Temporal Changes in Resting Heart Rate, Left Ventricular Dysfunction, Heart Failure and Cardiovascular Disease: CARDIA Study

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Temporal Changes in Resting Heart Rate, Left Ventricular Dysfunction, Heart Failure and Cardiovascular Disease: CARDIA Study

Running title: Longitudinal Heart Rate Changes and Cardiovascular Disease

Type of Study: Clinical Research Study

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Key words: Heart rate, left ventricular function, diastolic function, heart failure, cardiovascular disease

ABSTRACT

Introduction The prognostic significance of temporal changes in resting heart rate in young adults for premature heart failure and cardiovascular disease is unclear. We

investigated the association between temporal changes in resting heart rate in young adults and early adult risk factors, subsequent cardiac function, and the risk of heart failure and cardiovascular by middle age.

Materials and Methods We examined 4343 Coronary Artery Risk Development in Young Adults (CARDIA) study participants (mean (SD) age was 29.9 (3.6) years at the CARDIA Year-5 exam [1990-1991], 49% of participants were men, and 45% were African-American). Adjusted linear regression models were used to assess the association between temporal changes in resting heart rate, early life cardiovascular disease risk factors, and mid-life cardiac function. Cox proportional hazard regression models were used to relate temporal changes in resting heart rate to heart failure and cardiovascular disease. Outcomes were followed up until August 31, 2017.

Results Higher alcohol consumption (β=0.03, p<0.001), lower physical activity (β=0.002,p=001), smoking (β=1.58, p<0.001), men (p<0.001), African-Americans (p<0.001), impaired left ventricular relaxation (e´,β=-0.13, p=0.002), and worse diastolic function (E/e´,β=0.1, p=0.01) were associated with longitudinal increases in resting heart rate. We observed 268 cardiovascular disease and 74 heart failure events over a median of 26 years. In Cox models, baseline and temporal changes in resting heart rate were associated with higher risk of heart failure (hazard ratio (HR)=1.37 95% confidence interval (CI) [1.05-1.79] and HR=1.38 95%CI [1.02-1.86]) and a higher risk cardiovascular disease (HR=1.23 95%CI [1.07-1.42] and HR=1.23 95%CI [1.05-1.44]).

Conclusions Baseline and temporal changes in resting heart rate in young adults were associated with incident heart failure and cardiovascular disease by mid-life.

Contributory factors were associations between temporal increases in resting heart rate and early adult risk factors and subsequent cardiac dysfunction.

Clinical Significance

- Temporal changes in resting heart rate was associated with premature heart failure and cardiovascular disease by middle age.
- Suboptimal lifestyle factors are key drivers of long term heart rate increases and heart rate increases are related to cardiac dysfunction in later life.
- Enhanced monitoring of heart rate changes may be potentially useful for disease surveillance, risk-stratification, and decision making in everyday clinical practice

INTRODUCTION

Resting heart rate is an easily measured parameter that is routinely obtained in clinical practice and research settings. In the general population, higher resting heart rate at the time of risk assessment has been associated with an increased risk of cardiovascular disease, including heart failure.[1-3] A single time-point resting heart rate may however proffer limited clinical utility for risk assessment in the general population, because asymptomatic individuals in the community frequently present within a physiologic range of resting heart rate. Long-term changes in resting heart rate from baseline values may thus provide a more reliable target for disease surveillance or risk stratification. Few studies have assessed the impact of temporal changes in resting heart rate on cardiovascular health and these prior studies have focused on populations with either prevalent cardiovascular disease or those in mid-to-late adulthood.[2,4-8] It is however

increasingly clear that early life risk factors may increase the likelihood of future cardiovascular disease, independent of the impact of risk factor burden in late adulthood.[9] Quantifying the potential risk associated with resting heart rate changes in young adults is therefore essential. In this context, the association between temporal changes in resting heart rate and the risk of premature clinical outcomes are not well-described. Further, the risk factors that may be associated with long-term changes in resting heart rate and whether long-term changes in resting heart rate influence changes in cardiac function are incompletely understood. We therefore investigated the early adult risk factors associated with longitudinal changes in resting heart rate. Second, we assessed the association between temporal changes in resting heart rate in young adults and subsequent mid-life cardiac function. Finally, we explored the association between temporal changes in resting heart rate and the risk of heart failure and cardiovascular disease by middle age.

METHODS

Study Design and Participants

The aims and study design of the Coronary Artery Risk Development in Young Adults (CARDIA) study have been previously reported.[10] In summary, CARDIA is a biracial community-based cohort study that enrolled 5115 Men and Women from 4 field-centers in the United States located in Birmingham, AL; Oakland, CA; Chicago, IL; and Minneapolis, MN. Participants were aged 18 to 30 years and free of cardiovascular disease and heart rate or blood pressure medication use at baseline (Year 0 exam, 1985–1986). Study participants were subsequently followed up in 9 examination cycles over 30 years, with the most recent visit in 2015-2016 (Year-30 exam). The analytical sample for this study included 4343 participants who attended the Year-0 and Year-5 exams and had

available heart rate data and no cardiovascular disease events prior to the Year-5 exam. All participants provided written informed consent and the institutional review board of each study field center approved the study.

Resting Heart Rate

Participants were asked to present with a morning fast and to avoid smoking or any heavy physical activity prior to study visit. Heart rate in beats-per-minute was recorded in a quiet room after subjects had been seated for 5 minutes by palpation of the radial artery before the first blood pressure assessment. Temporal change in resting heart rate was defined as the change in heart rate from the CARDIA Year-0 to Year-5 exams.

Covariate Assessment

Standard questionnaires, clinical, and laboratory assessments were utilized to obtain data regarding age, race, sex, education, body mass index, blood pressure, smoking history, physical activity, diabetes mellitus, alcohol intake, plasma cholesterol, and medication use. These covariate assessment procedures have been described previously.[11] Blood pressure was measured 3 times in the right arm, with participants seated at 1-minute intervals after 5 minutes of rest. A physical activity score (exercise units) derived from a modified version of the Minnesota leisure time physical activity questionnaire was utilized to capture moderate to vigorous physical activity. Alcohol intake was obtained from a questionnaire where participants self-reported the number of drinks, beer, and liquor consumed per week under the assumption that the amount of ethanol in a drink of beer, wine, and liquor was 16.7 ml, 17.0 ml, and 19.2 ml, respectively. Diabetes mellitus was ascertained on the basis of one or more of a combination of history of medication

use, fasting glucose levels, or glycated hemoglobin. Plasma cholesterol was obtained using enzymatic assays by Northwest Lipids Research Laboratory (Seattle, WA).

Echocardiography

The CARDIA echocardiographic study procedures have been previously reported.[11,12] Using standardized protocols designed to ensure good reproducibility, trained sonographers across all field-centers acquired images. Experienced readers interpreted digitized images using a standard software offline image analysis system that was transmitted to a core laboratory. For this analysis, echocardiographic measures included left ventricular mass , left atrial diameter, left ventricular ejection fraction, and the ratio of the mitral inflow velocity to early diastolic mitral annular velocity (E/e'), e', global longitudinal strain, and global circumferential strain. Left ventricular mass was derived according to the American Society of Echocardiography guidelines.[13] Left ventricular ejection fraction was derived using Simpson's method. Early diastolic mitral annular velocity (e') was obtained from the average of septal and lateral mitral annular velocities. Speckle tracking echocardiography for left ventricular myocardial strain measures was performed offline with dedicated semi-automated two-dimensional wall motion tracking software (Toshiba Medical Systems, Tokyo, Japan). Global strain values were calculated as the average of segmental peak systolic strain. The CARDIA echocardiographic evaluations showed an excellent reproducibility profile.[14]

Cardiovascular Outcomes

Outcome ascertainment and adjudication procedures in the CARDIA study have been described elsewhere.[15] Outcome adjudication included semi-annual contacts and annual queries for hospitalizations and procedures. Cardiovascular disease events were a

composite that included coronary heart disease, stroke, heart failure, and peripheral artery disease. The national death index was periodically reviewed. Heart failure ascertainment was on the basis of admission for new-onset heart failure and a constellation of clinical symptoms, signs, and imaging. Participants were followed up for outcomes until August 31, 2017.

Statistical Analysis

Population characteristics were presented as mean ± standard deviation for continuous variables and frequencies and proportions for categorical variables. The goals of the analysis were 3-fold: (1) to examine associations between early adult risk factors and temporal changes in resting heart rate (2) to investigate the association between temporal changes in resting heart rate and mid-life cardiac function (3) to evaluate the association between temporal changes in resting heart rate and incident heart failure and cardiovascular disease.

For goal 1: multivariable linear regression models were utilized to assess the correlates of longitudinal change in resting heart rate (Year-0 to Year-5) with adjustment for the following Year-5 exam covariates: age, sex, race, education, blood pressure, body mass index, low density lipoprotein-and high density lipoprotein cholesterol, diabetes mellitus, blood pressure lowering medication use, alcohol intake, smoking, and physical activity.

For goal 2: multivariable linear regression models were also utilized with the following echocardiography measures at the Year-25 exam as the dependent variable: left ventricular mass, left ventricular ejection fraction, left atrial diameter, global longitudinal strain, global circumferential strain, e´, and E/e´ (separate models for each). Models were adjusted for a Year-5 echocardiography parameter, change in covariates from the Year-5

and Year-25 exams (body mass index, systolic blood pressure, high-density lipoprotein and low-density lipoprotein cholesterol, alcohol intake, and physical activity), and age, sex, race, education , blood pressure medication use, diabetes, and smoking history. For goal 3: restricted cubic splines with 3 knots in fully adjusted models were used to visualize the flexible association between temporal change in resting heart rate and outcomes. Proportional hazard assumptions were not violated based on Schoenfeld residuals. Nelson-Aalen cumulative hazard curves were plotted for longitudinal changes in resting heart rate using the following categories that were deemed clinically meaningful (stable resting heart rate (less than 5 beats-per-minute change in either direction), ≤5 beats-per-minute temporal reduction in resting heart rate, and ≥5 beats-per-minute temporal increase in resting heart rate). At the Year-5 exam, Cox proportional hazard models using baseline (Year-5) and temporal change in resting heart rate (Year-0 to Year-5) as explanatory variables were used to calculate hazard ratios and 95% confidence intervals for associations with incident heart failure and cardiovascular disease. Baseline resting heart rate cox models was adjusted for age, sex, race, education, blood pressure lowering agent use, atrial fibrillation status, diabetes mellitus, smoking status, preceding heart rate (Year-0), alcohol use, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, body mass index, physical activity. Cox models for temporal change in resting heart rate was additionally adjusted for time-varying covariates from the Year-0 to Year-5 exams. Differences by race or sex were also assessed. Statistical analyses were performed using Stata version 15.1 and SAS version 9.4.

RESULTS

Population Characteristics

Table 1 shows the population characteristic by longitudinal change in resting heart rate status. **Figure 1** shows the normal distribution of temporal change in resting heart rate for study participants. Mean (SD) age of study participants at Year-5 was 29.9 (3.6) years. Mean resting heart rate declined from Year-0 to Year-5 (69.3 ± 10.9 beats-per-minute to 68.3 ± 9.9 beats-per-minute). Correlation between baseline and temporal changes in resting heart rate was r=0.46. Participants with a greater than 5 beats-per-minute increase in resting heart rate over a 5-year interval were more likely to be men, African-American, not completed high school, reported less physical activity, and consumed more alcohol

Cardiovascular Risk Factors and Change in Resting Heart Rate

The associations between early adult risk factors and temporal change in resting heart rate are shown in **Table 2**. Higher alcohol consumption (β=0.03, standard error (SE) 0.01, P<0.001), lower physical activity (β=0.002,SE 0.001,p=001), current smoking (β =1.58, SE 0.4, p<0.001), Men (p<0.001), and African-Americans (p<0.001) were associated with a 5 year increase in resting heart rate.

Resting Heart Rate and Cardiac Structure and Function

The association between temporal change in resting heart rate and cardiac structure and function (Year-25) are shown in **Table 3.** A more positive E/e´ signifies worse diastolic function whereas a more negative e' denotes worse left ventricular relaxation. More positive strain values indicate worse systolic function. In fully adjusted multivariable linear regression models (per 1 standard deviation), temporal increases in resting heart rate was associated with worse left ventricular diastolic function (E/e´, β=0.1, SE 0.04,

p=0.01) and worse left ventricular relaxation (e´ β=-0.13, SE 0.04, p=0.002). There were no association between temporal changes in resting heart rate and left ventricular mass, ejection fraction, or global longitudinal strain.

Resting Heart Rate and Heart Failure and Cardiovascular Disease

During a median follow-up of 26 years, 268 cardiovascular disease and 74 heart failure events were observed. Nelson-Aalen cumulative hazard curves by categories of resting heart rate change (stable resting heart rate, ≥5 beats per minute decrease, and ≥5 beats per minute increase) and heart failure and cardiovascular disease are illustrated in **Figure 2**. In **Figure 3,** restricted cubic splines illustrate an approximately linear association between temporal changes in resting heart rate and heart failure and cardiovascular disease events. In fully adjusted Cox proportional hazard models (**Table 4),** baseline and temporal increases in resting heart rate were associated with a higher risk of heart failure and cardiovascular disease. For each 10 beats-per-minute longitudinal increase in resting heart rate there was an associated 38% and 23% higher risk of heart failure and cardiovascular disease, respectively. There were no sex or race differences in the association between temporal changes in resting heart rate and clinical outcomes.

DISCUSSION

In this large community-based sample of young adults followed up for a median of 26 years, our main findings were: (1) smoking, higher alcohol intake, low physical activity, men, and African-Americans were associated with greater temporal increases in resting heart rate . (2) Temporal increases in resting heart rate was associated with impaired left ventricular relaxation and worse diastolic function by middle age. (3) Baseline and temporal changes in resting heart rate were approximately linearly associated with

incident heart failure and cardiovascular disease by middle age. For each 10- beats-per-minute temporal rise in resting heart rate there was an associated 38 % and 23% higher risk of heart failure and cardiovascular disease, respectively.

Our study observations highlight the potential prognostic significance of long-term changes in resting heart rate in early adulthood for the risk of heart failure or cardiovascular disease in the community. Our results also underscore that suboptimal lifestyle habits and cardiovascular disease risk burden and subsequent alterations in myocardial function are possible contributory factors.

A substantial number of studies have provided evidence of an association between baseline resting heart rate at the time of risk assessment and deleterious outcomes in persons with extant cardiovascular disease as well as in community-dwelling individuals.[3,4,7,16] The prognostic importance of temporal changes in resting heart rate is however less well studied. More so in young adults, where early screening and risk factor modification may help mitigate the risk of adverse clinical outcomes in later life and risk factors may influence future outcomes irrespective of later life risk burden.[9] Prior studies that focused on older adults, showed that increasing resting heart rate was associated with a higher risk of cardiovascular outcomes.[6,8,17] Our study results are consistent with these reports and importantly add to the literature by providing prognostic data in early adulthood. In agreement with past reports of a trend towards declining resting heart rate in the general population that is perceived to have paralleled improvements in healthcare,[18] in our results, we noted a mean 5-year decrease in resting heart rate. However, in contrast, suboptimal early life risk factors and lifestyle habits (smoking,

alcohol use, and low physical activity) were associated with temporal increases in resting heart rate.

In the present study, relations between baseline and temporal changes in resting heart rate and adverse clinical outcomes persisted even after robust adjustments for confounding factors. It is however conceivable that resting heart rate and these risk factors cluster together and act synergistically along the cardiovascular disease risk continuum. Another novel finding in the present study was the association between temporal changes in resting heart rate and unfavorable diastolic function. There are a number of plausible explanations for this association. Higher heart rate is associated with less coronary and myocardial perfusion and lower diastolic filling time in the setting of increased myocardial oxygen consumption.[19] Concomitantly, a heightening allostatic load on the elastic conduit arteries from a rise in resting heart rate can induce pulsatile pressure and aortic remodeling. [20]Alterations in aortic material properties are linked to a cascade of events including higher left ventricular afterload and stiffness, impairments in left ventricular relaxation, and cardiac function. [11,21] In addition to the aforementioned, there are other possible pathways that may be supportive of relations between heart rate and cardiovascular outcomes. Heart rate is perceived to be a surrogate of basal metabolic rate and lower values have been linked with longevity across several mammalian species.[22] Baseline heart rate is a heritable trait and some genetic loci for heart rate are also linked to regulation of the sympathovagal balance.[23,24] Congruent with these genetic studies, a higher heart rate is generally associated with ensuing prokinetic sympathomimetic activity with potential downstream pleiotropic effects. In a prior study of young adults, a higher heart rate in normotensive participants was shown to precede the onset of blood

pressure elevation in later life.[25] Higher heart rate is also associated with cardiometabolic factors such as increased oxidative stress, inflammation (c-reactive protein, interleukin-6, and fibrinogen), glucose intolerance, and diabetes mellitus[19,26,27] Furthermore, in asymptomatic individuals, higher heart rate has been linked with subclinical atherosclerosis in part due to lower coronary blood flow and atherogenic endothelial shear stress patterns. [19] In clinical and experimental studies, higher heart rate has been linked with a variety of microvascular and macrovascular degenerative target organ disease that have implications for cardiovascular disease.[28,29]

Strengths and Limitations

The use of a community-based cohort of young Caucasian and African-American adults with rigorous quality control procedures, echocardiographic assessment, and long-term outcome ascertainment strengthens our findings. Although findings remained significant after accounting for atrial fibrillation status, the presence of heart rhythm disturbances in clinical practice may distort the interpretation of heart rate changes over time. Although observed absolute cardiovascular disease and heart failure events in the CARDIA study were not high, event rates are consistent with the expected incidence in early adulthood. [30] Subgroups of heart failure were not assessed due to the unavailability of ejection fraction at the onset of heart failure.

CONCLUSIONS

Our study results underscore an association between temporal changes in resting heart rate in young adults and the subsequent risk of heart failure and cardiovascular disease in the community. Contributory mechanisms were associations with early adult suboptimal lifestyle and risk factors and subsequent cardiac dysfunction. Our findings highlight the

potential utility of long-term changes in resting heart rate as a more reliable target for disease surveillance or risk stratification when compared to single time point resting heart rate values that fall within a physiological range.

AUTHOR CONTRIBUTIONS

Chike Nwabuo, Duke Appiah, and João Lima; conceptualization; investigation; data curation; methodology; formal analysis; validation; writing - original draft. João Lima, Donald Lloyd-Jones, Pamela Schreiner, and Samuel Gidding; conceptualization; investigation; resources; project administration; supervision; writing - review and editing. Queen Aghaji, Henrique Moreira, Henrique Vasconcellos, Jamal Rana, Bharath Ambale-Venkatesh, and Norrina Allen; conceptualization; investigation; writing - review and editing.

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COMPETING INTERESTS: None declared

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Figure Legends

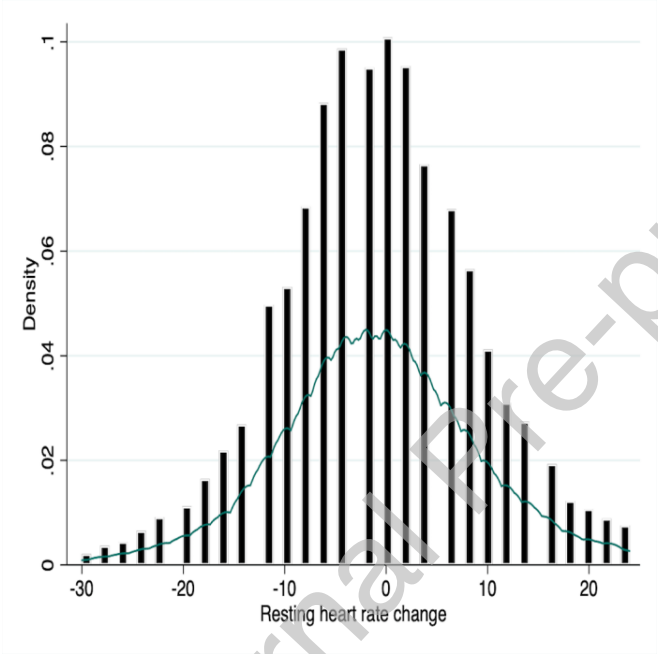

Figure 1

Title Distribution of temporal change in resting heart rate (Year-0 to Year-5 exam)

Description Histogram showing the distribution of 5-year change in resting heart rate

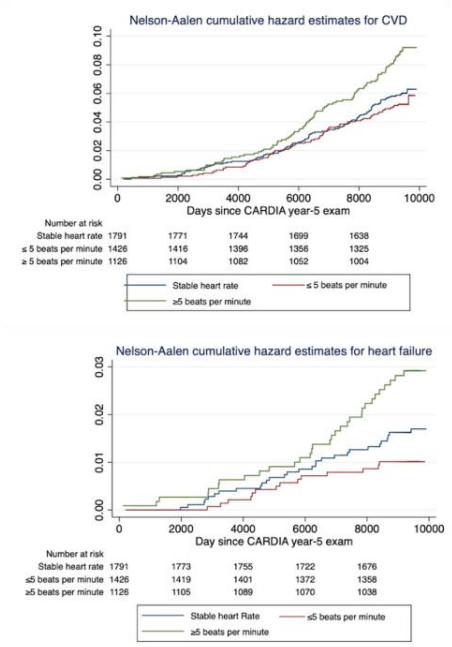

Figure 2

Title Nelson-Aalen cumulative hazard estimates for heart failure and cardiovascular disease by temporal resting heart rate categories.

Description Stable resting heart rate refers to a less than 5 beats per minute change in resting heart rate in 5 years.

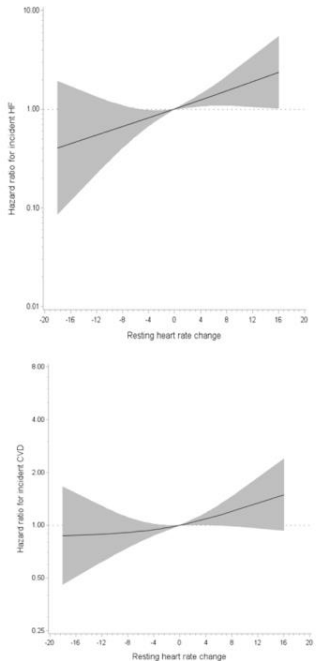

Figure 3

Title Associations between temporal changes in resting heart rate and incident heart failure and cardiovascular disease.

Description

Figure represents restricted cubic splines with 3 knots from fully adjusted Cox proportional hazard models. The gray margins represent the 95% confidence intervals. No change in resting heart rate (0 beats per minute) is taken as the reference. Associations between temporal change in resting heart rate and heart failure and cardiovascular disease were approximately linear.

Table 1. Population characteristics by categories of temporal change in resting heart rate

Covariates (Year-5 exam) (N=4343)	Temporal Change in Resting Heart Rate		
	≥5bpm drop (N=1426)	Stable heart rate (N=1791)	≥5bpm increase (N=1126)
Age, years	29.9 ±3.7	30.1±3.6	29.8 ± 3.6
Female, N(%)	852 (59.8)	967 (54)	571 (50.7)
White, N(%)	803 (56.3)	896 (50)	529 (47)
Completed high school, N(%)	1349 (94.6)	1689 (94.3)	1040 (92.4)
Body mass index, Kg/m^2	25.9 ±5.7	26.2 ±5.9	26.4 ±6.1
Systolic BP, mmHg	107.2±11.4	107.7±11.2	108.7±12.4
HDL-cholesterol ,mg/dL	53.7±14.1	52.9 ±13.9	53.3±14.5
LDL-cholesterol,mg/dL	107.6±31.9	109.6±31.7	107.9±32.7
Diabetes mellitus, N(%)	23 (1.6)	38 (2.1)	22 (2.0)
BP medication use, N(%)	25 (1.8)	22 (1.2)	23 (2.1)
Current smoker, N(%)	350 (24.6)	514 (28.8)	377 (33.5)
Alcohol, mL	9.3±18.0	10.7 ±19.5	14.5±38.7
Physical activity, eu	386.7±292.8	381.3±292.3	366±292.2
Resting heart rate, bpm	64.1±8.4	67.3±8.7	75.0±10.1
Echocardiography			
Left ventricular mass, g	165.0±50.5	168.3±52.2	170.8±55.5
Left atrial diameter, cm	49.6±15.5	49.9±15.8	49.8±16.7
Ejection fraction, %	61.4±6.85	61.4±7.4	61.3±7.3
Global longitudinal strain, %	-15.3±2.7	-15.3±2.8	-15.3±2.9
Circumferential strain, %	-15.2±2.4	-15.1±2.4	-14.9±2.4
E/e´	7.76±2.2	7.8±2.2	8.1±2.4

Population characteristics are presented for CARDIA year-5 while echocardiography measures are presented for CARDIA year-25. Stable heart rate was defined as a less than 5 beats-per-min (bpm) positive or negative change in heart rate.
Data are presented as mean ± standard deviation, or frequency (proportions)
Bpm, means beats per minute; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Eu, exercise units; E/e, ratio of mitral inflow velocity to early diastolic mitral annular velocity.

Table 2. Association between cardiovascular risk factors and temporal change in resting heart rate

Covariates	Beta coefficient (SE)	*p*-value
Age, years	0.05 (0.05)	0.28
Female	**-1.70(0.4)**	**<0.001**
White	**-1.63(0.36)**	**<0.001**
High school	0.72 (0.73)	0.33
Body mass index, mg/Kg^2	0.02(0.03)	0.57
Systolic BP,mmHg	-0.01(0.02)	0.63
HDL-cholesterol,mg/dL	0.01(0.01)	0.51
LDL-cholesterol, mg/dL	0.004 (0.005)	0.43
Diabetes Mellitus	0.28(0.38)	0.46
BP medication use	-1.40(1.4)	0.32
Smoking status		
Never	Reference	
Former	0.11(0.51)	0.83
Current	**1.58(0.4)**	**<0.001**
Physical activity,eu	**-0.002(0.0006)**	**0.001**
Alcohol intake, mL	**0.03(0.007)**	**<0.001**

Multivariable linear regression showing the association between cardiovascular risk profile and heart rate change (Year-0 to Year-5).

Models were adjusted for all covariates in the same model.

SE, means standard error; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Eu, exercise units;

Beta coefficients are for 1-unit increment in explanatory variable.

Table 3. Temporal changes in resting heart rate and cardiac structure and function

Echocardiography (R^2)	Temporal changes in Resting Heart Rate Beta coefficient (SE)
Left ventricular mass (R^2 0.48)	0.33(0.8)
Ejection fraction (R^2 0.04)	0.01(0.2)
Left atrial diameter (R^2 0.35)	-0.001(0.01)
Global longitudinal strain (R^2 0.14)	0.03(0.05)
Global circumferential strain (R^2 0.04)	0.05(0.06)
E/e´ (R^2 0.18)	0.1(0.04) **
E´ (R^2 0.22)	-0.13(0.04) ***

Multivariable linear regression showing the association between temporal change in heart rate (year-0 to year-5) and echocardiography measures (year-25). Beta estimates are per 1 standard deviation increase in explanatory variable. Models were adjusted for time varying covariates (body mass index, systolic blood pressure, high-density lipoprotein, low-density lipoprotein cholesterol, alcohol intake, and physical activity), age, sex, race, education (year-25), anti-hypertensive medication use (year-25), diabetes mellitus (year-25), and smoking history (year-25). E/e, ratio of mitral inflow velocity to early diastolic mitral annular velocity.

P<0.05*, P<0.01**, P<0.005***, P<0.001****

Table 4. Baseline and temporal change in resting heart rate and incident heart failure and cardiovascular disease

	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Heart failure		
Temporal change in heart rate	1.52 [1.21-1.91]	1.38 [1.02-1.86]
Baseline heart rate	1.29 [1.04-1.61]	1.37 [1.05-1.79]
Cardiovascular disease		
Temporal change in heart rate	1.27 [1.12-1.44]	1.23 [1.05-1.44]
Baseline heart rate	1.24 [1.11-1.39]	1.23 [1.07-1.42]

Cox proportional hazard models showing the association between baseline and temporal change in resting heart rate (explanatory variables) and incident heart failure and composite cardiovascular disease outcomes.

Baseline heart rate cox models was adjusted for age, sex, race, education, blood pressure lowering agent use, atrial fibrillation status, diabetes mellitus, smoking status, preceding heart rate (Year-0), alcohol use, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, body mass index, physical activity. Temporal change in heart rate cox models were additional adjusted for time-varying covariates from Year-0 to Year-5 exams. CI means confidence interval.