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ORIGINAL RESEARCH

Association of Heart Rate Variability With Cognitive Performance: The Multi-Ethnic Study of Atherosclerosis

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BACKGROUND: Heart rate variability (HRV) is associated with vascular risk factors for dementia, but whether HRV is associated with specific domains of cognitive performance is unclear.

METHODS AND RESULTS: In the Multi-Ethnic Study of Atherosclerosis (N=3018; mean age 59.3±9.2 years), we assessed the relationship of 10-second HRV to scores on tests of global cognitive performance (Cognitive Abilities Screening Instrument), processing speed (Digit Symbol Coding), and working memory (Digit Span). HRV was computed as the SD of normal-normal intervals (SDNN) and root mean square of successive differences (RMSSD) at Exam 1 (2000–2002) and Exam 5 (2010–2012). Cognitive tests were administered at Exam 5. We report regression coefficients (β [95% CI]) representing cognitive test score change per 2-fold increase in HRV. After adjustment for age, race/ethnicity, sex, education, apolipoprotein E genotype, and cardiovascular risk factors and incident disease, higher Exam 1 (β=0.37 [0.06, 0.67]) and Exam 5 (β=0.31 [0.04, 0.59]) SDNN were associated with better Cognitive Abilities Screening Instrument performance. Higher Exam 1 (β=0.80 [0.17, 1.43]) and Exam 5 (β=0.63 [0.06, 1.20]) SDNN, and Exam 5 RMSSD (β=0.54 [0.01, 1.08]) were associated with better Digit Symbol Coding performance. Finally, higher Exam 5 SDNN was associated with better Digit Span performance (β=0.17 [0.01, 0.33]). Associations were attenuated after adjustment for resting heart rate.

CONCLUSIONS: Higher HRV is generally associated with better cognitive performance in this multi-ethnic cohort of aging adults, and further study of the relationship of autonomic function to cognition is warranted.

Key Words: aging ■ autonomic nervous system ■ cognitive performance ■ heart rate variability

Age-related neurocognitive disorders, including mild cognitive impairment and dementia, share mid-life risk factors with cardiovascular diseases.[1,2] The relationship between cardiac autonomic function and cognition is not as well explored despite the association of autonomic dysfunction with increased cardiovascular morbidity and mortality,[3] abnormal prefrontal cortical activity,[4] and reduced regional cerebral blood flow.[5] Moreover, autonomic dysfunction may be present in most forms of dementia, at times before the onset of clinical symptoms.[6,7]

Heart rate variability (HRV) is the beat-to-beat fluctuation in normal sinus rhythm arising from the interaction between the sympathetic and parasympathetic divisions of the autonomic nervous system. HRV computed from ECG or continuous blood pressure monitoring is used as a standard index of cardiac autonomic function, with lower HRV indicating worse function.[8] Although HRV gradually declines with age, accelerated reduction in HRV is an indicator of autonomic dysfunction.[9] Lower mid-life HRV is independently associated with future cardiovascular diseases and mortality,[10,11] in addition to major vascular risk factors

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CLINICAL PERSPECTIVE

What Is New?

- In a multi-ethnic cohort of middle-aged and elderly adults free of baseline cardiovascular disease, 10-second heart rate variability measures were prospectively and cross-sectionally associated with performance on tests of global cognitive performance, processing speed, and working memory independent of age, race/ethnicity, sex, education, apolipoprotein E genotype, cardiovascular risk factors, and incident disease, but not resting heart rate.
- Longitudinal change in heart rate variability over 10 years was not associated with cognitive performance.

What Are the Clinical Implications?

- Short-term measures of cardiac autonomic function may be correlates of cognitive performance, but longer-duration autonomic measures and the role of resting heart rate should be examined.

Nonstandard Abbreviations and Acronyms

APOE	apolipoprotein E
CASI	Cognitive Abilities Screening Instrument
CESD	Center for Epidemiologic Studies Depression scale
DSC	Digit Symbol Coding
DS	Digit Span
HRV	heart rate variability
MESA	Multi-Ethnic Study of Atherosclerosis
RMSSD	root mean square of successive differences
RHR	resting heart rate
SDNN	standard deviation of normal-normal intervals
TIA	transient ischemic attack

for cognitive decline including hypertension,[12,13] type 2 diabetes mellitus,[14] and obesity.[15]

Whether a direct association exists between cardiac autonomic function and cognitive performance has received increased attention yet remains unclear. Smaller cross-sectional studies have generally reported positive associations between indices of HRV and cognitive performance,[16,17] whereas larger prospective or longitudinal studies in population-based samples have yielded inconsistent results.[18–21] Furthermore, it is unknown whether worsening autonomic function during mid- to late-life could predict worse cognitive performance. Identification of novel vascular biomarkers of cognitive impairment may facilitate an earlier intervention for dementia during the preclinical phase and prevent adverse cardiovascular events that may lead to worse cognition. Therefore, we evaluated cross-sectional and prospective relationships between HRV and cognitive performance in an ethnically diverse cohort of middle-aged and elderly US adults.

METHODS

Requests to access data sets from qualified researchers trained in human subject confidentiality protocols should be made through the MESA (Multi-Ethnic Study of Atherosclerosis) internal site at https://mesa-nhlbi.org.

Study Population

The MESA is an ongoing prospective, population-based cohort study initiated to track the onset and progression of subclinical cardiovascular disease. The enrollment, consent, and phenotyping of MESA participants are described in detail elsewhere.[22] Briefly, 6814 men and women participants were recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN) between July 2000 and September 2002. Participants were aged between 45 and 84 years and free of clinical cardiovascular disease at baseline. Participants provided informed consent and all procedures were approved by the Institutional Review Board of each field center. HRV was computed at MESA Exam 1 (2000–2002) and Exam 5 (2010–2012). Cognitive testing was administered at Exam 5. The present study focuses on the subset of participants with complete HRV data from Exams 1 and 5 and complete and valid cognitive testing. Of 4716 participants who returned for Exam 5, we excluded those with missing (n=566) or invalid/uncompleted (n=92) cognitive testing, missing HRV data from Exam 1 (n=233) or Exam 5 (n=474), missing apolipoprotein E (*APOE*) allele genotyping (n=199), missing incident cardiovascular event follow-up information or covariates from Exam 1 or Exam 5 (n=113), and those taking dementia medication (n=21). Accordingly, the present study includes a total analytic sample of 3018 participants. Excluded participants tended to be older, and more likely to be white and men (not shown).

Measurement of HRV—Exam 1 and Exam 5

HRV was computed using time-domain analysis of 3 consecutive 10-second, 12-lead ECGs obtained by trained technicians using a Marquette MAC 1200

instrument (GE Medical Systems, Milwaukee, WI), as previously described.[23] ECGs were obtained in the fasting state and in the supine position. All ECGs were digitally transmitted to the MESA ECG reading center at Wake Forest School of Medicine (Winston-Salem, NC) and processed using the GE Marquette 12-SL program after visual inspection for technical errors and quality. Tracings with evidence of ectopic beat or arrhythmia, including atrial fibrillation, were automatically excluded from analysis. HRV was quantified from individual durations between normal R-R intervals using 2 time-domain parameters: the SD of normal-normal intervals (SDNN), and the root mean square of successive differences of normal-normal intervals (RMSSD). SDNN is used as an index of global autonomic regulation of the heart and thus represents joint sympathetic and parasympathetic modulation, whereas RMSSD reflects the parasympathetic modulation of heart rate.[8] SDNN and RMSSD values represent the average from the 3 consecutive 10-second ECGs obtained from participants. Change in HRV from Exam 1 to Exam 5 was calculated as Exam 1 values subtracted from Exam 5.

Assessment of Cognitive Performance—Exam 5

Cognitive performance was assessed with a battery that included 3 standardized and validated tests to evaluate performance across different cognitive domains, previously described in detail.[24] The MESA cognitive battery included the Cognitive Abilities Screening Instrument (CASI, version 2), the Digit Symbol Coding test (DSC), and the Digit Span test (DS, forward and backward). The CASI is a test of global cognitive function that contains 25 items representing 9 cognitive domains, including short- and long-term memory, attention, concentration, orientation, language, verbal fluency, visual construction, and abstraction/judgment.[25] Scores from individual items on the CASI were summed to provide an overall cognitive function score (range 0–100). The DSC (range 0–133) and DS forward and backward (range 0–28) are subtests of the Wechsler Adult Intelligence Scale III[26] and measure processing speed and working memory, respectively. Scores on the forward and backward portions of the DS were summed to create a total score used in the present analyses. For each test, a higher score indicates better cognitive performance.

Measurement of Covariates

MESA participants reported their age, race/ethnicity, sex, and education level via standardized questionnaires administered at Exam 1. Participants self-reported their smoking status (never/former or current) and use of antihypertensive medications including alpha blockers, beta blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Resting brachial systolic blood pressure (mm Hg) was measured while seated using a standard automated blood pressure device (Dinamap Monitor Pro 100); 3 measurements were recorded and the average of the second and third used. Body mass index (kg/m^2) was calculated using measured height and weight. Resting heart rate (RHR) was derived from 10-second ECG as part of the automated processing described above. Physical activity was assessed using the Typical Week Physical Activity Survey[27] and defined as the number of MET minutes per week spent doing intentional moderate and vigorous activity. Diabetes mellitus was defined as fasting glucose ≥7 mmol/L (126 mg/dL) or use of hypoglycemic medication. Symptoms of depression were assessed using the Center for Epidemiologic Studies Depression scale (range 0–60), with a cutoff score of ≥16 indicating depression.[28] Carriage of the *APOE* ε4 allele (0 versus 1 or 2 copies), a strong genetic risk factor for cognitive decline[29] and associated with worse HRV,[30] was estimated from single nucleotide polymorphisms rs429358 and rs7412 from the genotyping conducted in all consenting MESA participants, as previously described.[24] Incidence of myocardial infarction, heart failure, and stroke/transient ischemic attack events was assessed by telephone interviews every 6 to 9 months and during MESA examinations.

Statistical Analysis

In preliminary analyses, we found the unadjusted relationship between indices of HRV and cognitive test scores to be broadly linear. Thus, we evaluated associations between Exam 1 and Exam 5 HRV and Exam 5 cognitive test performance using multivariable linear regression. Because of skewed distributions, SDNN and RMSSD values were normalized by log2-transformation when entered into models. Therefore, regression coefficients (β) correspond to the change in cognitive test score per 2-fold increase in HRV. Change in HRV values were standardized but not log2-transformed so that regression coefficients indicate the change in cognitive score per 1 SD increment change in HRV between Exam 1 and Exam 5. Two models were constructed: the first (Model 1) was adjusted for age, race/ethnicity, sex, and education level; the second (Model 2) was additionally adjusted for *APOE* ε4 allele status, cardiovascular risk factors (systolic blood pressure, body mass index, smoking status, physical activity, use of antihypertensive medication, Center for Epidemiologic Studies Depression scale score, and diabetes mellitus), and incident cardiovascular disease including myocardial infarction, heart failure, and stroke/transient ischemic attack. Models with Exam 5 HRV measures included Exam 5 covariates. To examine whether the association of HRV with cognitive performance differed

Table 1. MESA Baseline Sample Characteristics (2000–2002)

N	3018
Age, y, mean (SD)	59.1 (9.2)
Women, n (%)	1657 (54.9)
Race/ethnicity, n (%)	
White	1214 (40.2)
Black	690 (22.9)
Hispanic	730 (24.2)
Chinese-American	384 (12.7)
Education, n (%)	
High school or less	938 (31.1)
Some college	888 (29.4)
Bachelor degree or higher	1192 (39.5)
APOE ε4 allele carriage, n (%)	805 (26.7)
Systolic blood pressure, mm Hg, mean (SD)	123.2 (20.0)
Resting heart rate, bpm, mean (SD)	62.6 (9.0)
Body mass index, kg/m^2, mean (SD)	28.1 (5.3)
Physical activity, MET-min/wk, median (Q1, Q3)	4470.0 (2248.1, 8028.8)
Depression, CESD ≥16, n (%)	341 (11.3)
Smoker, n (%)	384 (12.4)
Hypertension medication, n (%)	
Alpha blockers	99 (3.3)
Angiotensin-converting enzyme inhibitors	327 (10.8)
Angiotensin receptor blockers	130 (4.3)
Beta blockers	247 (8.2)
Calcium channel blockers	306 (10.1)
Diuretics	308 (10.2)
Antiarrhythmic medication, n (%)	7 (0.2)
Diabetes mellitus, n (%)	298 (9.9)
Incident disease, n (%)	
Myocardial infarction	93 (3.1)
Heart failure	64 (2.1)
Stroke/TIA	114 (3.8)
Heart rate variability, ms, median (Q1, Q3)	
Exam 1 SDNN	19.4 (13.3, 27.8)
Exam 5 SDNN	17.6 (11.9, 26.2)
Exam 1 RMSSD	21.0 (14.0, 32.0)
Exam 5 RMSSD	19.7 (13.0, 30.6)
Cognitive test scores (2010–2012), mean (SD)	
CASI	88.2 (8.2)
Digit symbol coding	51.8 (18.3)
Digit span (total)	15.3 (4.6)

APOE indicates apolipoprotein E; CASI, Cognitive Abilities Screening Instrument; CESD, Center for Epidemiological Studies Depression scale; MESA, Multi-Ethnic Study of Atherosclerosis; RMSSD, root mean square of successive differences; SDNN, SD of normal-normal intervals; and TIA, transient ischemic attack.

by sex, race/ethnicity, or *APOE* ε4 allele status, we included respective interaction terms in regression models. As a sensitivity analysis, we imputed missing data for the entire MESA baseline cohort (N=6814) using multiple imputation by chained equations.[31] Results from 20 imputed data sets were combined for valid statistical inference, adjusted for Model 2 covariates as described above. Analyses were performed with JMP Pro version 13.0.0 and SAS version 9.4 software (The SAS Institute, Cary, NC). Significance testing was 2-sided, with $P<0.05$ considered significant.

RESULTS

Baseline characteristics of the study population are summarized in Table 1. The mean age of the 3018 participants was 59.1±9.2 years at baseline and 68.6±9.1 years at cognitive testing; 54.9% were women; 59.8% were non-white; 86.4% completed high school. The *APOE* ε4 allele was carried by 26.7% of the sample. Log2-transformed SDNN and RMSSD were significantly correlated with each other at Exam 1 (Pearson correlation coefficient [r]=0.93, $P<0.001$) and Exam 5 ($r=0.93$, $P<0.001$). Furthermore, RHR at Exam 1 was significantly correlated to log2-transformed SDNN ($r=-0.33$; $P<0.001$) and RMSSD ($r=-0.46$; $P<0.001$). A decline in SDNN from Exam 1 to Exam 5 was experienced by 57.9% of participants; 55.8% experienced a decline in RMSSD. Participants who experienced a decline in SDNN, as a potential marker of worsening cardiac autonomic function, were younger, more likely to be men, more likely to have completed high school, and had lower systolic blood pressure (not shown).

Tables 2 through 4 show the prospective and cross-sectional associations between HRV and Exam 5 cognitive test scores from linear regression models, presented as the regression coefficient (β) of log2-transformed HRV values. Higher Exam 1 and Exam 5 SDNN were significantly associated with better CASI performance after adjustment for age, race/ethnicity, sex, and education level. These associations persisted after further adjustment for baseline cardiovascular and cognitive risk factors and incident disease (Table 2). There were no associations between Exam 1 or Exam 5 RMSSD and CASI score. In contrast, higher SDNN and RMSSD from Exams 1 and 5 were significantly associated with a better DSC score in Model 1 (Table 3). Exam 1 and Exam 5 SDNN and Exam 5 RMSSD remained significantly associated with the DSC after further adjustment for Model 2 covariates. Finally, we found that higher Exam 5 SDNN was significantly associated with better DS performance after Model 2 adjustment (Table 4). Neither measure of longitudinal change in HRV was associated with any cognitive test score. No significant interactions by sex, race/ethnicity, or *APOE* ε4 allele carrier status were found. As a sensitivity analysis, we excluded participants taking beta blocker medication at Exam 1 or Exam 5; results

Table 2. Associations Between Heart Rate Variability and Exam 5 CASI Scores From Linear Regression Models

	Model 1			Model 2		
	β	95% CI	*P* Value	β	95% CI	*P* Value
SDNN						
Exam 1	0.43	0.13–0.73	0.005	0.37	0.06–0.67	0.018
Exam 5	0.39	0.12–0.66	0.005	0.31	0.04–0.59	0.027
Change	−0.06	−0.30–0.19	0.660	−0.07	−0.32–0.17	0.553
RMSSD						
Exam 1	0.25	−0.03–0.52	0.082	0.20	−0.07–0.48	0.150
Exam 5	0.26	0.00–0.52	0.047	0.19	−0.07–0.45	0.143
Change	−0.04	−0.29–0.21	0.768	−0.03	−0.28–0.22	0.803

Model 1 adjusted for age, race, sex, and education level. Model 2 additionally adjusted for systolic blood pressure, Center for Epidemiologic Studies Depression scale score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes mellitus, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/transient ischemic attack. β represents regression coefficients for log2-transformed heart rate variability values. *APOE* indicates apolipoprotein E; CASI, Cognitive Abilities Screening Instrument; CESD, Center for Epidemiological Studies Depression scale; HRV, heart rate variability; RMSSD, root mean square of successive differences; SDNN, SD of normal-normal intervals; and TIA, transient ischemic attack.

remained broadly similar (Table S1). Adjusting for Exam 1 or Exam 5 RHR attenuated associations between HRV and cognitive performance (Table S2). As an independent predictor adjusted for Model 2 covariates, standardized Exam 1 and Exam 5 RHR were significantly associated with performance on the CASI and DSC, but not the DS (Table S3).

Results from a multiple imputation analysis adjusted for Model 2 covariates are shown in Table S4. Associations between HRV measures and performance on the DSC were similar to the primary analysis; however, the association between SDNN and DS performance was attenuated (β=0.14; 95% CI=−0.02, 0.29). The multiple imputation analysis also suggested an association between Exam 5 RMSSD and CASI performance (β=0.34; 95% CI=0.02, 0.65), but only a marginal association between Exam 1 SDNN and the CASI (β=0.35; 95% CI=−0.002, 0.70).

DISCUSSION

In this study, we evaluated prospective and cross-sectional associations between 10-second HRV and cognitive performance in a multi-ethnic cohort of middle-aged and elderly US adults. Our findings indicate that higher antecedent and contemporaneous SDNN, representing global autonomic regulation of the heart, was significantly associated with better performance on the CASI, a test of global cognitive performance. Furthermore, higher antecedent and contemporaneous SDNN and contemporaneous RMSSD, a measure of cardiac parasympathetic activity, were associated with better performance on the DSC, a test of processing speed/executive function. Finally, we found that higher SDNN was cross-sectionally associated with better performance on the DS, a test of working memory. These associations

Table 3. Associations Between Heart Rate Variability and Exam 5 Digit Symbol Coding Scores From Linear Regression Models

	Model 1			Model 2		
	β	95% CI	*P* Value	β	95% CI	*P* Value
SDNN						
Exam 1	1.12	0.48–1.76	<0.001	0.80	0.17–1.43	0.013
Exam 5	1.03	0.45–1.60	<0.001	0.63	0.06–1.20	0.030
Change	−0.22	−0.74–0.30	0.410	−0.25	−0.76–0.26	0.343
RMSSD						
Exam 1	0.72	0.14–1.30	0.015	0.49	−0.08–1.07	0.094
Exam 5	0.85	0.31–1.39	0.002	0.54	0.01–1.08	0.048
Change	−0.14	−0.66–0.38	0.602	−0.16	−0.67–0.35	0.540

Model 1 adjusted for age, race, sex, and education level. Model 2 additionally adjusted for systolic blood pressure, Center for Epidemiological Studies Depression scale score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes mellitus, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/heart rate variability. β represents regression coefficients for log2-transformed HRV values. *APOE* indicates apolipoprotein E; CESD, Center for Epidemiological Studies Depression scale; RMSSD, root mean square of successive differences; SDNN, SD of normal-normal intervals; and TIA, transient ischemic attack.

Table 4. Associations Between Heart Rate Variability and Exam 5 Digit Span (Total) Scores From Linear Regression Models

	Model 1			Model 2		
	β	95% CI	*P* Value	β	95% CI	*P* Value
SDNN						
Exam 1	0.15	−0.02–0.32	0.093	0.09	−0.08–0.27	0.276
Exam 5	0.22	0.06–0.37	0.007	0.17	0.01–0.33	0.034
Change	0.07	−0.07–0.21	0.330	0.08	−0.06–0.22	0.272
RMSSD						
Exam 1	0.13	−0.03–0.29	0.108	0.08	−0.08–0.24	0.336
Exam 5	0.14	−0.01–0.29	0.068	0.11	−0.04–0.26	0.160
Change	0.07	−0.07–0.22	0.325	0.09	−0.05–0.24	0.201

Model 1 adjusted for age, race, sex, and education level. Model 2 additionally adjusted for systolic blood pressure, Center for Epidemiological Studies Depression scale score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes mellitus, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/ transient ischemic attack. β represents regression coefficients for log2-transformed HRV values. *APOE* indicates apolipoprotein E; CESD, Center for Epidemiological Studies Depression scale; RMSSD, root mean square of successive differences; SDNN, SD of normal-normal intervals; and TIA, transient ischemic attack.

were not independent of RHR, which was inversely associated with the CASI and DSC. Collectively, these results broadly support the hypothesis that short-term indices of worse cardiac autonomic function may be associated with worse performance in specific cognitive domains including global cognitive performance, processing speed, and working memory, but mechanisms underlying these associations require further elucidation with more sensitive and specific measures of autonomic activity.

Our findings are consistent with some previous epidemiologic studies of autonomic function and cognitive performance. For example, results from the Irish Longitudinal Study on Ageing showed a cross-sectional association between lower quintiles of SDNN and worse performance on the Montreal Cognitive Assessment,[19] a test of global cognitive performance. In the Sacramento Area Latino Study on Aging, HRV measured as the mean circular resultant was cross-sectionally associated with performance on the Mini-Mental State Examination in elderly Mexican-Americans.[32] Notably, our findings are in agreement with those from the Prospective Study of Pravastatin in the Elderly at Risk which showed that lower 10-second SDNN at baseline was associated with worse processing speed indexed by the Letter-Digit Coding test, but not with immediate or delayed memory recall in an older cohort of adults (mean age=75.0 years) at high risk for cardiovascular diseases.[20] Our results differed from the Coronary Artery Risk Development in Young Adults study, which found no relationship between 10-second SDNN and performance on the Digit Symbol Substitution test after adjustment for cardiovascular risk factors, possibly because of the younger age of participants (mean age=45.3 years).[21] In addition, the Whitehall II study cohort showed no consistent cross-sectional or longitudinal associations between HRV and cognitive performance in men and women aged ≈55 years at baseline cognitive testing.[18] However, this study assessed different cognitive domains than the current, including short-term verbal memory, reasoning, vocabulary, and phonemic and semantic fluency. Furthermore, Whitehall II is composed of individuals in stable civil service white-collar jobs at baseline, unlike the multi-ethnic MESA cohort which consists of participants across the socioeconomic spectrum. Differences in study samples and in the cognitive domains explored may account for general inconsistency in the literature on HRV and cognition.

A previous study reported that vascular risk factors are more strongly related to processing speed than to memory.[33] In contrast, we found that SDNN was cross-sectionally associated with the DS (forward and backward) test after adjusting for age, race/ethnicity, sex, and education level, and this association persisted after further adjustment for risk factors and disease. We did not observe consistent associations between RMSSD and cognitive performance; only Exam 5 RMSSD was marginally associated with performance on the DSC. Unlike SDNN, which represents joint sympathetic and parasympathetic regulation, RMSSD primarily reflects parasympathetic activity mediated by the vagus nerve.[8] Therefore, it is possible that global cognitive performance and working memory are in part a reflection of the sympathetic and parasympathetic nervous systems acting simultaneously.

Several mechanisms may link HRV to cognitive performance. The autonomic nervous system regulates important cardiovascular functions including the maintenance of blood pressure within a normal range to sustain adequate cerebral perfusion.[34] Reduced HRV is associated with poor baroreflex sensitivity, increased blood pressure variability, and orthostatic hypotension,[35,36] which could contribute

to cerebral hypoperfusion.[37] Increased blood pressure variability is also associated with structural brain changes related to hypertension and stroke, including white matter lesions and lacunar infarctions.[38,39] Given that the brain is at risk of suboptimal perfusion during fluctuations in blood pressure[40] and greater blood pressure variability may lead to microvascular damage,[41] it is plausible that reduced HRV may affect cognitive performance through mechanisms related to blood pressure dysregulation. Indeed, dysfunction of the baroreceptor reflex has been associated with cerebrovascular disease and worse cognitive function.[42,43]

Neurodegenerative changes during dementia may also influence cardiac autonomic function via altered autonomic pathways in the insular cortex and brainstem.[44,45] For example, insular lesions are associated with cardiac arrhythmias, reduced HRV, and increased cardiac mortality.[46] Alzheimer disease pathology exhibits a hierarchical progression that includes the insular cortex and brainstem during the preclinical stage of the disease before a dementia diagnosis can be made.[47] Therefore, disruption to central autonomic nuclei secondary to preclinical Alzheimer pathology is a possible explanation for reduced cardiac autonomic function in non-demented elderly persons, suggesting that autonomic dysfunction may be an additional manifestation of early dementia-related neurodegenerative changes.[7]

Mid-life risk factors for cardiovascular disease such as hypertension and type 2 diabetes mellitus are proposed to be important precipitants to cognitive decline[1,2] and are associated with reduced HRV.[12,14] Substantial evidence suggests that reduced HRV may precede these risk factors,[3,48] establishing clinical utility for low HRV as a potential non-invasive preclinical marker for cardiovascular disease and cognitive decline. Reduced HRV is also associated with future cardiovascular events,[10] which may result in cognitive impairment.[33] This suggests that cardiovascular risk factors and disease may mediate the association between HRV and cognitive performance. We found that associations between HRV and cognitive performance persisted after adjustment for cardiovascular risk factors and incident disease, demonstrating that these factors do not account for the observed associations. Additional adjustment for RHR attenuated these associations, while higher RHR itself was significantly associated with lower CASI and DSC performance. A possible explanation for this is that like HRV, RHR reflects a balance of the sympathetic and parasympathetic nervous systems. Thus, adjustment for RHR may remove meaningful variance in outcomes of interest that can be attributed to autonomic phenomena.[49] Despite the contribution of the autonomic nervous system to RHR, it should not be considered a surrogate for HRV based on the independent influence of vagal activity over HRV (see de Geus et al[49] for review). The main goal of using HRV metrics is to draw more specific inferences about cardiac autonomic activity than can be derived from RHR alone.

Study Limitations

Our study has several limitations that should be considered. Cognitive testing was not conducted at MESA Exam 1 so we were unable to assess the association of change in cognitive performance with HRV. The MESA cognitive test battery was not a comprehensive assessment of cognitive function; the DS test captures working memory performance but not other dimensions of memory (eg, delayed recall, which is among the memory domains most affected by Alzheimer disease[50]), so the relationship between HRV and memory should be studied further.

A key limitation is the 10-second duration of ECG recordings which does not allow the evaluation of more sensitive frequency domain measures of HRV. Guidelines for the measurement of HRV recommend obtaining ECG recordings of at least several minutes in length,[8] whereas the HRV indices in MESA were computed from 3 consecutive 10-second ECGs. The repeatability of 10-second HRV is lower compared with HRV derived from 5- and 10-minute recordings but was found to improve considerably when using the mean from 2 or 3 records,[51] as performed in MESA. In addition, 10-second HRV measures correlated strongly with values obtained from 6-minute ECG (Pearson *r* coefficients were 0.76 for SDNN and 0.82 for RMSSD).[51] Furthermore, the prognostic validity of 10-second HRV has been demonstrated with respect to incident cardiovascular disease within MESA.[23] Thus, 10-second ECG may have the advantage of being less time-consuming and easier to apply in clinical settings while providing comparable predictive value. Nevertheless, future studies should take advantage of emerging technology enabling long-term ambulatory ECG recordings,[52] which would better capture autonomic function in real-world settings.

Selection bias and selective attrition are also potential concerns because of the 10-year gap between baseline and Exam 5 HRV measurements. We attempted to mitigate these biases via multiple imputation, which revealed a weaker cross-sectional association between SDNN and performance on the DS, and suggested a cross-sectional association between RMSSD and the CASI. Therefore, interpretation of results warrants caution. We further caution that we did not account for multiple comparisons. However, these results and the results of other epidemiologic studies on HRV and cognition suggest the presence of associations that may generate new hypotheses about the relationship of the autonomic nervous system to cognitive performance.

Finally, despite adjusting our regression models for demographic and cardiovascular covariates and *APOE* ε4 allele carriage, we cannot discount the possibility of residual confounding. For example, analyses did not include all incident diseases that may be in the causal pathway between HRV and cognitive performance, such as atrial fibrillation. Strengths of our study include a large, multi-ethnic sample with detailed vascular phenotyping, antecedent and contemporaneous measures of 2 indices of HRV allowing the study of prospective and cross-sectional associations, and 3 cognitive tests to assess performance across multiple cognitive domains.

CONCLUSIONS

Our findings reveal that higher HRV may be associated with better global cognitive performance, processing speed, and working memory independent of cardiovascular risk factors and disease. These associations were observed in a multi-ethnic cohort of middle-aged and elderly adults free of cardiovascular disease at baseline, and were consistent across racial/ethnic groups. While consideration should be given to RHR as a mediator or reflection of cardiac autonomic activity, our findings generally support the use of autonomic metrics as correlates of future and contemporaneous cognitive performance. Identifying novel early correlates for cognitive performance provides an opportunity to improve targeted strategies to prevent or slow cognitive decline during the middle- and late-life period. Future studies are needed to examine the association between longer-duration autonomic measures and change in cognitive performance over time, and to elucidate underlying brain pathways connecting autonomic function to cognitive performance.

ARTICLE INFORMATION

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Disclosures

None.

Supporting Materials

Tables S1 to S4

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SUPPLEMENTAL MATERIAL

Table S1. Associations between heart rate variability and Exam 5 CASI scores from linear regression models after excluding participants taking beta blocker medication at Exam 1 (n = 247) or Exam 5 (n = 535).

	CASI			Digit Symbol Coding			Digit Span (total)		
	β	95% CI	*P* value	*β*	95% CI	*P* value	*β*	95% CI	*P* value
SDNN									
Exam 1	**0.36**	**0.05, 0.68**	**0.025**	**0.94**	**0.28, 1.60**	**0.005**	0.11	-0.07, 0.30	0.237
Exam 5	**0.34**	**0.04, 0.65**	**0.029**	**0.71**	**0.07, 1.34**	**0.030**	0.15	-0.03, 0.32	0.107
Change	-0.01	-0.27, 0.24	0.920	-0.27	-0.80, 0.27	0.328	0.10	-0.05, 0.25	0.178
RMSSD									
Exam 1	0.18	-0.11, 0.47	0.219	**0.61**	**0.00, 1.12**	**0.049**	0.09	-0.08, 0.26	0.294
Exam 5	0.23	-0.06, 0.52	0.114	**0.64**	**0.04, 1.23**	**0.037**	0.07	-0.10, 0.24	0.413
Change	0.03	-0.23, 0.29	0.830	-0.15	-0.70, 0.40	0.591	0.12	-0.03, 0.27	0.125

β represents regression coefficients for $\log_2$-transformed HRV values adjusted for age, race/ethnicity, sex, education level, systolic blood pressure, CESD score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/TIA.

CASI: Cognitive Abilities Screening Instrument; CESD: Center for Epidemiological Studies Depression scale; CI: confidence interval; RMSSD: root mean square of successive differences; SDNN: standard deviation of normal-normal intervals; TIA: transient ischemic attack.

Table S2. Associations between heart rate variability and Exam 5 cognitive test scores from linear regression models adjusted for Model 2 covariates and RHR.

	CASI			Digit Symbol Coding			Digit Span (total)		
	β	95% CI	*P* value	β	95% CI	*P* value	β	95% CI	*P* value
SDNN									
Exam 1	0.29	-0.04, 0.61	0.085	0.44	-0.23, 1.12	0.199	0.05	-0.13, 0.24	0.582
Exam 5	0.16	-0.14, 0.45	0.298	0.22	-0.39, 0.83	0.478	0.16	-0.01, 0.33	0.066
Change	-0.02	-0.27, 0.23	0.864	-0.17	-0.68, 0.34	0.518	0.09	-0.05, 0.23	0.214
RMSSD									
Exam 1	0.07	-0.25, 0.39	0.667	-0.04	-0.70, 0.62	0.898	0.02	-0.17, 0.20	0.854
Exam 5	-0.02	-0.31, 0.27	0.869	0.01	-0.59, 0.61	0.982	0.08	-0.09, 0.25	0.321
Change	0.00	-0.25, 0.25	0.982	-0.04	-0.56, 0.48	0.875	0.11	-0.03, 0.25	0.135

β represents regression coefficients for $\log_2$-transformed HRV values adjusted for age, race/ethnicity, sex, education level, RHR, systolic blood pressure, CESD score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/TIA.

CASI: Cognitive Abilities Screening Instrument; CESD: Center for Epidemiological Studies Depression scale; CI: confidence interval; RHR: resting heart rate; RMSSD: root mean square of successive differences; SDNN: standard deviation of normal-normal intervals; TIA: transient ischemic attack.

Table S3. Associations between RHR and Exam 5 cognitive test scores from linear regression models.

	CASI			Digit Symbol Coding			Digit Span (total)		
	β	95% CI	*P* value	*β*	95% CI	*P* value	*β*	95% CI	*P* value
Exam 1	**-0.29**	**-0.55, -0.03**	**0.029**	**-1.01**	**-1.55, -0.47**	**<0.001**	-0.13	-0.28, 0.02	0.100
Exam 5	**-0.48**	**-0.75, -0.21**	**<0.001**	**-1.22**	**-1.78, -0.66**	**<0.001**	-0.09	-0.26, 0.07	0.256
Change	-0.25	-0.51, 0.02	0.074	-0.30	-0.86, 0.26	0.290	0.03	-0.13, 0.18	0.733

β represents regression coefficients for standardized RHR values adjusted for age, race/ethnicity, sex, education level, systolic blood pressure, CESD score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/TIA.

CESD: Center for Epidemiological Studies Depression scale; CI: confidence interval; RHR: resting heart rate; RMSSD: root mean square of successive differences; SDNN: standard deviation of normal-normal intervals; TIA: transient ischemic attack.

Table S4. Associations between heart rate variability and Exam 5 CASI scores from linear regression models after multiple imputation (N = 6,814).

	CASI			Digit Symbol Coding			Digit Span (total)		
	β	95% CI	*P* value	*β*	95% CI	*P* value	*β*	95% CI	*P* value
SDNN									
Exam 1	0.35	-0.00, 0.70	0.051	**0.62**	**0.14, 1.11**	**0.012**	0.08	-0.06, 0.23	0.268
Exam 5	**0.43**	**0.08, 0.78**	**0.016**	**0.79**	**0.21, 1.37**	**0.009**	0.14	-0.02, 0.29	0.084
Change	0.10	-0.19, 0.39	0.505	0.02	-0.47, 0.50	0.942	0.04	-0.07, 0.16	0.442
RMSSD									
Exam 1	0.23	-0.08, 0.54	0.144	0.30	-0.14, 0.74	0.185	0.06	-0.07, 0.20	0.351
Exam 5	**0.34**	**0.02, 0.65**	**0.038**	**0.67**	**0.15, 1.19**	**0.012**	0.10	-0.03, 0.23	0.134
Change	0.09	-0.18, 0.37	0.504	0.11	-0.35, 0.57	0.641	0.06	-0.05, 0.16	0.288

β represents regression coefficients for $\log_2$-transformed HRV values adjusted for age, race/ethnicity, sex, education level, systolic blood pressure, CESD score, smoking status, body mass index, physical activity, antihypertensive and antiarrhythmic medication use, diabetes, *APOE* genotype, and incident myocardial infarction, heart failure, and stroke/TIA.

CASI: Cognitive Abilities Screening Instrument; CESD: Center for Epidemiological Studies Depression scale; CI: confidence interval; RMSSD: root mean square of successive differences; SDNN: standard deviation of normal-normal intervals; TIA: transient ischemic attack.