. of Events/No. at Risk	**Hazard Ratio**	**95%CI**	**P Value**	**No. of Events/No. at Risk**	**Hazard Ratio**	**95%CI**	**P Value**	**No. of Events/No. at Risk**	**Hazard Ratio**	**95%CI**	**P Value**
All Cause Mortality	1,045/6,437	2.46	1.77 - 3.42	**<0.001**	869/5,252	1.39	0.97 - 2.00	0.071	1,039/6,390	1.34	0.95 - 1.90	0.091
CHF	260/6,412	5.79	3.63 - 9.24	**<0.001**	201/5,234	3.17	1.79 - 5.62	**<0.001**	259/6,368	2.62	1.58 - 4.36	**<0.001**
CVD†	798/6,414	2.71	1.87 - 3.92	**<0.001**	653/5,235	1.80	1.19 - 2.73	**0.006**	793/6,369	1.56	1.06 - 2.32	**0.026**
CHD	532/6,414	2.73	1.75 - 4.27	**<0.001**	431/5,235	1.91	1.16 - 3.14	**0.011**	531/6,369	1.54	0.95 - 2.48	0.079
MI	252/6,413	3.16	1.73 - 5.78	**<0.001**	205/5,234	2.44	1.26 - 4.71	**0.008**	252/6,368	1.99	1.05 - 3.78	**0.034**
Angina	302/6,412	2.55	1.40 - 4.66	**0.002**	248/5,233	2.23	1.16 - 4.30	**0.016**	302/6,367	1.80	0.96 - 3.37	0.069
Stroke	243/6,412	1.78	0.79 - 4.01	0.163	206/5,233	0.80	0.29 - 2.18	0.666	240/6,367	0.99	0.43 - 2.28	0.982

*Model 1 was adjusted for demographics (age, sex and ethnicity), traditional risk factors (BMI, heart rate, systolic BP, smoking, diabetes, antihypertensive medication use, and eGFR), and NT-proBNP. Model 2 was adjusted for demographics, traditional risk factors, and ECG-LVH.

†CVD includes MI, resuscitated cardiac arrest, coronary heart disease death, stroke, and stroke death.

CHD = coronary heart disease; CI = confident interval; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HF = heart failure; HR = hazard ratio; MI = myocardial infarction.

Figure S1. Subgroup-Specific Adjusted Hazard Ratios for All-Cause Death, Heart Failure, Myocardial Infarction, and the Composite Cardiovascular Disease (CVD) in the ECG Strain (+) and ECG Strain (-) Groups.



The forest plot summarizes multivariable-adjusted HRs with 95% CI. Models were adjusted for sex (if not stratified by sex), age (if not stratified by age), ethnicity (if not stratified by ethnicity), BMI, heart rate, systolic BP, smoking, diabetes, antihypertensive medication use, and eGFR. There was no evidence for interaction. BMI = body mass index; BP = blood pressure; CI = confident interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVH = left ventricular hypertrophy.

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