HHS Public Access

Author manuscript

J Electrocardiol. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

J Electrocardiol. 2016 ; 49(5): 686–690. doi:10.1016/j.jelectrocard.2016.06.008.

Reference Ranges for Short-Term Heart Rate Variability Measures in Individuals Free of Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis (MESA)

Wesley T. O'Neal, MD, MPH[1], **Lin Y. Chen, MD, MS**[2], **Saman Nazarian, MD, PhD**[3], and **Elsayed Z. Soliman, MD, MSc, MS**[4,5]

[1]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

[2]Department of Medicine, Division of Cardiology, University of Minnesota Medical School, Minneapolis, MN, USA

[3]Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[4]Department of Internal Medicine, Section on Cardiology, Wake Forest School of Medicine, Winston-Salem, NC, USA

[5]Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC, USA

Abstract

Background—Normative values for heart rate variability (HRV) measures from 10-second electrocardiograms (ECG) have not been defined.

Methods—We reported borderline abnormal (<5th percentile) and abnormal (<2nd percentile) values of standard deviation of all normal-to-normal R-R intervals (SDNN) and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD) from 10-second ECGs in 1,175 participants (mean age=59±10; 59% female; 47% white) ≥45 years of age from the Multi-Ethnic Study of Atherosclerosis (MESA) who were free of cardiovascular disease (CVD) and CVD risk factors. We validated the prognostic significance of these measures in a subset of the MESA cohort with complete data.

Results—Borderline abnormal and abnormal SDNN and rMSSD varied by sex and race. Borderline abnormal and abnormal SDNN and rMSSD were associated with an increased risk of CVD and all-cause mortality.

Corresponding Author: Wesley T. O'Neal, MD, Department of Medicine, Division of Cardiology, Emory University School of Medicine, 101 Woodruff Circle, Woodruff Memorial Building, Atlanta, GA 30322, Phone: +1.404.727.2273, wesley.oneal@emory.edu.

Conclusions—The references ranges provided in this report will guide future research using these common HRV parameters.

Keywords

heart rate variability; electrocardiogram; epidemiology

INTRODUCTION

Heart rate variability (HRV), a reflection of cardiac autonomic function, is traditionally measured from long-term electrocardiogram (ECG) recordings [1]. However, long-term ECG recordings are not always feasible in population-based cohort studies due to participant burden and cost. Hence, two time-domain measures derived from the standard 12-lead ECG (10-second tracing) have been proposed as alternatives. These two measures are: standard deviation of all normal-to-normal R-R intervals (SDNN) and root mean square of successive differences between normal-to-normal R-R intervals (rMSSD).

Several reports have shown that these HRV measures from 10-second ECGs are associated with an increased risk for adverse events, including cardiovascular disease (CVD) development and all-cause mortality [2–5]. However, despite the prognostic significance of HRV obtained from the 10-second ECG, these measures have not been widely adopted for CVD risk assessment due to a lack of agreement regarding normative values [6]. Notably, even HRV derived from long-term ECG recordings lack agreement regarding normal values. To address this gap in knowledge, we defined the normative range of HRV measures (SDNN and rMSSD) obtained from the 10-second ECG in a sample of participants from the Multi-Ethnic Study of Atherosclerosis (MESA) without CVD or CVD risk factors. We then validated the prognostic significance of the derived abnormal HRV measures in the entire MESA cohort.

METHODS

Study Population

Details of MESA have been reported previously [7]. Briefly, between July 2000 and September 2002, a total of 6,814 persons were recruited at 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Participants were required to be between 45 and 84 years of age and to have no clinical CVD at baseline. All participants provided informed consent and the study protocol was approved by the Institutional Review Boards at each participating institution.

To define the normative range of SDNN and rMSSD, we excluded participants who reported smoking, or who had diabetes, hypertension, dyslipidemia, or obesity. Those with major ECG abnormalities as defined by Minnesota code classification also were excluded [8]. After all exclusions, 1,175 participants (mean age=59±10 years, range=45–84 years; 59% female; 47% white; 19% Chinese-American; 16% black; 18% Hispanic) were included in this analysis. For the validation analysis, we included participants from the entire MESA

cohort, including the 1,175 participants without baseline CVD risk factors. We excluded participants with missing baseline characteristics and missing follow-up data. A total of 6,332 participants (mean age=62±10 years, range=45–84 years; 54% female; 38% white; 12% Chinese-American; 27% black; 23% Hispanic) were included in the validation cohort.

Heart Rate Variability

In MESA, 12-lead digital ECGs were obtained by trained technicians using GE MAC 1200 electrocardiographs using standardized procedures. ECGs were obtained in participants in the fasting state to negate dietary influences on recordings. ECGs were transmitted electronically to the MESA ECG Reading Center located at the Epidemiological Cardiology Research Center (Wake Forest School of Medicine, Winston-Salem, NC). All ECGs were automatically processed, after visual inspection for technical errors and inadequate quality, using the 2001 version of the GE Marquette 12-SL program (GE, Milwaukee, Wisconsin, USA). SDNN and rMSSD were obtained from baseline ECGs. In MESA, 3 consecutive 10-second ECGs were obtained and the mean values for SDNN and rMSSD were computed from these 3 tracings. As part of the automated measurement of HRV, the beat before and the beat after premature atrial contractions (PAC) were excluded from HRV measurements. PACs were detected by visual inspection or automatically by software. Also, if the number of PACs exceeded 50%, the whole ECG was excluded from the HRV analysis and HRV was not computed for these participants. The repeatability of short-term HRV measures obtained from 10-second ECGs has been shown to improve when 2–3 recordings are used [9]. Sex- and race-specific ranges were presented due to baseline differences in SDNN (sex: p=0.21; race: p=0.0034) and rMSSD (sex: p=0.030; race: p=0.0005) by race and sex.

Baseline Characteristics

Participant characteristics were collected during the initial MESA visit. Age, sex, race/ethnicity, income, and education were self-reported. Annual income was categorized as < $20,000 or ≥$20,000 and education was categorized as "high school or less," or "some college or more." Smoking was defined as ever (e.g., current or former) versus never smoker. Blood samples were obtained after a 12-hour fast and measurements of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and plasma glucose were used. Diabetes was defined as fasting glucose values ≥126 mg/dL or a history of diabetes medication use. Blood pressure was measured for each participant after 5 minutes in the seated position. Systolic and diastolic measurements were recorded 3 separate times and the mean of the last two values was used. Aspirin, statin, antihypertensive, and lipid-lowering medication use were self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Left ventricular hypertrophy was defined by the Cornell criteria (R wave amplitude aVL plus S wave amplitude $V_3 \geq 2.8$ mV in males and ≥ 2.0 mV in females) using baseline ECG data [10].

Cardiovascular Disease and All-Cause Mortality

The adjudication process of incident CVD events in MESA has been previously described [11]. Briefly, at intervals of 9–12 months, a telephone interviewer contacted each participant to inquire about interim hospital admissions, outpatient diagnoses, and deaths. Copies of all

death certificates and medical records for hospitalizations and outpatient CVD diagnoses were reviewed. Next-of-kin interviews were conducted for out of hospital CVD deaths. Two physicians, blinded to information from MESA examinations, independently reviewed and classified CVD events and assigned incidence dates. If they disagreed, they adjudicated their differences via discussion. For this report CVD events included definite and probable myocardial infarction, definite coronary heart disease death, resuscitated cardiac arrest, definite angina, probable angina associated with coronary revascularization, definite or probable heart failure, stroke, or other atherosclerotic CVD death. All-cause mortality was defined as death due to any cause.

Statistical analysis

Baseline characteristics of study participants were stratified by race. Sex- and race-specific reference ranges for borderline abnormal (<5th percentile) and abnormal (<2nd percentile) values of SDNN and rMSSD were computed. The cut-off points to define borderline abnormal and abnormal values were chosen based on prior work to define normative values for PR interval and P-wave indices in MESA [12]. The borderline abnormal and abnormal values of SDNN and rMSSD were then used to determine if these measures were associated with incident CVD and all-cause mortality in a validation cohort of MESA. Follow-up was complete from the baseline examination until the first CVD event, loss to follow-up, death, or end of follow-up (December 31, 2012). Multivariable Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between borderline abnormal and abnormal HRV measures with incident CVD and all-cause mortality, separately. Models were adjusted as follows: Model 1 adjusted for age, sex, race/ethnicity, income, and education; Model 2 adjusted for Model 1 covariates plus systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, statins, aspirin, and left ventricular hypertrophy. Statistical significance was defined as $p < 0.05$. SAS Version 9.4 (Cary, NC) was used for all analyses.

RESULTS

The baseline characteristics of the study participants used to define normative ranges for HRV measures are shown in Table 1. This sample included 554 (62% women) white participants, 227 (60% women) Chinese-Americans, 189 (57% women) black participants, and 205 (55% women) Hispanic participants. The mean SDNN and rMSSD values for the study population were 24.1±16.4 ms (median= 20.8, 25th–75th percentile=14.2–29.3) and 27.3±22.2 ms (median= 22.0, 25th–75th percentile=15.0–34.0), respectively. The distribution and reference ranges for borderline abnormal and abnormal SDNN and rMSSD for the entire sample are shown in Table 2. The sex- and race-specific reference ranges for borderline abnormal and abnormal SDNN and rMSSD also are shown in Table 2.

The validation cohort included 6,332 participants. Of these, 494 (7.8%) and 478 (7.6%) had borderline abnormal SDNN and rMSSD values, respectively. There were 198 (3.1%) with abnormal SDNN values and 170 (2.7%) with abnormal rMSSD values. The baseline characteristics of the validation cohort are shown in Table 3. Over a median follow-up of 11

years, a total of 441 (7.0%) CVD events and 734 (12%) deaths occurred. In a Cox regression analysis adjusted for baseline characteristics, including potential confounders, borderline abnormal and abnormal values for SDNN and rMSSD were significantly associated with CVD events and all-cause mortality (Table 4). In all analyses, the associations of abnormal values of HRV with CVD events and all-cause mortality were stronger than those with borderline abnormal values.

DISCUSSION

In this analysis from MESA, we report the sex- and race-specific reference ranges for two commonly reported time-domain HRV measures (e.g., SDNN and rMSSD) obtained from 10-second ECG recordings. The findings of this analysis provide researchers with normative values to distinguish HRV abnormalities obtained on 10-second ECG recordings and will improve comparability between future epidemiologic studies which use these measures. Additionally, we have shown that borderline abnormal and abnormal values for SDNN and rMSSD are associated with an increased risk for CVD events and all-cause mortality, and confirm the prognostic significance of the proposed values.

To our knowledge, this is the first report to define the normal values for SDNN and rMSSD obtained from 10-second ECGs. This study addresses a need for normal reference ranges of these measures from a population-based study of healthy adults [6]. Additionally, we were able to report sex- and race-specific ranges due to the racial/ethnic diversity of MESA. The observed sex and race variation in the distribution of SDNN and rMSSD values demonstrate a need for future studies to account for these differences when reporting HRV measures obtained from 10-second ECG tracings.

Our findings also demonstrate that important prognostic information is obtained from HRV measures on 10-second ECG recordings, and these findings are consistent with several reports. Data from the Action to Control Cardiovascular Risk in Diabetes trial showed that SDNN values in the lowest quartile (<7.185 ms) combined with prolonged QT intervals were associated with an increased risk for cardiovascular and all-cause mortalities in patients with type 2 diabetes [2]. A report from the Diabetes Prevention Program study found that increased SDNN over time was associated with a reduced risk of diabetes [3]. Both low and high rMSSD values also were associated with an increased risk for all-cause mortality in 3,245 patients with chronic kidney disease from the Chronic Renal Insufficiency Cohort study [4]. Additionally, reduced HRV (rMSSD <8 ms) was associated with an increased risk of coronary heart disease mortality in the Women's Health Initiative study [5].

The aforementioned findings demonstrate a utility for reduced HRV (e.g., SDNN and rMSSD) obtained from 10-second ECG recordings in the prediction of adverse events. However, these reports did not use cut-off points to define abnormal HRV that were obtained from healthy populations. In lieu of normative ranges, the lowest quartile of each measure was commonly used to define abnormal HRV. Nonetheless, these reports demonstrate that reduced HRV from 10-second ECG tracings predicts adverse events. Although longer recordings are preferred [1], a recent report has shown that 10-second ECG tracings provide accurate assessments of SDNN and rMSSD compared with 4- and 5-minute recordings [13].

Overall, the findings of the current study confirm that reduced HRV on the 10-second ECG is an important marker with regards to CVD risk assessment and provide researchers with reference ranges to identify persons who have underlying cardiac autonomic neuropathy.

This study should be interpreted in the context of certain limitations. The reported reference ranges were derived in a healthy cohort of individuals aged 45 years and older, and therefore, may not be applicable to younger populations. Also, automatic measurements of SDNN and rMSSD were obtained from resting ECGs and we did not validate these measurements. Nevertheless, the GE Marquette 12-SL program used in MESA is an FDA approved software for ECG interpretation, and the results obtained in this report are presumably valid. Therefore, we feel that validating the measurements would be beyond the scope of this paper. Furthermore, we validated the prognostic significance of the reference ranges provided and acknowledge that our multivariable models possibly were incomplete similar to other epidemiological reports.

In conclusion, we provide the sex- and race-specific reference ranges for two time-domain HRV measures obtained from the 10-second ECG in a healthy subset of the MESA cohort. Additionally, reduced HRV, as defined by SDNN and rMSSD, was as independent predictor of adverse events. The references ranges provided in this report will guide future research projects using these common time-domain HRV parameters and allow for comparability between future epidemiological studies.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

FUNDING

This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from NCRR.

DISCLOSURES

Dr. Nazarian is principal investigator for research funds awarded to Johns Hopkins University from Biosence Webster Inc and is also a consultant to Biosense Webster, St Jude Medical, CardioSolv, and Spectranetics.

REFERENCES

1. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996; 17:354–381. [PubMed: 8737210]
2. Pop-Busui R, Evans GW, Gerstein HC, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010; 33:1578–1584. [PubMed: 20215456]
3. Carnethon MR, Prineas RJ, Temprosa M, et al. The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. Diabetes Care. 2006; 29:914–919. [PubMed: 16567837]

4. Drawz PE, Babineau DC, Brecklin C, et al. Heart rate variability is a predictor of mortality in chronic kidney disease: a report from the CRIC Study. Am J Nephrol. 2013; 38:517–528. [PubMed: 24356377]
5. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006; 113:473–480. [PubMed: 16449726]
6. Nunan D, Sandercock GR, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. Pacing Clin Electrophysiol. 2010; 33:1407–1417. [PubMed: 20663071]
7. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]
8. Prineas, RJ.; Crow, RS.; Blackburn, HW. The Minnesota code manual of electrocardiographic findings : standards and procedures for measurement and classification. Boston, Mass: J. Wright; 1982.
9. Schroeder EB, Whitsel EA, Evans GW, Prineas RJ, Chambless LE, Heiss G. Repeatability of heart rate variability measures. J Electrocardiol. 2004; 37:163–172. [PubMed: 15286929]
10. Devereux RB, Casale PN, Eisenberg RR, Miller DH, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy using echocardiographic determination of left ventricular mass as the reference standard. Comparison of standard criteria, computer diagnosis and physician interpretation. J Am Coll Cardiol. 1984; 3:82–87. [PubMed: 6228571]
11. Bluemke DA, Kronmal RA, Lima JA, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol. 2008; 52:2148–2155. [PubMed: 19095132]
12. Soliman EZ, Alonso A, Misialek JR, et al. Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). J Electrocardiol. 2013; 46:702–706. [PubMed: 23806475]
13. Munoz ML, van Roon A, Riese H, et al. Validity of (Ultra-)Short Recordings for Heart Rate Variability Measurements. PLoS One. 2015; 10:e0138921. [PubMed: 26414314]

HIGHLIGHTS

- We defined the normative ranges of heart rate variability (HRV) measures (SDNN and rMSSD) obtained from the 10-second ECG in a sample of participants from the Multi-Ethnic Study of Atherosclerosis (MESA) ≥45 years of age without cardiovascular disease (CVD) or CVD risk factors.
- Borderline abnormal and abnormal values for SDNN and rMSSD were found to vary by sex and race.
- Borderline abnormal and abnormal values for SDNN and rMSSD were significantly associated with CVD events and all-cause mortality in the entire MESA cohort.

Table 1

Baseline Characteristics (N=1,175)

Characteristic	All participants (n=1,175)	White (n=554)	Chinese-American (n=227)	Black (n=189)	Hispanic (n=205)
Age, mean±SD, years	59±10	60±10	57±9.8	58±10	58±10
45–64 years (%)	817 (70)	366 (66)	170 (75)	132 (70)	149 (73)
65–84 years (%)	358 (30)	188 (34)	57 (25)	57 (30)	56 (27)
Male (%)	477 (41)	213 (38)	90 (40)	82 (43)	92 (45)
Body mass index, mean±SD, kg/m^2	25±3.0	25±2.8	23±2.7	26±2.9	26±2.7
Fasting glucose, mg/dL	86±9.3	84±8.9	89±9.9	86±8.7	87±9.1
Systolic blood pressure, mean±SD, mm Hg	112±13	112±13	112±14	115±13	112±13
Diastolic blood pressure, mean±SD, mm Hg	68±8.7	67±8.7	68±8.7	71±7.9	68±8.5
Total cholesterol, mean±SD, mg/dL	189±25	191±25	187±24	185±26	189±25
HDL cholesterol, mean±SD, mg/dL	58±14	60±15	55±11	60±15	53±11
LDL cholesterol, mean±SD, mg/dL	113±24	113±24	111±23	111±25	116±23
Triglycerides, mean±SD, mg/dL	92±37	91±36	101±39	74±29	99±38
Heart rate, mean±SD, bpm	62±8.3	61±8.4	63±7.8	61±8.2	63±8.5

bpm=beats per minute; HDL=high-density lipoprotein; LDL=low-density lipoprotein; SD=standard deviation.

Table 2

Sex- and Race-Specific Ranges for SDNN and rMSSD (N=1,175)

		All Participants	White		Chinese		Black		Hispanic	
			Men (n=213)	Women (n=341)	Men (n=90)	Women (n=137)	Men (n=82)	Women (n=107)	Men (n=92)	Women (n=113)
SDNN (ms)	Mean±SD	24.1±16.4	22.5±12.0	24.3±14.6	21.7±12.6	21.5±12.6	29.2±22.1	25.8±16.8	21.6±12.7	27.9±27.9
	Borderline Abnormal	8.2	8.0	8.5	8.5	7.6	9.8	9.0	6.1	7.9
	Abnormal	6.1	6.3	6.0	5.1	6.5	5.2	6.5	4.3	6.7
rMSSD (ms)	Mean±SD	27.3±22.2	23.8±13.1	27.6±20.2	24.1±16.0	24.4±14.6	33.6±33.3	31.9±22.0	24.4±16.8	32.7±39.0
	Borderline Abnormal	8.0	8.0	9.0	9.0	9.0	11.0	10.0	6.0	9.0
	Abnormal	6.0	6.0	6.0	6.0	7.0	5.0	8.0	5.0	8.0

*Borderline abnormal and abnormal values defined as <5th and <2nd percentiles for the sex- and race-specific references ranges, respectively.

SD=standard deviation; SDNN=standard deviation of all normal-to-normal R-R intervals; rMSSD=root mean square of successive differences between normal-to-normal R-R intervals.

J Electrocardiol. Author manuscript; available in PMC 2017 September 01.

Table 3

Baseline Characteristics in Validation Cohort (N=6,332)

Characteristic	All participants (n=6,332)	SDNN*		rMSSD*	
		Borderline Abnormal (n=494)	Abnormal (n=198)	Borderline Abnormal (n=478)	Abnormal (n=170)
Age, mean±SD, years	62±10	67±9.4	68±9.4	66±9.7	66±10
Male (%)	2,944 (46)	243 (49)	82 (41)	227 (47)	60 (35)
Race/Ethnicity					
White (%)	2,410 (38)	200 (40)	89 (45)	197 (41)	60 (35)
Chinese-American (%)	767 (12)	68 (14)	19 (10)	61 (13)	17 (10)
Black (%)	1,727 (27)	137 (27)	44 (22)	136 (28)	41 (24)
Hispanic (%)	1,428 (23)	92 (19)	46 (23)	84 (18)	52 (31)
Education, high school or less (%)	2,315 (37)	211 (43)	91 (46)	198 (41)	80 (47)
Income, <$20,000 (%)	1,688 (27)	171 (35)	78 (39)	165 (35)	73 (43)
Ever smoker (%)	3,136 (50)	251 (51)	95 (48)	240 (50)	69 (41)
Diabetes (%)	889 (14)	143 (29)	65 (33)	134 (28)	54 (32)
Body mass index, mean±SD, kg/m^2	28±5.5	29±5.9	29±6.3	29±5.9	29±6.3
Systolic blood pressure, mean±SD, mm Hg	126±21	133±21	135±23	132±21	134±23
Total cholesterol, mean±SD, mg/dL	194±36	194±37	193±34	195±37	194±35
HDL cholesterol, mean±SD, mg/dL	51±15	51±15	51±15	51±15	52±15
Antihypertensive medications (%)	2,312 (37)	245 (50)	111 (56)	234 (49)	90 (53)
Aspirin (%)	1,470 (23)	152 (31)	67 (34)	149 (31)	54 (32)
Statin (%)	927 (15)	99 (20)	46 (23)	89 (19)	31 (18)
Left ventricular hypertrophy (%)	237 (3.7)	27 (5.5)	11 (5.6)	22 (4.6)	13 (7.7)

*Borderline abnormal and abnormal values defined as <5th and <2nd percentiles for the sex- and race-specific references ranges, respectively.

HDL=high-density lipoprotein; LDL=low-density lipoprotein; SD=standard deviation.

Table 4

Association of Borderline Abnormal and Abnormal SDNN and rMSSD with Incident CVD and All-Cause Mortality (N=6,332)

Outcome	Measure	Category*	Model 1† HR (95%CI)	P-value	Model 2‡ HR (95%CI)	P-value
Cardiovascular Disease	SDNN	Borderline Abnormal	1.55 (1.18, 2.04)	0.0015	1.37 (1.04, 1.80)	0.025
		Abnormal	1.99 (1.39, 2.87)	0.0002	1.64 (1.14, 2.37)	0.0083
	rMSSD	Borderline Abnormal	1.53 (1.16, 2.03)	0.0027	1.34 (1.01, 1.77)	0.043
		Abnormal	1.81 (1.20, 2.74)	0.0049	1.57 (1.04, 2.39)	0.034
All-Cause Mortality	SDNN	Borderline Abnormal	1.54 (1.27, 1.89)	<0.0001	1.48 (1.22, 1.81)	0.0001
		Abnormal	1.89 (1.44, 2.47)	<0.0001	1.78 (1.35, 2.33)	<0.0001
	rMSSD	Borderline Abnormal	1.43 (1.16, 1.77)	0.0007	1.37 (1.11, 1.69)	0.0038
		Abnormal	1.59 (1.16, 2.18)	0.0043	1.53 (1.11, 2.11)	0.0087

*Borderline abnormal and abnormal values defined as <5th and <2nd percentiles for the sex- and race-specific references ranges, respectively.

†Adjusted for age, sex, race/ethnicity, income, and education.

‡Adjusted for Model 1 covariates plus systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, body mass index, smoking, diabetes, antihypertensive medications, statins, aspirin, and left ventricular hypertrophy.

CVD=cardiovascular disease; SDNN=standard deviation of all normal-to-normal R-R intervals; rMSSD=root mean square of successive differences between normal-to-normal R-R intervals.