ORIGINAL RESEARCH

Apolipoprotein E Genotype Modifies the Association Between Cardiac Output and Cognition in Older Adults

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***Background*—**Subtle reductions in cardiac output relate to lower cerebral blood flow, especially in regions where Alzheimer's disease pathology first develops. Apolipoprotein E (*APOE*)-ε4 is a genetic susceptibility risk factor for Alzheimer's disease that also moderates vascular damage. This study investigated whether *APOE*-ε4 carrier status modifies the cross-sectional association between cardiac output and cognition.

***Methods and Results*—**Vanderbilt Memory & Aging Project participants free of clinical stroke and dementia (n=306, 73±7 years, 42% female) underwent echocardiography to determine cardiac output (L/min), comprehensive neuropsychological assessment, and venous blood draw to determine *APOE* genotype and ε4 carrier status. Linear regressions related cardiac output to neuropsychological test performance, adjusting for age, sex, education, race/ethnicity, body surface area, cognitive diagnosis, Framingham Stroke Risk Profile, and *APOE*-ε4 status. Main effect models were null (P>0.19). With identical covariates, models were repeated testing a *cardiac output*×*APOE*-ε4 status interaction and again stratified by ε4 carrier status. *Cardiac output*×*APOE*-ε4 status related to naming (β=0.91, P=0.0009), category fluency (β=1.2, P=0.01), information processing speed (β=−5.4, P=0.001), visuospatial skill (β=0.85, P=0.003), and executive function performances (β=0.22, P=0.002). Stratified models suggested that lower cardiac output was associated with worse neuropsychological performances among *APOE*-ε4 carriers.

Conclusions*—APOE*-ε4 carrier status appears to modify the cross-sectional association between cardiac output and neuropsychological performance such that lower cardiac output relates to poorer performances among carriers of the ε4 allele. These findings add to increasing evidence that *APOE*-ε4 carrier status has important implications for associations between vascular and brain health in aging adults. **(*J Am Heart Assoc*. 2019;8:e011146. DOI: 10.1161/JAHA.118.011146.)**

Key Words: Alzheimer's disease • apolipoprotein E ε4 • cardiac output • cognition • vascular risk factors

The brain receives 12% of cardiac output despite accounting for only 2% of overall body weight,[1] emphasizing that preserved cardiac function is essential to cerebral blood flow delivery and hemodynamic regulation. Subclinical cardiac dysfunction, therefore, may affect brain health, especially among older adults with a lifetime burden of vascular risk factor exposure and damage. Evidence suggests that subtle reductions in cardiac output relate to increased risk of dementia, including clinical Alzheimer's disease (AD), in community-based aging adults.[2]

The apolipoprotein E ε4 allele (*APOE*-ε4) is a genetic susceptibility risk factor for AD. Possession of 1 ε4 allele increases risk of clinical AD 3-fold and both alleles increase risk 12-fold.[3] *APOE*-ε4 is purportedly a moderator of cerebrovascular damage that precedes neuronal dysfunction[4,5] and contributes to blood–brain barrier (BBB) degradation.[6] Additionally, among older adults, *APOE*-ε4 carriers have lower cross-sectional cerebral blood flow (CBF)[7] and greater CBF decline over time than noncarriers.[8] Interestingly, there has been limited investigation into whether *APOE*-ε4 carrier status

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Clinical Perspective

What Is New?

- The present study suggests that among participants with no prior history of clinical stroke or heart failure, cardiac output interacts with apolipoprotein E ε4 carrier status on neuropsychological tests of language, information processing speed, and executive function wherein lower cardiac output levels are associated with worse cognitive performances among carriers of the ε4 allele.

What Are the Clinical Implications?

- Subclinical cardiac dysfunction in the form of lower cardiac output may confer an increased risk of poorer cognitive performance among individuals who are apolipoprotein E ε4 positive, and these study results add to a growing body of evidence that among individuals with genetic susceptibility to Alzheimer's disease, subclinical cardiac dysfunction may result in worse cognition.
- The current study also strengthens the notion that a major pathway by which apolipoprotein E ε4 promotes Alzheimer's disease risk is through vascular etiologies; findings illustrate the importance, among apolipoprotein E ε4 positive individuals, of maintaining healthy cardiovascular integrity to reduce vulnerability to adverse cognitive aging.

modifies the association between subclinical cardiac output and abnormal brain health.[9]

The present study investigates detailed connections between cardiac output and cognition in a cohort of aging adults with normal cognition (NC) or mild cognitive impairment (MCI), a prodromal phase of dementia.[10] We also examine whether the genetic susceptibility risk factor for AD, *APOE*-ε4, moderates the association between cardiac output and cognitive performance. Because *APOE*-ε4 is an effect modifier in the association between cardiovascular and brain health[2,11] and subclinical reductions in cardiac output are associated with increased risk of dementia,[2] we hypothesize that cardiac output and cognitive performance associations will be stronger in ε4 carriers. Next, we test interactions between cardiac output and cognitive diagnosis with the hypothesis that associations will be stronger in participants with MCI who (because of pathological processes underlying their clinical symptoms) likely have diminished CBF compensatory mechanisms.[12] We hypothesize that subclinical cardiac output reductions increase the risk of dementia in *APOE*-ε4 carriers and participants with MCI through progressive declines in episodic memory, information processing speed, and executive function. Episodic memory[13] and the temporal lobes[14] (which support episodic memory functions) are vulnerable to alterations in blood delivery because of compromised cardiovascular function. Plus, both information processing speed and executive function are partially mediated by frontal–subcortical networks[15,16] perfused by small perforating arteries,[17,18] which theoretically are more susceptible to subtle fluctuations in cerebral blood delivery. The present study aims to provide a better understanding of whether subclinical reductions in cardiac output predispose aging adults to unique patterns of cognitive impairment.

Methods

Study Cohort

The Vanderbilt Memory & Aging Project is a longitudinal study investigating vascular health and brain aging, enriched for participants with MCI.[19] Inclusion required that participants be age ≥60 years, speak English, have adequate auditory and visual acuity, and have a reliable study partner. At eligibility, participants underwent medical history and record review, clinical interview (including activities of daily living questionnaire and Clinical Dementia Rating[20] with a loved one), and neuropsychological assessment. Participants were excluded for a cognitive diagnosis other than NC, early MCI,[21] or MCI[10]; magnetic resonance imaging contraindication (eg, ferrous metal in the body or claustrophobia); and history of neurological disease (eg, stroke), heart failure, major psychiatric illness, head injury with loss of consciousness >5 minutes, and systemic or terminal illness affecting longitudinal participation. At enrollment, participants completed a comprehensive evaluation, including (but not limited to) fasting blood draw, physical examination, clinical interview, medication review, neuropsychological assessment, and echocardiogram. Participants were excluded from the current study for missing covariate or neuropsychological data. For this study, given the emphasis on diagnostic interactions, participants with early MCI[21] were excluded for their small sample size. NC was defined as (1) Clinical Dementia Rating=0; (2) no deficits in activities of daily living directly attributable to cognitive impairment; and (3) no evidence of neuropsychological impairment defined as standard scores falling 1.5 SDs within the age-adjusted mean. MCI was defined as (1) Clinical Dementia Rating=0 or 0.5; (2) relatively spared activities of daily living; (3) impairment in at least 1 cognitive domain defined as falling 1.5 SDs outside the age-adjusted mean; (4) concern about a cognitive change by the participant, study partner, or clinician; and (5) absence of a dementing syndrome. See Figure 1 for inclusion and exclusion details.

Standard Protocol Approvals, Registrations, and Participant Consent

The protocol was approved by the Vanderbilt University Medical Center Institutional Review Board. Written informed consent was obtained before data collection. Because of

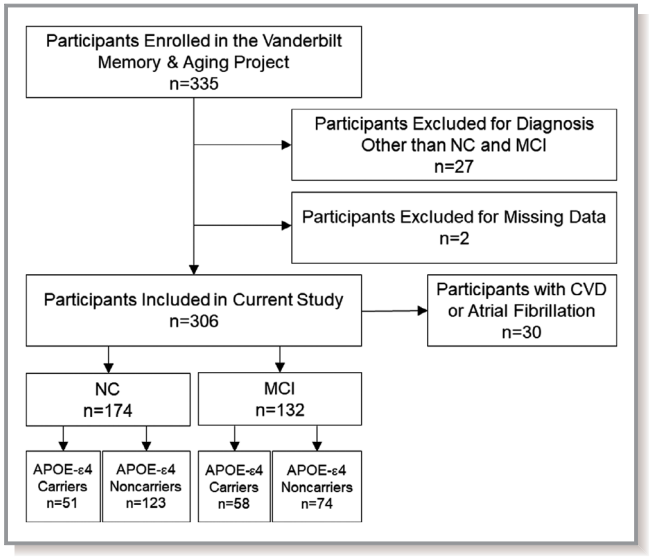

Figure 1. Participant inclusion and exclusion details. Missing data categories are mutually exclusive and included missing at least 1 neuropsychological outcome (n=1) or covariate (n=1). Sensitivity analyses excluded participants with CVD or atrial fibrillation. *APOE*-ε4 indicates apolipoprotein E ε4; CVD, cardiovascular disease; MCI, mild cognitive impairment; NC, normal cognition.

participant consent restrictions in data sharing, a subset of data is available to others for purposes of reproducing the results or replicating procedures. These data, analytical methods, and study materials can be obtained by contacting the corresponding author.

Echocardiogram

A standard 2-dimensional, M-mode, and Doppler transthoracic echocardiogram was performed by a research sonographer on a Philips IE33 cardiac ultrasound machine (Philips Medical, Andover, MD). Using commercially available software (Heartlab; AGFA Healthcare, Greenville, SC), digital images with measurements were confirmed by board-certified cardiologists (D.K.G., L.A.M.) blinded to clinical information. Image acquisition and quantification were performed according to American Society of Echocardiography guidelines.[22] Left ventricular volume was calculated by the biplane Simpson method. Stroke volume was calculated from the left ventricular outflow tract velocity–time integral and diameter. Cardiac output was calculated as stroke volume multiplied by heart rate. Final measurements were taken from a single cycle for participants in normal sinus rhythm or average of 3 cardiac cycles for atrial fibrillation.

APOE Genotyping

As previously published,[19] a TaqMan single-nucleotide polymorphism genotyping assay from Applied Biosystems (Foster City, CA) was applied to determine the 2 single-nucleotide polymorphisms that define the ε2, ε3, and ε4 alleles. Polymerase chain reaction in 5-μL reactions was performed on the Life Technologies 7900HT real-time polymerase chain reaction machine. Results were analyzed using Life Technologies SDS 2.4.1 software.

Neuropsychological Assessment

Participants completed a common, comprehensive neuropsychological protocol assessing language, information processing speed, executive function, visuospatial ability, and episodic memory (Table 1). Measures differed from tests used to screen participants for study inclusion or to determine cognitive diagnosis. To minimize multiple comparisons, *z*-scores were derived separately for composite episodic memory and executive function performances using a latent variable approach as previously described.[13]

Analytical Plan

Covariates were defined as follows: body surface area (m^2) was calculated as $weight^{0.425} \times height^{0.725} \times 0.007184$. Systolic blood pressure was the mean of 2 measurements. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, hemoglobin A1c ≥6.5%, or oral hypoglycemic or insulin medication use. Medication review determined antihypertensive medication use. Left ventricular hypertrophy was defined from echocardiography as left ventricle mass index >115 g/m^2 in men or >95 g/m^2 in women. Self-report atrial fibrillation was corroborated by any 1 of the following sources: echocardiogram, cardiac magnetic resonance imaging, documented prior procedure/ablation for atrial fibrillation, or medication use for atrial fibrillation. Current cigarette smoking (yes/no within the year before baseline) was ascertained by self-report. Self-reported prevalent cardiovascular disease (CVD) with supporting medical record evidence included coronary heart disease, angina, or myocardial infarction (heart failure was a parent study exclusion). Framingham Stroke Risk Profile score was calculated by applying points by sex for age, systolic blood pressure, antihypertensive medication use, diabetes mellitus, current cigarette smoking, left ventricular hypertrophy, CVD, and atrial fibrillation.[23] *APOE*-ε4 carrier status was defined as positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3).

Linear regression models with ordinary least-square estimates related cardiac output to neuropsychological performance (1 test per model), adjusting for age, sex, race/ethnicity, education, body surface area, *APOE*-ε4 status, cognitive diagnosis, and Framingham Stroke Risk Profile (excluding points assigned for age). Models were repeated testing a *cardiac output×APOE-ε4 carrier status*

Table 1. Participant Characteristics

	Total (n=306)	NC (n=174)	MCI (n=132)	*P* Value
Demographic and health characteristics				
Age, y	73±7	72±7	73±8	0.37
Sex, % male	58	59	56	0.58
Race, % non-Hispanic white	87	87	86	0.66
Education, y	16±3	16±2	15±3	<0.001
Montreal Cognitive Assessment, total	25±3	27±2	23±3	<0.001
APOE-ε4, % carrier	36	29	44	0.008
APOE genotype				
ε2/ε2, count	3	3	0	0.13
ε2/ε3, count	37	23	14	0.49
ε2/ε4, count	7	3	4	0.45
ε3/ε3, count	157	97	60	0.07
ε3/ε4, count	84	44	40	0.33
ε4/ε4, count	18	4	14	0.002
Body surface area, m^2	1.9±0.2	1.9±0.2	1.9±0.2	0.51
Framingham Stroke Risk Profile, total†	12±4	12±4	13±4	0.04
Systolic blood pressure, mm Hg	142±18	140±17	145±19	0.02
Antihypertensive medication use, %	55	53	56	0.65
Diabetes mellitus, %	18	16	21	0.25
Cigarette smoking, % current	2	2	3	0.45
Prevalent CVD, %	5	6	3	0.26
Atrial fibrillation, %	6	6	7	0.70
Left ventricular hypertrophy, %	5	3	6	0.28
Cardiac output, L/min	5.0±1.3	5.0±1.3	4.9±1.3	0.58
Neuropsychological performances				
Boston Naming Test (30 Item)	27±3	28±2	25±4	<0.001
Animal Naming	19±6	21±5	16±5	<0.001
DKEFS Number Sequencing Test, s‡	43±20	36±13	51±24	<0.001
WAIS-IV coding	53±13	57±12	46±12	<0.001
Executive Composite	−0.01±0.94	0.43±0.61	−0.60±0.98	<0.001
Hooper Visual Organization Test	24±3	25±2	23±4	<0.001
Memory Composite	0.00±0.98	0.57±0.71	−0.75±0.75	<0.001

Values are denoted as mean±SD or frequency; all neuropsychological performance values are total correct excluding timed tasks measured in seconds. Boston Naming Test was the 30-item odd version. *APOE*-ε4 indicates apolipoprotein E ε4 allele; CVD, cardiovascular disease; DKEFS, Delis-Kaplan Executive Function System; MCI, mild cognitive impairment; NC, normal cognition; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition.

†A modified Framingham Stroke Risk Profile Score was included in statistical models, which excluded points assigned to age (total=6.5±3.2, NC=6.2±3.1, MCI=6.9±3.3).

‡Higher values reflect worse performance.

interaction term followed by stratification by *APOE*-ε4 status, a *cardiac output×diagnosis* interaction term followed by stratification by diagnosis (NC, MCI), and a *cardiac output×sex* interaction term followed by stratification by sex (male, female). To better characterize the effects of *APOE*-ε2, ε3, and ε4, secondary analyses were conducted to test a *cardiac output×APOE genotype* interaction term with *APOE*-ε3/ε3 as the referent group. ANOVA tested the overall interaction effect using identical covariates (see Data S1 for details). Significance was set a priori at $P<0.05$.

Results

Participant Characteristics

Participants included 306 adults (73±7 years, 58% male, 87% self-identified as non-Hispanic white), including 174 with NC and 132 with MCI. At least 1 *APOE*-ε4 allele was present in 36% (n=109) of the cohort, with *APOE*-ε4 allele prevalence higher in the MCI (44%) compared with the NC group (29%), as expected. Cardiac output ranged from 2.0 to 8.7 L/min (5.0±1.3) and did not differ between NC and MCI participants (P=0.58). Of note, 99% of the cohort had preserved cardiac function as defined by left ventricular ejection fraction, which did not differ between NC and MCI participants (P=0.13). As expected, the MCI group performed worse on all neuropsychological measures compared with the NC group (P<0.001). See Table 1 for full details.

Cardiac Output and Neuropsychological Performance

In main effect models, cardiac output was unrelated to all neuropsychological performances (P>0.19). Results were similar in sensitivity models excluding participants with CVD and atrial fibrillation (Table 2). Results did not change when excluding *APOE*-ε4 status as a covariate (P>0.20).

Cardiac Output×APOE-ε4 Carrier Status and Neuropsychological Performance

APOE-ε4 carrier status interacted with cardiac output on Boston Naming Test (β=0.91, P=0.0009), Animal Naming (β=1.2, P=0.01), Number Sequencing (β=−5.4, P=0.001), Hooper Visual Organization Test (β=0.85, P=0.003), and Executive Function Composite performances (β=0.22, P=0.002) (Table 3). For all measures (ie, Boston Naming Test, Animal Naming, Number Sequencing, Hooper Visual Organization Test, and Executive Function Composite), lower cardiac output corresponded to worse neuropsychological performance among *APOE*-ε4 carriers. See Figures 2A through 2E for illustration of stratified results. Results were similar when excluding participants with CVD and atrial fibrillation. In secondary models where *APOE* genotypes were used for categorization into *APOE*-ε4 carriers (ε3/ε4, ε4/ε4), *APOE*-ε2 carriers (ε2/ε2, ε2/ε3), *APOE*-ε3/ε3, and *APOE*-ε2/ε4 (see Tables S1 and S2 for details), results among the *APOE*-ε4 carriers (ε4/ε4, ε3/ε4) were largely consistent with the prior *APOE*-ε4 carrier results (ε4/ε4, ε3/ε4, ε2/ε4). Lower cardiac output was associated with worse Boston Naming Test (β=1.0, P=0.0004), Animal Naming (β=1.3, P=0.007), Number Sequencing (β=−4.7, P=0.009), Hooper Visual Organization Test (β=0.82, P=0.005), and Executive Function Composite performances (β=0.21, P=0.004) among the *APOE*-ε4 carriers (ε3/ε4, ε4/ε4) compared with the referent group (ε3/ε3). In addition to the expected ε4 associations, 2 *APOE*-ε2 genotype interactions emerged whereby lower cardiac output was associated with worse Boston Naming Test (β=0.76, P=0.04) and Hooper Visual Organization Test performances (β=0.75, P=0.048) among the *APOE*-ε2 carriers (ε2/ε2, ε2/ε3) compared with the referent group (ε3/ε3) (Table S3 and Figure S1).

Table 2. Cardiac Output Main Effect Associations With Neuropsychological Performance

	β	95% CI	*P* Value
Boston Naming Test (30 Item)	0.13	−0.15, 0.41	0.35
Animal Naming	−0.09	−0.56, 0.37	0.69
DKEFS Number Sequencing Test*	−0.96	−2.7, 0.78	0.28
WAIS-IV Coding	−0.72	−1.8, 0.36	0.19
Executive Composite	0.001	−0.07, 0.07	0.98
Hooper Visual Organization Test	0.02	−0.27, 0.31	0.90
Memory Composite	0.002	−0.07, 0.07	0.94

Analyses were performed on 306 participants. Models were adjusted for age, sex, race/ethnicity, education, body surface area, *APOE*-ε4 status, cognitive diagnosis, and Framingham Stroke Risk Profile (excluding points assigned for age); neuropsychological performance values are total correct excluding timed tasks measured in seconds. The Boston Naming Test was the 30-item odd version. DKEFS indicates Delis-Kaplan Executive Function System; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition.
*Higher values reflect worse performance.

Cardiac Output×Diagnosis and Neuropsychological Performance

The *cardiac output×diagnosis* term was unrelated to all neuropsychological performances (P>0.18) with similar results in sensitivity analyses excluding participants with CVD and atrial fibrillation. Results were unchanged when excluding *APOE*-ε4 carrier status as a covariate (Table 4).

Cardiac Output×Sex and Neuropsychological Performance

The *cardiac output×sex* term was unrelated to all neuropsychological performances (P>0.12) with similar results in sensitivity analyses excluding participants with CVD and atrial fibrillation (Table S4).

Discussion

This study investigated detailed associations between cardiac output and cognition as well as the impact of *APOE*-ε4 status and cognitive diagnosis on these associations among older

Table 3. Cardiac Output×*APOE*-ε4 Interaction Models and Stratified by *APOE*-ε4 Status

	β	95% CI	*P* Value
APOE-ε4 carriers vs noncarriers			
Boston Naming Test (30 Item)	0.91	0.38, 1.4	0.0009†
Animal Naming	1.2	0.27, 2.1	0.01
DKEFS Number Sequencing Test‡	−5.4	−8.8, −2.1	0.001†
WAIS-IV Coding	1.9	−0.16, 4.0	0.07
Executive Composite	0.22	0.08, 0.36	0.002†
Hooper Visual Organization Test	0.85	0.30, 1.4	0.003†
Memory Composite	0.10	−0.03, 0.24	0.13
APOE-ε4 carriers			
Boston Naming Test (30 Item)	0.66	0.04, 1.3	0.04
Animal Naming	0.69	−0.09, 1.5	0.08
DKEFS Number Sequencing Test‡	−5.5	−9.4, −1.6	0.006†
WAIS-IV Coding	0.68	−1.4, 2.7	0.52
Executive Composite	0.14	0.008, 0.27	0.04
Hooper Visual Organization Test	0.52	−0.09, 1.1	0.09
Memory Composite	0.05	−0.08, 0.18	0.45
APOE-ε4 noncarriers			
Boston Naming Test (30 Item)	−0.08	−0.37, 0.21	0.58
Animal Naming	−0.37	−1.0, 0.21	0.20
DKEFS Number Sequencing Test‡	0.59	−1.2, 2.3	0.51
WAIS-IV Coding	−1.3	−2.5, −0.005	0.05
Executive Composite	−0.04	−0.13, 0.04	0.30
Hooper Visual Organization Test	−0.17	−0.49, 0.14	0.27
Memory Composite	−0.01	−0.09, 0.07	0.80

Analyses performed on 306 participants and subsequently stratified by *APOE*-ε4 status for 109 *APOE*-ε4 positive participants and 197 *APOE*-ε4 negative participants. Models were adjusted for age, sex, race/ethnicity, education, body surface area, cognitive diagnosis, *APOE*-ε4 status, and Framingham Stroke Risk Profile (excluding points assigned for age); neuropsychological performance values are total correct excluding timed tasks measured in seconds. β values for interaction terms represent the difference in β values between *APOE*-ε4 carriers and noncarriers. The Boston Naming Test was the 30-item odd version. *APOE*-ε4 indicates apolipoprotein E ε4 allele; DKEFS, Delis-Kaplan Executive Function System; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition.

†Models that meet the significance threshold after applying a Bonferroni correction for each set of models (ie, 0.05/7 comparisons per hypothesis=0.007).

‡Higher scores reflect worse performance.

adults. While cardiac output was not associated with cognition in main effect models, lower cardiac output was associated with worse cognitive performance among *APOE*-ε4 carriers but not noncarriers. The pattern of results implicated language, information processing speed, and executive function. By contrast, associations between cardiac output and cognition were not significantly different between cognitive diagnosis groups (NC or MCI) or between males and females. Importantly, these findings were observed in an aging cohort free of clinical stroke and heart failure, adjusting for key demographic variables and vascular risk factors.

Our results suggest that *APOE*-ε4 carriers are particularly vulnerable to worse cognitive performance in the context of subclinical reductions in cardiac output. As a robust genetic susceptibility risk factor for AD[24,25] and molecular moderator of vascular damage,[24] the *APOE*-ε4 allele may promote a stronger association between cardiac output and cognitive aging through multiple pathways, such as disruption in autoregulation,[4,26,27] BBB dysfunction,[4] neuroinflammation,[28,29] and oxidative stress.[30–33] The brain has complex autoregulatory mechanisms, including vasodilation,[26,34] to protect it from damaging fluctuations and reductions in blood flow delivery. These mechanisms may be compromised in *APOE*-ε4 carriers.[4] Transgenic *APOE*-ε4 mouse models suggest that *APOE*-ε4 relates to more extensive BBB breakdown because of upregulation of metalloproteinase 9.[4] Vasodilation factors function at the neurovascular unit,[26,27] so damage to the BBB, a core component of the neurovascular unit, may result in a weakened dilatory response and reduced regional CBF.[4] Additionally, among humanized *APOE* targeted-replacement mice, the *APOE*-ε4 allele is associated with elevated brain levels of proinflammatory cytokine tumor necrosis factor alpha,[28] which is upregulated in heart failure[29] and could be modestly upregulated with subclinical cardiac dysfunction. Tumor necrosis factor alpha correlates with brain natriuretic peptide in patients with chronic heart failure,[35] and growing evidence suggests that an association exists between brain natriuretic peptide and cognitive impairment, separate from atherogenic or AD risk factors.[36] Though speculative, taken together, *APOE*-ε4 status may relate to worse cognition in the presence of chronic subclinical cardiac dysfunction by degrading capillary basement membrane and BBB tight-junction proteins through metalloproteinase 9 upregulation.[37,38] Additional burden is likely promoted because of tumor necrosis factor alpha–associated inflammation.

As expected, we found subclinical cardiac output reductions related to information processing speed and executive function in our *APOE*-ε4 carrier status and cardiac output interaction models. These cognitive functions are thought to be mediated by frontal–subcortical networks[15,16] supplied by particularly vulnerable, small perforating arteries.[17,18] It is plausible in the setting of subtle reductions in cardiac output that these structures accumulate burden and subclinical damage throughout midlife with late-life cognitive consequences. This explanation is supported by extensive evidence linking hemodynamic

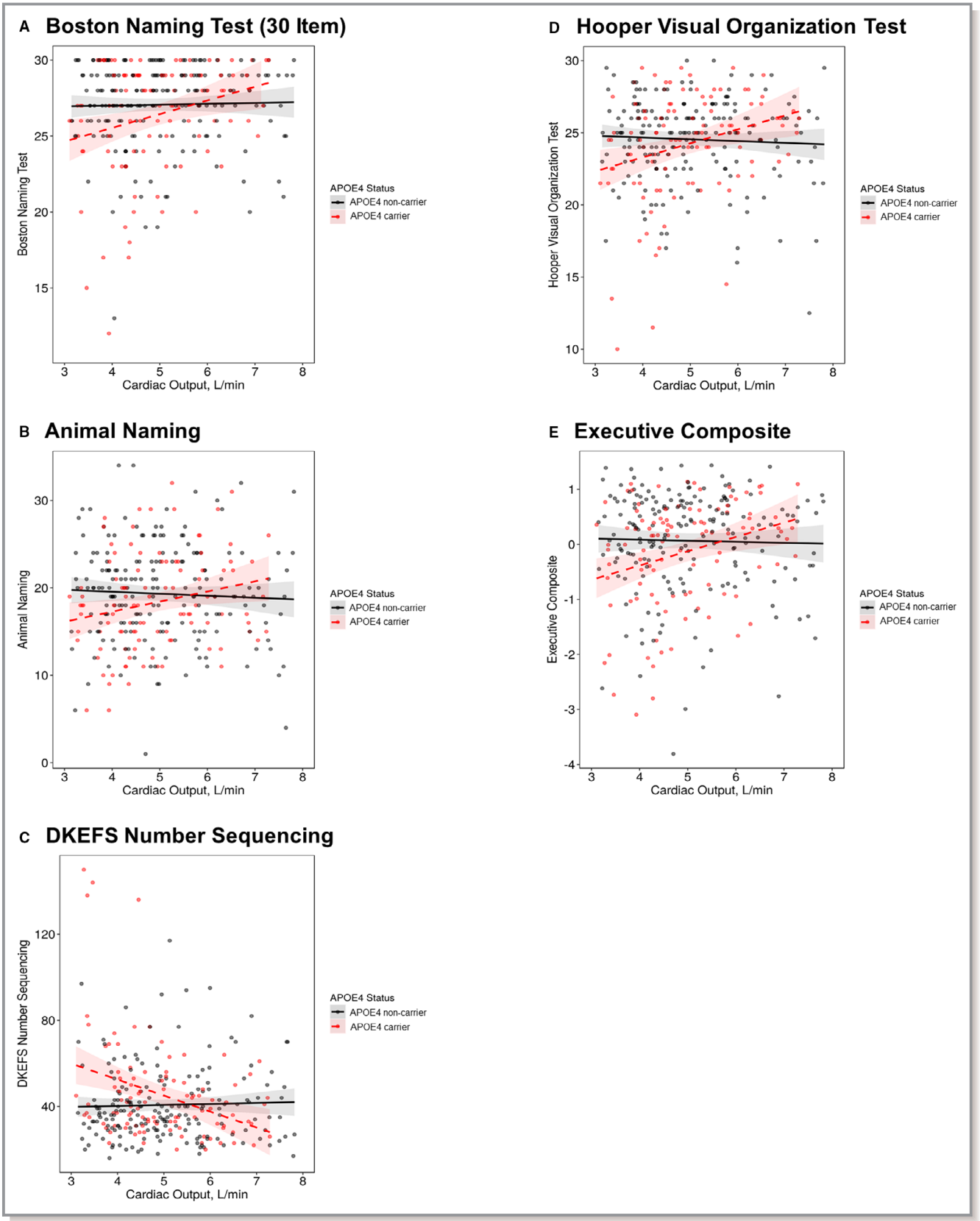

Figure 2. Cardiac output×*APOE*-ε4 interactions on neuropsychological performances. (**A**) Boston Naming Test (30-Item), (**B**) Animal Naming, (**C**) DKEFS Number Sequencing, (**D**) Hooper Visual Organization Test, and (**E**) Executive Composite. *APOE*-ε4 indicates apolipoprotein E ε4 allele; DKEFS, Delis-Kaplan Executive Function System.

Table 4. Cardiac Output×Diagnosis Interaction Models

Normal vs MCI	β	95% CI	*P* Value
Boston Naming Test (30 Item)	0.26	−0.23, 0.76	0.30
Animal Naming	−0.54	−1.4, 0.28	0.19
DKEFS Number Sequencing Test*	−0.44	−3.5, 2.6	0.78
WAIS-IV Coding	−1.3	−3.2, 0.59	0.18
Executive Composite	−0.05	−0.17, 0.08	0.45
Hooper Visual Organization Test	−0.04	−0.55, 0.47	0.88
Memory Composite	−0.03	−0.15, 0.09	0.66

Analyses were performed on 306 participants. Models were adjusted for age, sex, race/ethnicity, education, body surface area, cognitive diagnosis, *APOE*-ε4 status, and Framingham Stroke Risk Profile (excluding points assigned for age); neuropsychological performance values are total correct excluding timed tasks measured in seconds. β values for interaction terms represent the difference in β values between normal cognition and MCI participants. The Boston Naming Test was the 30-item odd version. DKEFS indicates Delis-Kaplan Executive Function System; *APOE*, apolipoprotein E; MCI, mild cognitive impairment; WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition.
*Higher scores reflect worse performance.

fluctuations and ischemic damage to slowed information processing speed[39,40] and executive dysfunction.[39–41] Contrary to expectation, we found no association between cardiac output and episodic memory in models comparing *APOE*-ε4 carrier status groups, but we did find cardiac output related to language performance, which localizes, in part, to temporal lobe structures. Temporal lobe structures may be more vulnerable to reduced cardiac output and corresponding reductions in CBF as we recently reported,[14] presumably because of poor collateral circulation[42] or age-related autoregulation dysfunction that localizes to the hippocampus.[14,43] However, the absence of episodic memory results here suggests that mechanisms involved in the modifying effect of *APOE*-ε4 may be more complex in temporal lobe regions. Collectively, results suggest that subtle reductions in cardiac output predispose aging adults to cognitive changes especially in language, information processing speed, and executive function domains before the onset of dementia. Given the common co-occurrence of cerebral small vessel disease and AD pathology,[44] clinical dementia may manifest because of a combination of AD-related neurodegeneration and coexisting tissue vulnerability secondary to chronic, subtle hemodynamic fluctuations. This latter injury may affect regions or networks mediating language, executive function, and information processing speed.

The *APOE*-ε2 allele has a well-known protective effect against the development of AD,[45] but it is also associated with cardiovascular disease,[46] cerebral white matter hyperintensities,[47,48] and cerebral infarcts.[49] Interestingly, our results suggest that lower cardiac output is associated with worse language and visuospatial performances in the presence of an ε2 allele, albeit with smaller effect sizes than discovered in *APOE*-ε4 carriers (which would not survive correction for multiple comparisons). Nevertheless, these results suggest the *APOE*-ε2 allele may have a similar modifying effect on cardiac output as the *APOE*-ε4 allele. Further study is needed in a larger sample size with greater representation of *APOE*-ε2 to confirm this observation.

Contrary to expectation, we did not find any interactions between diagnosis and cardiac output on cognitive performances, suggesting similar effects across NC and MCI participants. Participants with MCI likely have greater underlying neuropathology than NC participants based on their worse clinical status. Such neuropathology in these symptomatic individuals may represent extensive neurodegeneration that in a cross-sectional context is not vulnerable to the effects of subclinical cardiac dysfunction. Alternatively, if participants with MCI have neurodegeneration and are susceptible to the effects of lower cardiac output, then one might expect a more adverse clinical picture in the form of frank dementia rather than MCI. Future studies should address this discrepancy by following participants longitudinally and examining potential 3-way interactions with *APOE* genotype, diagnosis, and cardiac output on cognitive outcomes.

The present study had many strengths, including detailed neuropsychological assessment, the utilization of a clinical standard (echocardiogram) for cardiac output quantification, and comprehensive covariate ascertainment. The emphasis on age-related cardiovascular changes offers an opportunity to broaden knowledge in the field regarding concomitant pathological pathways driving adverse cognitive aging beyond core pathological features of AD. Limitations include the cross-sectional design inhibiting causal conclusions. Generalizability of findings is restricted given the well-educated, predominantly white, older sample. Finally, multiple comparisons were made, raising the likelihood of a false-positive finding. However, even with the application of a strict Bonferroni correction for each set of analyses, many results implicating language, information processing speed, and executive function would have persisted. Future research should emphasize performing similar analyses in more diverse ethnic and racial groups of older adults and leveraging longitudinal models to further elucidate how cardiac function relates to early cognitive trajectory in MCI and AD.

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Disclosures

None.

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Supplemental Material

Data S1

APOE Genotype Modeling Analytical Plan

To better characterize the effects of *APOE*-ε2, ε3, and ε4, secondary analyses were conducted assessing *cardiac output x APOE genotype* interaction. Genotypes were classified into four groups: *APOE*-ε2 carriers (ε2/ε2 or ε2/ε3), *APOE*-ε4 carriers (ε3/ε4 or ε4/ε4), *APOE* ε2/ε4, and *APOE* ε3/ε3 (referent). Analysis of variance was used to assess the overall *cardiac output x APOE genotype* interaction. To examine how specific genotype groups related to the association between cardiac output and neuropsychological outcomes, we tested an *APOE genotype x cardiac output* interaction term comparing the *APOE*-ε2 carriers (ε2/ε2 or ε2/ε3), *APOE*-ε4 carriers (ε3/ε4 or ε4/ε4), and *APOE* ε2/ε4 genotype to the referent (*APOE*-ε3/ε3). Models adjusted for age, sex, race/ethnicity, education, body surface area, cognitive diagnosis, *APOE* genotype, and Framingham Stroke Risk Profile (excluding points assigned for age).

Table S1. Participant Characteristics by *APOE*-ε4 Carrier Status.

	Combined n=306	Carriers n=109	Noncarriers n=197	*p*-value
Demographic and Health Characteristics				
Age, years	73±7	71±6	74±8	**0.008**
Sex, % male	58	63	55	0.15
Race, % non-Hispanic white	87	87	86	0.83
Education, years	16±3	16±3	16±3	0.51
Montreal Cognitive Assessment, total	25±3	25±4	26±3	**0.02**
Diagnosis, % Normal	57	47	62	**0.008**
APOE Genotype				
ε2/ε2, count	3	0	3	--
ε2/ε3, count	37	0	37	--
ε2/ε4, count	7	7	0	--
ε3/ε3, count	157	0	157	--
ε3/ε4, count	84	84	0	--
ε4/ε4, count	18	18	0	--
Framingham Stroke Risk Profile, total*	12±4	12±4	13±4	0.09
Systolic blood pressure, mmHg	142±18	141±19	142±18	0.20
Antihypertensive medication usage, %	55	53	56	0.65
Diabetes, %	18	16	21	0.25
Cigarette smoking, % current	2	2	3	0.45
Prevalent CVD, %	5	6	3	0.26
Atrial fibrillation, %	6	6	7	0.70
Left ventricular hypertrophy, %	5	3	6	0.28
Cardiac output, L/min	5.0±1.3	5.0±1.3	4.9±1.3	0.58
Neuropsychological Performances				
Boston Naming Test (30 Item)	27±3	26±4	27±3	**<0.001**
Animal Naming	19±6	18±6	19±6	0.05
DKEFS Number Sequencing Test, s†	43±20	46±24	41±17	0.07
WAIS-IV Coding	53±13	51±14	53±13	0.21
Executive Composite	-0.01±0.94	-0.16±0.98	0.07±0.91	**0.04**
Hooper Visual Organization Test	24±3	24±4	25±3	0.63
Memory Composite	0.00±0.98	-0.22±1.0	0.13±0.94	**0.005**

Values denoted as mean±SD or frequency; all neuropsychological performance values are total correct excluding timed tasks measured in seconds. Carriers have at least one *APOE*-ε4 allele, noncarriers do not have any. The Boston Naming Test was the 30-item odd version. *APOE*-ε4 indicates apolipoprotein E ε4 allele. CVD, cardiovascular disease. D-KEFS, Delis-Kaplan Executive Function System. MCI, mild cognitive impairment. NC, normal cognition. WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition. *****A modified Framingham Stroke Risk Profile Score was included in statistical models, which excluded points assigned to age (total=6.5±3.2, Carriers=6.5±3.4, Noncarriers=6.5±3.1). †Higher values reflect worse performance.

Table S2. ANOVA Test for Cardiac Output Interaction with *APOE* Genotype on Neuropsychological Performance.

	F-value	P-value
Boston Naming Test	4.8	**0.003†**
Animal Naming	2.6	0.06
DKEFS Number Sequencing Test	4.3	**0.006†**
WAIS-IV Coding	1.4	0.26
Executive Composite	2.9	**0.04**
Hooper Visual Organization Test	3.4	**0.02**
Memory Composite	0.77	0.51

Analyses performed on 306 participants except for the Memory Composite (n=305). Degrees of freedom for all ANOVA numerators were 3 and for denominators ranged between 286 and 291 depending on missing data. Neuropsychological performance values are total correct excluding timed tasks measured in seconds. The Boston Naming Test was the 30-item odd version. *APOE*-ε4, apolipoprotein E ε4 allele. CI, confidence interval. DKEFS, Delis-Kaplan Executive Function System. WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition. †Models that meet the significance threshold after applying a Bonferroni correction for each set of models (i.e., 0.05/7 comparisons per hypothesis=0.007).

Table S3. Contrasts for Cardiac Output x *APOE* Genotype Interaction on Neuropsychological Performance.

	β	95% CI	P-value
***APOE*-ε2 carriers (ε2/ε2, ε2/ε3)**			
Boston Naming Test (30 Item)	0.76	0.03, 1.5	**0.04**
Animal Naming	0.70	-0.53, 1.9	0.27
DKEFS Number Sequencing Test*	-1.2	-5.8, 3.3	0.59
WAIS-IV Coding	0.62	-2.2, 3.4	0.67
Executive Composite	0.07	-0.11, 0.26	0.43
Hooper Visual Organization Test	0.75	0.005, 1.5	**0.048**
Memory Composite	0.003	-0.18, 0.19	0.97
***APOE*-ε4 carriers (ε3/ε4, ε4/ε4)**			
Boston Naming Test (30 Item)	1.0	0.46, 1.6	**0.0004†**
Animal Naming	1.3	0.37, 2.3	**0.007**
DKEFS Number Sequencing Test*	-4.7	-8.2, -1.2	**0.009**
WAIS-IV Coding	1.5	-0.72, 3.6	0.19
Executive Composite	0.21	0.07, 0.36	**0.004†**
Hooper Visual Organization Test	0.82	0.25, 1.4	**0.005†**
Memory Composite	0.11	-0.04, 0.25	0.15
***APOE*-ε2/ε4 carriers**			
Boston Naming Test (30 Item)	0.97	-1.6, 3.6	0.47
Animal Naming	0.52	-3.9, 4.9	0.82
DKEFS Number Sequencing Test*	-21	-37, -4.6	**0.01**
WAIS-IV Coding	8.1	-2.0, 18	0.11
Executive Composite	0.09	-0.57, 0.76	0.78
Hooper Visual Organization Test	1.1	-1.5, 3.8	0.40
Memory Composite	-0.07	-0.73, 0.59	0.84

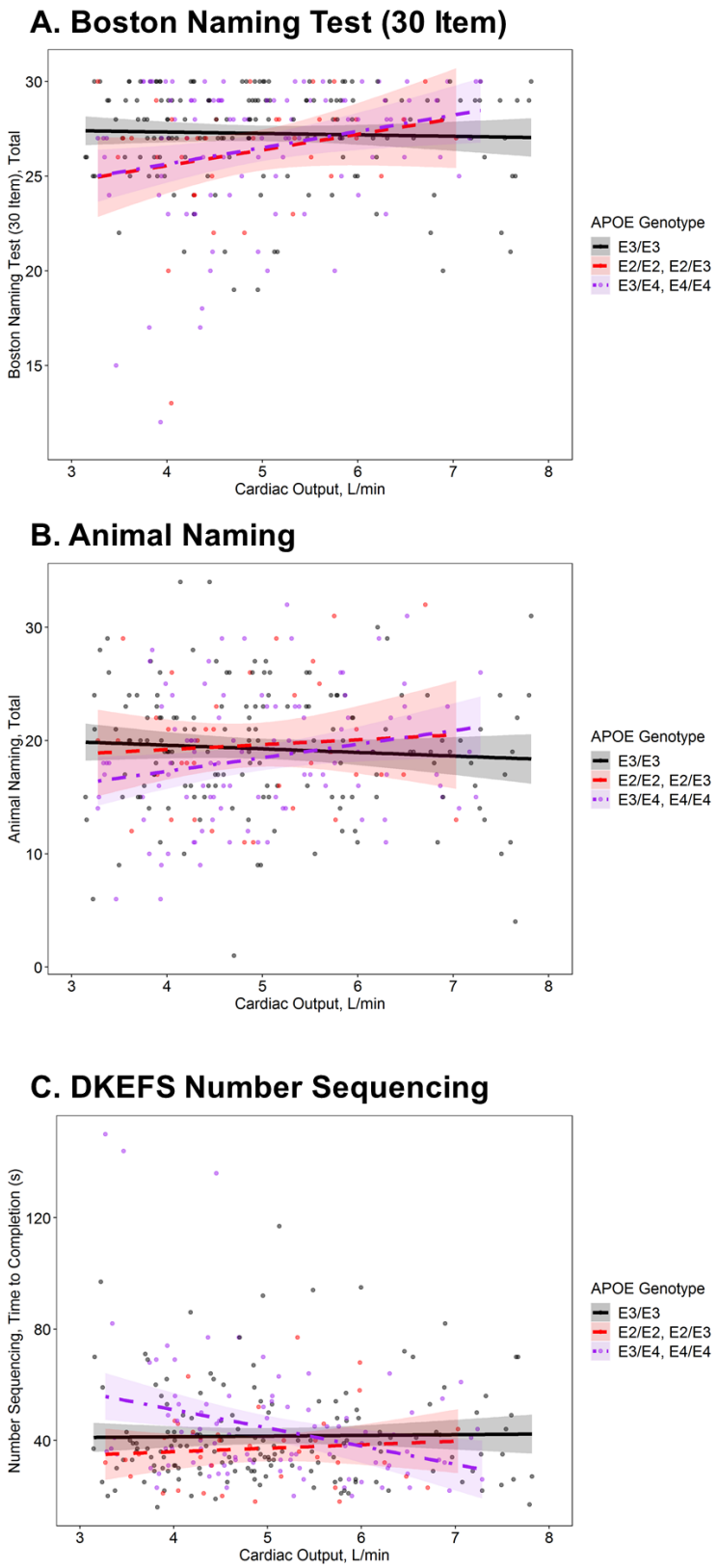
Analyses performed on 40 participants with an *APOE*-ε2/ε2 or *APOE*-ε2/ε3 genotype, 7 participants with an *APOE*-ε2/ε4 genotype, and 102 participants with an *APOE*-ε3/ε4 or *APOE*-ε4/ε4 genotype with a referent of 157 participants with an *APOE*-ε3/ε3 genotype. Models were adjusted for age, sex, race/ethnicity, education, body surface area, diagnosis, and Framingham Stroke Risk Profile (excluding points assigned for age); neuropsychological performance values are total correct excluding timed tasks measured in seconds. β values for interaction terms represent the difference in β values between the specified *APOE* genotype group and the *APOE*-ε3/ε3 referent group. The Boston Naming Test was the 30-item odd version. *APOE*-ε2, apolipoprotein E ε2 allele. CI, confidence interval. DKEFS, Delis-Kaplan Executive Function System. WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition. *Higher scores reflect worse performance. †Models that meet the significance threshold after applying a Bonferroni correction for each set of models (i.e., 0.05/7 comparisons per hypothesis=0.007).

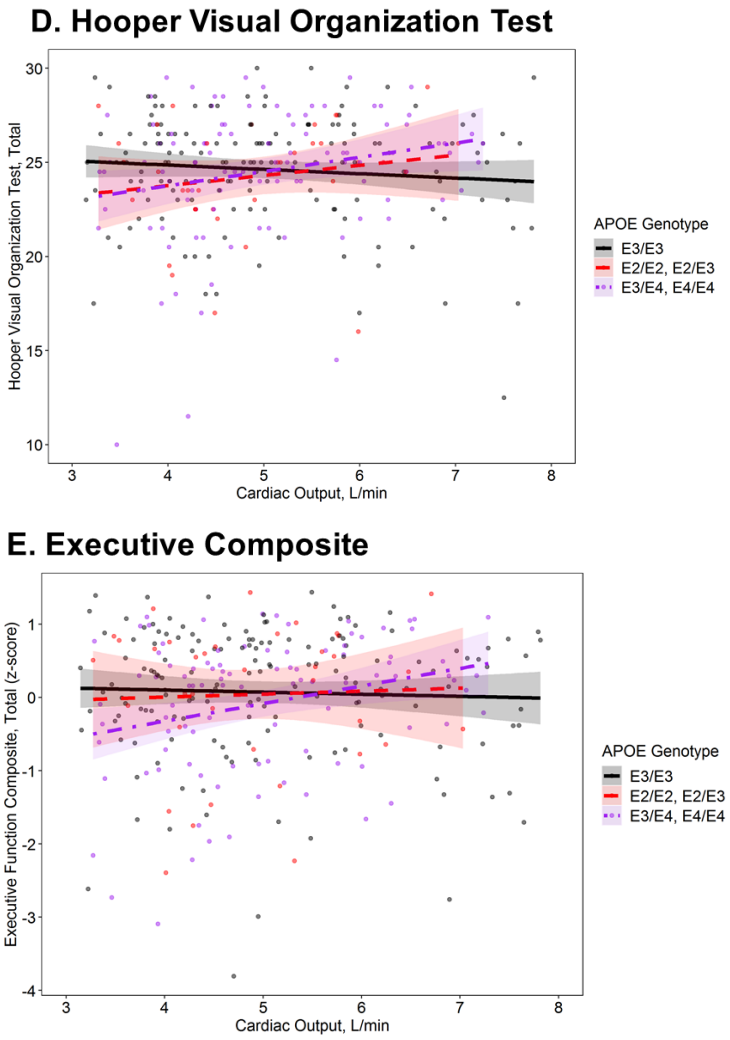
Table S4. Cardiac Output x Sex Interaction Models and Stratified by Sex.

	β	95 % CI	P-value
Males versus Females			
Boston Naming Test (30 Item)	-0.02	-0.58, 0.53	0.93
Animal Naming	0.04	-0.88, 0.95	0.94
DKEFS Number Sequencing Test*	-0.03	-3.46, 3.40	0.99
WAIS-IV Coding	1.65	-0.45, 3.76	0.12
Executive Composite	0.07	-0.07, 0.21	0.34
Hooper Visual Organization Test	0.25	-0.31, 0.82	0.38
Memory Composite	-0.05	-0.19, 0.08	0.46
Males			
Boston Naming Test (30 Item)	0.18	-0.14, 0.50	0.27
Animal Naming	-0.10	-0.68, 0.48	0.73
DKEFS Number Sequencing Test*	-1.22	-3.46, 1.02	0.28
WAIS-IV Coding	-1.20	-2.61, 0.21	0.10
Executive Composite	-0.02	-0.11, 0.06	0.60
Hooper Visual Organization Test	-0.09	-0.45, 0.27	0.62
Memory Composite	0.01	-0.07, 0.09	0.80
Females			
Boston Naming Test (30 Item)	0.08	-0.45, 0.60	0.77
Animal Naming	-0.08	-0.88, 0.72	0.84
DKEFS Number Sequencing Test*	-0.57	-3.46, 2.31	0.70
WAIS-IV Coding	0.35	-1.37, 2.07	0.69
Executive Composite	0.06	-0.07, 0.19	0.39
Hooper Visual Organization Test	0.21	-0.28, 0.71	0.39
Memory Composite	-0.02	-0.15, 0.10	0.72

Analyses performed on 306 participants and subsequently stratified by sex for 177 male participants and 129 female participants. Models were adjusted for age, sex, race/ethnicity, education, body surface area, cognitive diagnosis, *APOE*-ε4 status, and Framingham Stroke Risk Profile (excluding points assigned for age); neuropsychological performance values are total correct excluding timed tasks measured in seconds. β values for interaction terms represent the difference in β values between males and females. The Boston Naming Test was the 30-item odd version. CI, confidence interval. DKEFS, Delis-Kaplan Executive Function System. WAIS-IV, Wechsler Adult Intelligence Scale, 4th edition. *Higher scores reflect worse performance.

Figure S1. *Cardiac Output x APOE* Genotype Interaction on Neuropsychological Performances.





Cardiac Output x APOE genotype interaction on neuropsychological performances, including a) Boston Naming Test (30-item), b) Animal Naming, c) DKEFS Number Sequencing, d) Hooper Visual Organization Test and e) Executive Composite. *APOE*-ε4, apolipoprotein E ε4 allele. DKEFS, Delis-Kaplan Executive Function System.