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Heart Rate Variability and Cognitive Function In Middle-Age Adults: The Coronary Artery Risk Development in Young Adults

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BACKGROUND
Low heart rate variability (HRV), a marker of cardiac autonomic dysfunction, has been associated with major risk factors of cognitive impairment. Yet, the direct association of HRV with cognitive function remains relatively unexplored, particularly in midlife.

METHODS
In 2005, 2 measures of short-term HRV, the SD of normal-to-normal intervals (SDNN) and the root mean square of successive differences (RMSSD), were calculated for participants of the Coronary Artery Risk Development in Young Adults study, and then categorized into quartiles. Five years later, 3 cognitive tests were administered for verbal memory ("Rey Auditory-Verbal Learning Test", RAVLT, range 0–15), processing speed ("Digit Symbol Substitution Test", DSST, range 0–133), and executive function ("Stroop interference").

RESULTS
Two thousand one hundred and eighteen participants (57.7% female, 42.2% Black) with a mean baseline age of 45.3 years were included in this analysis. In demographic-adjusted models, compared to participants with quartile 1 SDNN (lowest quartile), participants in the upper quartiles of SDNN scored better on the DSST (quartile 4: $\beta = 1.83$ points better, $P = 0.03$; and quartile 3: $\beta = 1.95$ points better, $P = 0.03$) and on the stroop (quartile 3: $\beta = 1.19$ points better, $P < 0.05$; and quartile2: $\beta = 1.44$ points better, $P = 0.02$). After adjusting for behavioral and cardiovascular risk factors, higher quartile SDNN remained significantly associated with better stroop score (quartile 3: $\beta = 1.21$ points better, $P = 0.04$; and quartile 2: $\beta = 1.72$ points better, $P < 0.01$) but not with DSST. There was no association between quartile of RMSSD and cognitive function, from fully adjusted models.

CONCLUSIONS
Our findings suggest that higher quartile SDDN is associated with better executive function in midlife, above, and beyond cardiovascular risk factors.

Keywords: Aging; autonomic function; blood pressure; cognition; epidemiology; heart rate variability; hypertension.

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Heart rate variability (HRV) represents beat-to-beat alterations in normal sinus rhythm, and results from the interaction between sympathetic and parasympathetic activity of the autonomic nervous system. HRV is widely used as a noninvasive measure to quantitatively assess cardiovascular autonomic function.[1,2] Low HRV is significantly associated with cardiovascular events and mortality.[3–6] Reduced HRV has also been shown to be associated with major risk factors for worse cognitive function, including hypertension,[7–9] diabetes,[10,11] depression,[12] and subclinical inflammation.[13] In spite of that, the direct association between HRV and cognitive function remains relatively unexplored.

Most prior work has explored the relationship of HRV and cognitive function cross-sectionally and among older adults.[2,14–18] Findings from the Irish Longitudinal Study on Aging (mean age = 61.7 years) have shown a cross-sectional association between HRV (measured using SD of the normal-to-normal interval (SDNN) and frequency domain features) and performance on the Montreal Cognitive Assessment (MOCA), a test of global cognitive function.[15] Other findings from the Sacramento Area Latino Study on Aging, a cohort of older adult Mexican Americans (mean age = 75.6 years), have shown a cross-sectional association between HRV (measured by the mean circular resultant) and performance on the Modified Mini Mental State Exam, a test of global cognition.[18] Furthermore, recent findings from the Prospective study of Pravastatin in the Elderly at Risk (PROSPER, mean age = 75.0 years) have shown cross-sectional and longitudinal associations between HRV (measured by SDNN) and executive function and processing speed.[17] While it is becoming

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increasingly clear that maintaining cognitive health is a lifelong process,[19,20] the relationship of HRV with cognitive function in a cohort early in the life course remains relatively unexplored.

The aim of our present study was to evaluate the association between short-term HRV, using 10-second 12-lead electrocardiogram, and cognitive performance on multiple tests in a large and biracial cohort of middle-aged adults who are members of the Coronary Artery Risk Development in Young Adults study. We hypothesized that HRV will be associated with cognitive function, especially on tests of processing speed and executive function. Identifying easy noninvasive measures that may provide clues to subclinical mechanisms of development of cognitive impairment could have important clinical implications for more targeted screening to delay the progression of cognitive impairment.

METHODS

Study population

A total of 5,115 adults aged 18 to 30 years old at baseline in 1985–86 were recruited into the Coronary Artery Risk Development in Young Adults study (CARDIA) from 4 field centers: the University of Alabama at Birmingham (Birmingham, AL), the University of Minnesota (Minneapolis, MN), Northwestern University (Chicago, IL), and Kaiser Permanente (Oakland, CA). Recruitment was balanced within center by sex, age, and education. Standardized questionnaires were used to gather sociodemographic. Details of the study have been described elsewhere.[21] HRV was assessed in year 2005 (our study baseline) and cognitive function was assessed 5 years later in 2010. In year 2005, a total of 3,549 participants were present, and of these a total of 2,404 participants had codable electrocardiography (ECGs). HRV in milliseconds was calculated according to the current guidelines limiting the analysis to participants on sinus rhythm with no evidence of arrhythmias (e.g., atrial fibrillation, frequent atrial or ventricular ectopic beats, etc.); thus, those with arrhythmias did not have HRV measurement.[1] Of these 2,404 participants with codable ECGs, we further excluded 286 subjects who had missing cognitive battery in 2010, resulting in a final analytical sample of 2,118 participants (shown later Figure 1). Those included vs. excluded from the final analytical sample were significantly older, more likely to be white and female (data not shown). Appropriate informed consent was obtained from study participants, and the study was approved by the institutional review boards from each field center and the coordinating center.

MEASURES

Assessment of HRV

In 2005 (our study baseline), digital resting 10-second 12-lead electrocardiograms (ECG) were obtained for CARDIA participants by trained technicians using a GE MAC 1200 electrocardiograph according to standardized procedures. Details of the ECGs has been described elsewhere.[22] ECG tracings were transmitted electronically to the CARDIA ECG Reading Center located at the Epidemiology Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston-Salem, NC. The study ECGs were automatically processed, after visual inspection for technical errors and quality, using the 2011 version of the GE Marquette 12-SL program (GE, Milwaukee, WI).

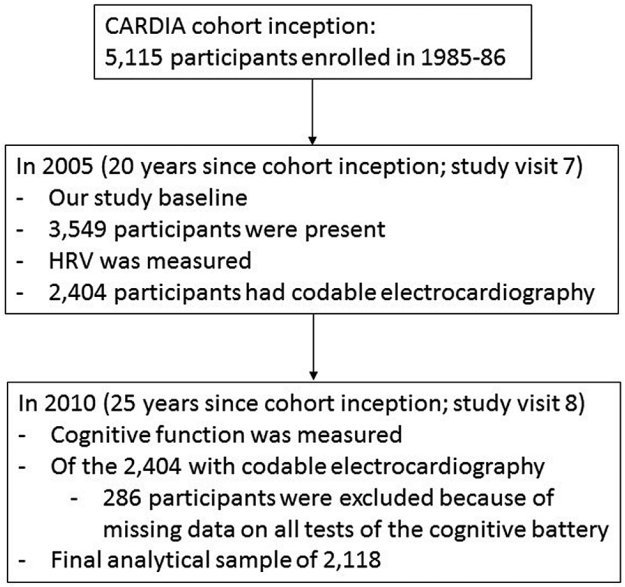

Figure 1. Study sample flow chart.

Briefly, HRV is the change in the time of consecutive heart beats; with a heart beat measured as the time between the peak of one *R* wave to the peak of the next, also referred as the R–R interval. Changes in the length of the normal R–R interval are what define HRV. Two-time domain measures of HRV, the SDNN, and the root mean square of successive differences (RMSSD) were automatically calculated from the individual durations between normal R–R intervals. SDNN represents overall or total variability and thus joint sympathetic and parasympathetic modulation of HRV, whereas RMSSD represents high-frequency variations in the heart rate and thus primarily reflects the parasympathetic modulation of HRV.[1] Higher SDNN and RMSSD indicate better autonomic function.

Assessment of cognitive function

In 2010, all CARDIA participants were administered a cognitive battery that included 3 cognitive tests. The "Rey Auditory-Verbal Learning Test" (RAVLT, range 0–15) measures verbal memory and assesses the ability to memorize and retrieve words, with higher score (in words) indicating better performance.[23] The "Digit Symbol Substitution Test" (DSST, range 0–133) is a subtest of the Wechsler Adult Intelligence Scale and measures performance on speed test, with higher score (in symbols) indicating better performance.[24] The interference score on the "Stroop" test (executive skills) measures the additional amount of processing needed to respond to one stimulus while suppressing another. The test was scored by seconds to spell out color words printed in a different color plus number of errors, thus lower score (seconds + errors) indicates better performance.[25]

Other measures

CARDIA participants reported their sex, race, and years of education completed. Participants reported their current smoking status (never, former, current), and also reported the amount of time per week spent in 13 categories of physical activity over the past year, and then the total amount in exercise units was calculated. Body mass index (kg/m^2) was calculated using measured weight and height. Systolic blood pressure (mm Hg) and diastolic blood pressure (mm Hg) were measured while seated and after a 5-minute rest using a standard automated blood pressure measurement monitor. Three measurements were taken and the last 2 were averaged. Use of antihypertension medications was self-reported. Type-2 diabetes was ascertained based on fasting glucose levels ≥126 mg/dl, self-report of oral hypoglycemic medications or insulin, a 2-hour postload glucose ≥200 mg/dl, or a glycated hemoglobin A_{1c} ≥6.5%. Participants reported their history of stroke/TIA and myocardial infarction. Symptoms of depression were assessed using the 20-item Center for Epidemiologic Studies Depression Scale (range 0–60).[26]

Statistical analysis

There are no established clinical thresholds for the categorization of HRV. Consistent with other studies,[2,14–18] we found that the relationship between indicators of HRV and cognition was nonlinear. Thus, for ease of interpretation, we used quartiles of HRV (SDDN and RMSSD). First, we compared the distribution of important covariates across quartiles of HRV and compared whether the values of those covariates significantly differed from that of quartile 1 (reference category) (Table 1). This analysis uses baseline covariates that were assessed at the same study visit as HRV. Then, to examine the associations of HRV with cognitive function, we fit linear regression models in which quartile 1 HRV (lowest quartile) was set as the reference category (Table 2). First, we fit an unadjusted model, then we fit a demographic-adjusted model in which we added baseline age, sex, race, and education. Finally, we fit a fully adjusted model in which we additionally adjusted for baseline behavioral and cardiovascular disease risk factors including current smoking status, body mass index, physical activity, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, diabetes, MI, stroke/TIA, and depressive symptoms. Adjustment for covariates was based on a priori literature addressing the relationship of HRV and cognitive function, as well as the association of these covariates with HRV and cognition. Using the fully adjusted linear regression model estimates, we showed the predicted mean cognitive scores across quartiles of HRV (Figure 2). To examine whether the association of HRV with cognitive function varied by race or sex, we included appropriate interaction terms in the regression models; there were no significant interactions. All analyses were performed with SAS version 9.3. Significance testing was 2-sided with 5% significance level.

RESULTS

The correlation between the 2 measures of HRV, SDNN, and RMSSD, was 0.85. Quartile 1 SDNN (lowest quartile) ranged from 2.6 ms to 17.4 ms, Q2 ranged from 17.4 ms to 26.6 ms, Q3 ranged from 26.6 ms to 40.7 ms, and Q4 (highest quartile) ranged from 40.7 ms to 194.6 ms. Quartile 1 RMSSD (lowest quartile) ranged from 2.2 ms to 17.8 ms, Q2 ranged from 17.8 ms to 27.4 ms, Q3 ranged from 27.4 ms to 41.9 ms, and Q4 ranged from 42.0 ms to 269.1 ms.

In our cohort of 2,118 participants, those with higher quartile HRV—whether SDNN or RMSSD—were younger, had lower mean body mass index, lower mean systolic and diastolic blood pressure, and lower prevalence of comorbidities such as diabetes and lower depressive symptoms score, compared with participants with quartile 1 HRV (Table 1).

Table 2 shows the multivariable associations between quartiles HRV and cognitive function. As compared with participants with quartile 1 SDNN (i.e., lowest SDNN), participants with higher quartile SDNN scored better on processing speed (DSST) in the unadjusted model (quartile 4: β = 3.69 points better, 95% confidence interval (CI) = 1.76, 5.63; quartile 3: β = 3.11 points better, 95% CI = 1.17, 5.04;

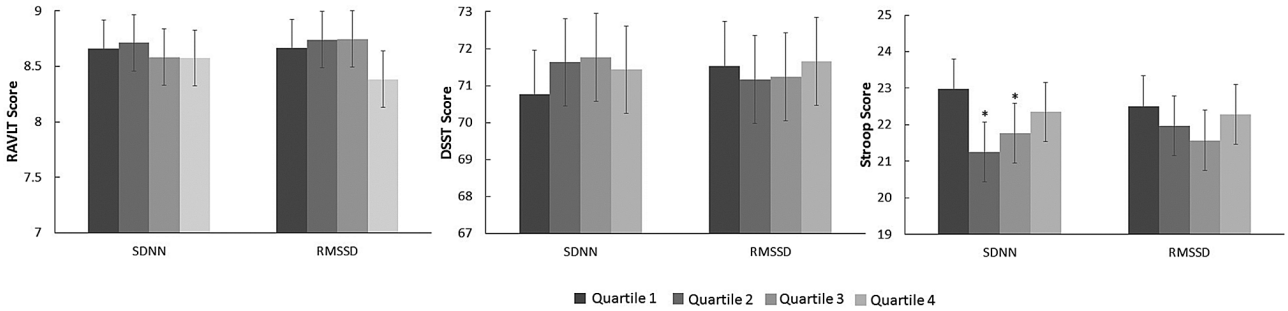

Figure 2. Predicted mean cognitive score by HRV, from fully adjusted linear regression models. Results are adjusted for age, sex, race, education, smoking status, body mass index, physical activity, depressive symptoms score, systolic blood pressure, diastolic blood pressure, diabetes, myocardial infarction, stroke/TIA, and antihypertensive medication use. Higher RAVLT and DSST score indicates better performance, and lower Stroop score indicates better performance. SDNN quartiles: Q1 (lowest quartile SDNN): 2.6 ms to 17.4 ms; Q2: 17.4 ms to 26.6 ms; Q3: 26.6 ms to 40.7 ms; Q4 (highest quartile SDNN): 40.7 ms to 194.6 ms. RMSSD quartiles: Q1 (lowest quartile RMSSD): 2.2 ms to 17.8 ms; Q2: 17.8 ms to 27.4 ms; Q3: 27.4 ms to 41.9 ms; Q4 (highest quartile RMSSD): 42.0 ms to 269.1 ms. *P < 0.05 vs. quartile 1. Abbreviation: HRV, heart rate variability.

Table 1. Distribution of baseline sample characteristics by quartiles of heart rate variability

	SDNN quartile, ms[a]				RMSSD quartile, ms[a]			
	Q1 *n* = 529	Q2 *n* = 530	Q3 *n* = 530	Q4 *n* = 529	Q1 *n* = 529	Q2 *n* = 530	Q3 *n* = 530	Q4 *n* = 529
Age, years, mean (SD)	45.7 (3.5)	45.3[b] (3.6)	45.4 (3.5)	44.9[b] (3.6)	45.6 (3.5)	45.8 (3.4)	45.0[b] (3.6)	44.9[b] (3.6)
Sex, % female, *n* (%)	291 (55.0%)	313 (59.1%)	309 (58.3%)	309 (58.4%)	253 (47.8%)	314 (59.3%[b])	292 (55.1%)	340 (64.3%[b])
Race, % White, *n* (%)	290 (54.8%)	313 (59.1%)	230 (43.4%)	208 (39.3%)	317 (59.9%)	318 (60.0%)	299 (56.4%)	290 (54.8%)
Education, years, mean (SD)	15.0 (2.6)	15.3 (2.5)	15.2 (2.6)	15.3[b] (2.6)	15.0 (2.6)	15.3 (2.6)	15.2 (2.6)	15.1 (2.6)
BMI, kg/m^2, mean (SD)	30.1 (8.2)	29.3 (6.5)	28.8[b] (6.8)	28.5[b] (6.1)	30.4 (8.2)	28.7[b] (6.3)	28.7[b] (6.4)	28.9[b] (2.6)
Physical activity, mean (SD)	310.3 (272.0)	353.4[b] (276.5)	366.9[b] (285.7)	359.1[b] (268.1)	304.9 (262.2)	351.3[b] (280.7)	371.5[b] (282.2)	362.0[b] (275.7)
Smoking, % current, *n* (%)	112 (21.2%)	77 (14.5%[b])	83 (15.7%[b])	79 (14.9%[b])	109 (20.6)	76 (14.3%[b])	87 (16.4%)	79 (14.9%[b])
MI, *n* (%)	4 (0.8%)	2 (0.4%)	4 (0.8%)	2 (0.4%)	4 (0.8%)	3 (0.6%)	4 (0.8%)	1 (0.2%)
Stroke/TIA, *n* (%)	4 (0.8%)	5 (0.9%)	8 (1.5%)	2 (0.4%)	4 (0.8%)	3 (0.6%)	7 (1.3%)	5 (1.0%)
Diabetes, *n* (%)	94 (17.8%)	73 (13.8%)	50 (9.4%[b])	59 (11.2%[b])	100 (18.9%)	61 (11.5%[b])	56 (10.6%[b])	59 (11.2%[b])
SBP, mm Hg, mean (SD)	116.2 (15.4)	114.9 (13.2)	114.3[b] (14.3)	113.5[b] (14.5)	116.5 (14.5)	114.8 (14.8)	114.3[b] (13.4)	113.2[b] (14.6)
DBP, mm Hg, mean (SD)	73.1 (11.4)	71.7[b] (10.7)	70.9[b] (10.6)	69.7[b] (10.8)	73.6 (10.8)	71.4[b] (11.0)	70.8[b] (10.3)	69.6[b] (11.2)
CESD score, mean (SD)	10.2 (8.1)	9.1[b] (7.9)	8.3[b] (7.0)	8.4[b] (7.8)	10.5 (8.5)	8.6[b] (7.4)	8.5[b] (7.3)	8.3[b] (7.5)
Antihypertensive medication, n (%)	105 (19.9%)	86 (16.2%)	76 (14.3%[b])	67 (12.7%[b])	110 (20.8%)	82 (15.5%[b])	65 (12.3%[b])	77 (14.6%[b])
SDNN, ms, mean (SD)	12.3 (3.5)	21.9[b] (2.7)	32.9[b] (4.0)	62.8[b] (23.0)	14.3 (6.4)	23.9[b] (8.5)	33.1[b] (11.7)	58.6[b] (25.8)
RMSD, ms, mean (SD)	14.2 (5.5)	24.7[b] (7.5)	35.1[b] (12.6)	61.7[b] (31.8)	12.5 (3.6)	22.6[b] (2.8)	33.9[b] (4.1)	66.8[b] (28.3)

Physical activity is measured in exercise units. Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; DBP, diastolic blood pressure; MI, myocardial infarction; RMSSD, root mean square of the successive differences in normal R–R intervals; SBP, systolic blood pressure; SDNN, SD of all normal R–R intervals.

[a]SDNN Q1 (lowest quartile): 2.6 ms to 17.4 ms; Q2: 17.4 ms to 26.6 ms, Q3: 26.6 ms to 40.7 ms, Q4: 40.7 ms to 194.6 ms. RMSSD Q1 (lowest quartile): 2.2 ms to 17.8 ms; Q2: 17.8 ms to 27.4 ms; Q3: 27.4 ms to 41.9 ms, Q4: 42.0 ms to 269.1 ms.

[b]Value is significantly different than reference category (Q1), $P < 0.05$.

Table 2. Prospective associations between heart rate variability and cognition function from linear regression models

	SDNN[a]				RMSSD[a]			
	β	95% CI	*P* value	R^2	β	95% CI	*P* value	R^2
Rey Auditory-Verbal Learning Test[d]								
Unadjusted								
Q4 vs. Q1	0.33	−0.05, 0.72	0.09		0.01	−0.38, 0.40	0.96	
Q3 vs. Q1	0.16	−0.23, 0.55	0.42	0.2%	0.20	−0.19, 0.59	0.32	0.1%
Q2 vs. Q1	0.35	−0.04, 0.74	0.08		0.27	−0.12, 0.66	0.18	
Demographic-adjusted[b]								
Q4 vs. Q1	0.03	−0.32, 0.39	0.85		−0.13	−0.48, 0.22	0.47	
Q3 vs. Q1	−0.01	−0.36, 0.34	0.96	20.0%	0.13	−0.22, 0.48	0.48	20.1%
Q2 vs. Q1	0.09	−0.26, 0.44	0.62		0.12	−0.23, 0.47	0.50	
Fully-adjusted[c]								
Q4 vs. Q1	−0.09	−0.45, 0.28	0.64		−0.28	−0.65, 0.08	0.13	
Q3 vs. Q1	−0.08	−0.44, 0.28	0.67	20.0%	0.08	−0.29, 0.44	0.67	20.2%
Q2 vs. Q1	0.05	−0.31, 0.41	0.78		0.07	−0.29, 0.44	0.69	
Digit Symbol Substitution Test[d]								
Unadjusted								
Q4 vs. Q1	3.69	1.76, 5.63	<0.01		2.40	0.46, 4.34	0.02	
Q3 vs. Q1	3.11	1.17, 5.04	<0.01	0.8%	1.55	−0.39, 3.49	0.12	0.3%
Q2 vs. Q1	3.21	1.28, 5.13	<0.01		1.43	−0.50, 3.37	0.15	
Demographic-adjusted[b]								
Q4 vs. Q1	1.83	0.14, 3.51	0.03		1.71	0.02, 3.40	<0.01	
Q3 vs. Q1	1.95	0.27, 3.64	0.03	25.2%	0.77	−0.91, 2.45	0.37	25.1%
Q2 vs. Q1	1.49	−0.19, 3.17	0.08		0.62	−1.06, 2.29	0.47	
Fully-adjusted[c]								
Q4 vs. Q1	0.68	−1.02, 2.37	0.44		0.13	−1.58, 1.85	0.88	
Q3 vs. Q1	1.00	−0.70, 2.70	0.25	28.7%	−0.28	−1.99, 1.42	0.74	28.7%
Q2 vs. Q1	0.87	−0.81, 2.56	0.31		−0.35	−2.05, 1.35	0.69	
Stroop Interference[d]								
Unadjusted								
Q4 vs. Q1	−1.66	−2.93, −0.40	0.01		−0.33	−1.60, 0.94	0.61	
Q3 vs. Q1	−1.62	−2.89, −0.36	0.01	0.6%	−1.23	−2.50, 0.04	0.06	0.2%
Q2 vs. Q1	−2.13	−3.39, −0.87	<0.01		−0.89	−2.16, 0.38	0.17	
Demographic-adjusted[b]								
Q4 vs. Q1	−0.79	−1.97, 0.39	0.19		−0.46	−1.64, 0.72	0.45	
Q3 vs. Q1	−1.19	−2.36, −0.01	<0.05	15.1%	−1.05	−2.22, 0.13	0.08	15.0%
Q2 vs. Q1	−1.44	−2.62, −0.27	0.02		−0.82	−1.99, 0.36	0.17	
Fully-adjusted[c]								
Q4 vs. Q1	−0.62	−1.79, 0.55	0.30		−0.23	−1.41, 0.96	0.71	
Q3 vs. Q1	−1.21	−2.38, −0.04	0.04	18.7%	−0.93	−2.11, 0.24	0.12	18.4%
Q2 vs. Q1	−1.72	−2.89, −0.56	<0.01		−0.54	−1.72, 0.62	0.36	

[a]SDNN quartiles: Q1 (lowest quartile): 2.6 ms to 17.4 ms; Q2: 17.4 ms to 26.6 ms; Q3: 26.6 ms to 40.7 ms; Q4: 40.7 ms to 194.6 ms. RMSSD quartiles: Q1 (lowest quartile): 2.2 ms to 17.8 ms; Q2: 17.8 ms to 27.4 ms; Q3: 27.4 ms to 41.9 ms; Q4: 42.0 ms to 269.1 ms. β denotes raw regression coefficient.

[b]Adjusted for age, sex, race, and education.

[c]Additionally adjusted for smoking status, BMI, physical activity, depressive symptoms score, systolic blood pressure, diastolic blood pressure, diabetes, myocardial infarction, stroke/TIA, and antihypertensive medication use.

[d]Higher scores on the RAVLT and the DSST indicate better performance; lower score on the Stroop indicates better performance.

and quartile 2: β = 3.21 points better, 95% CI = 1.28, 5.13) and in the demographic-adjusted model (quartile 4: β = 1.83 points better, 95% CI = 0.14, 3.51; quartile 3: β = 1.95 points better, 95% CI = 0.27, 3.64). The association between SDNN and processing speed became nonsignificant after we additionally adjusted for behavioral and cardiovascular disease risk factors in the fully adjusted models. Furthermore, as compared with participants with quartile 1 SDNN, participants with higher quartile SDNN scored better on executive function (Stroop interference) in the unadjusted model (quartile 4: β = 1.66 points better, 95% CI = −2.93, −0.40; quartile 3: β = 1.62 points better, 95% CI = −2.89, −0.36; and quartile 2: β = 2.13 points better, 95% CI = −3.39, −0.87) and in the demographic-adjusted model (quartile 3: β = 1.19 points better, 95% CI = −2.36, −0.01; and quartile 2: β = 1.44 points better, 95% CI: −2.62, −0.27). The association between SDNN and executive function remained significant after we additionally adjusted for behavioral and cardiovascular disease risk factors (compared to quartile 1, quartile 3: β = 1.21 points better, 95% CI = −2.38, −0.04; and quartile 2: β = 1.72 points better, 95% CI = −2.89, −0.56). There was no association between quartiles of SDNN and verbal memory. Similarly, there were no associations between quartiles of RMSSD and any of the cognitive tests.

Figure 2 displays predicted mean cognitive scores across quartiles of HRV based on the model estimates of the fully adjusted linear regression models. While there seems to be a U shaped association between SDNN quartile and mean cognitive score, the effect estimate for quartile 4 was not statistically different from that of quartiles 2 and 3.

DISCUSSION

In this study, we examined the association between HRV and cognitive function assessed 5 years later among middle-aged adults of the CARDIA cohort. Our findings showed that higher quartile SDNN was significantly associated with better performance on executive function and processing speed, but not with verbal memory from demographic-adjusted models. When we further adjusted for behavioral and cardiovascular risk factors, higher quartile SDNN remained significantly associated with better executive function.

There are several potential mechanisms through which HRV may influence brain structure and function. The sympathetic and parasympathetic activity interact to maintain blood pressure within a normal range and regulate proper perfusion to the brain.[7,8,27] Failure to do so, resulting in higher blood pressure variability, has been associated with cognitive impairment,[28,29] and with structural brain changes related to hypertension, including cerebral white matter lesions,[30] and to stroke, including lacunar infarctions.[31] Furthermore, depressive symptoms[12,32] and cardiovascular disease risk factors[33] such as type-2 diabetes[10,11] and hypertension[7–9,34] have been associated with both lower HRV and worse cognitive function. As such, it has been suggested that cardiovascular disease risk factors might play a role in the association of HRV with cognitive function. However, our findings showed that SDNN was significantly associated with executive function, above and beyond major cardiovascular disease risk factors. As it remains unclear whether low HRV is a consequence of cardiovascular disease risk factors or whether low HRV is actually an indicator for future underlying disease mechanisms and comorbidities,[4] we adjusted for prevalent cardiovascular disease risk factors (Table 2, Figure 2); however, we did not adjust for incident events as these are hypothesized to be on the pathway between HRV and cognition.

We found that better executive function was associated with higher quartile SDNN, which accounts for the joint sympathetic and parasympathetic activity, but not RMSSD, which only reflects parasympathetic activity. Because SDNN may reflect the joint sympathetic and parasympathetic activity, these findings could represent autonomic regulation of the baroreceptor reflex which controls blood pressure, and which has been associated with cerebral small vessel disease and cognitive function.[28–31] A measure of just the parasympathetic activity, as in RMSSD, may not capture this phenomenon, since both branches of the autonomic nervous system act simultaneously.

The association observed between HRV and cognitive function on tests of processing speed and executive function is not surprising, since vascular risk factors influence performance on processing speed and executive function to a greater extent, and are not necessarily related to memory.[35] It has been suggested that HRV is associated with neuronal activity of the prefrontal cortex of the brain which in turn regulates executive function.[36]

Most prior work on the relationship between HRV and cognitive function was cross-sectional and has focused on cohorts of older adults. To our knowledge, our study is the first to examine such associations earlier in the life course. Our findings were consistent with some of these studies, including results from the Irish Longitudinal Study on Aging,[15] the Sacramento Area Latino Study on Aging,[18] and the Prospective study of Pravastatin in the Elderly at Risk (PROSPER).[17] In particular, our findings were in accordance with those in PROSPER showing significant cross-sectional associations between SDNN and executive function (stroop test), and no association with memory function (measuring immediate and delayed memory recall). However, our findings were not consistent with other studies[14,16] such as the Whitehall II cohort study which showed no associations between HRV and performance on several cognitive tests, including tests of memory (word recall test), vocabulary, phonemic, and semantic fluency functions.[14]

Our study has limitations that are worth noting. While our study design is prospective in nature, with a 5 year lag between HRV and cognitive function measurement, our measures of both HRV and cognitive function were not repeated longitudinally. Cognitive function was not administered at baseline (year 20) and as such we could not rule out the possibility that HRV is a consequence of cognitive function or ongoing brain changes. Further, despite study attrition, any resulting bias would likely lead to more conservative estimates as attrition was unrelated to HRV; mean RMSD and SDNN scores at baseline were statistically equivalent among those included vs. excluded 5 years later. We also acknowledge that the cognitive test battery

is limited: for example, we did not have any visuospatial tasks or language tests, we also had just one measure of verbal memory and one measure of executive function, and our DSST measure has properties of processing speed and executive function. In future studies, it is important to have more comprehensive batteries assessing cognitive domains with multiple tests. While HRV is a reliable measure of autonomic function for use in population-based studies, short-term HRV measures determined from ECGs are not as well correlated with the longer 5- and 10-minute measures.[37] However, a recent study has validated the prognostic significance of 10-second ECG.[38] Furthermore, because SDNN is an overall measure of autonomic function, future research using methods to ascertain only sympathetic function are warranted. Use of antihypertensive medication was self-reported; however, this has been shown to be fairly accurate according to the literature.[39] We realize that polypharmacy and the use of medications other than antihypertensive medication are important aspects, however, are not addressed within the scope of the current analysis. In future studies, it is important to assess more the role of medications and individual categories. In a sensitivity analysis, we excluded 52 participants who reported using beta-blocking agents; our findings and conclusions remained similar. Given the multiple predictors and cognitive tasks, we conducted multiple testing and our associations remained significant. Finally, while we adjusted for potential confounders, we cannot rule out the possibility of residual confounding in the observed associations.

Despite these limitations, this study has significant strengths that contribute to a sparse existing literature on the relationship between HRV and cognitive function. This is among the few studies to our knowledge to have examined the association between HRV and cognitive function among middle-age adults (mean age of 45.3 years). The nature of the study design enabled us to examine the associations prospectively—as cognitive function was assessed 5 year later than HRV. Furthermore, unlike the vast majority of the literature that included small sample sizes and patient or clinical samples, our data come from a large and ongoing biracial cohort of middle-aged adults which enabled us to test for race and sex interactions. Our study included a rich collection of well-established risk factors of cognitive function such as behavioral and cardiovascular disease risk factors. Finally, unlike long-term ECG recordings, our 10-second ECG recording is less time-consuming and more easily amenable to translation to clinical settings. Subjects with low HRV or taking medications which may lower their HRV should be followed closely as they may be vulnerable to HRV-related cognitive deficit.

In conclusion, our findings showed an association between HRV and executive function in an ongoing cohort of middle-age adults, and our findings were independent of cardiovascular risk factors. Furthermore, although the associations were of modest magnitude, the fact that they were observed as early as middle age provides a potential opportunity for preventive strategies, early in the life course, to delay the progression of cognitive impairment. Future studies are needed to explore underlying pathways including brain imaging studies.

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DISCLOSURE

The authors declared no conflict of interest.

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