

Lower Cardiac Output Relates To Reduced Cerebral Blood Flow In *APOE*-ε4 Non-Carriers Over An 11-Year Follow-Up



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HEALTH

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Background

- The brain receives a disproportionately high share of systemic blood flow, such that subclinical reductions in cardiac output relate cross-sectionally to reduced cerebral blood flow (CBF).
- This study examines associations between cardiac output and longitudinal CBF and cerebrovascular reactivity (CVR; a proxy for cerebral autoregulation) among older adults over an 11-year follow-up.
- We further investigate the modifying effects of apolipoprotein E (*APOE*)-ε4, a genetic susceptibility risk factor for Alzheimer's disease (AD), and plasma p-tau₂₃₁, an AD pathology biomarker.

Methods & Analytical Plan

- Vanderbilt Memory and Aging Project participants, free of clinical dementia and stroke at study enrollment completed a comprehensive evaluation including brain MRI and echocardiogram to quantify cardiac output (L/min) over a mean follow-up period of 4.5±3.0 years.
- Linear regression models related baseline cardiac output cross-sectionally and longitudinally to regional CBF (mL/100 grams/min) and hypercapnia-induced CVR (quantified from pseudo-continuous arterial spin labeling), adjusting for baseline age, sex, education, race/ethnicity, body surface area, *APOE*-ε4 status, modified Framingham Stroke Risk Profile score, and cognitive status.
- Follow-up models assessed *APOE*-ε4 status *x* cardiac output and plasma p-tau₂₃₁ *x* cardiac output interactions on CBF and CVR outcomes.

Table 1. Participant Characteristics at Baseline

	Combined (n=751)	<i>APOE</i> -ε4 Negative (n=485)	<i>APOE</i> -ε4 Positive (n=266)	p-value ^b
Age, years	67±9	68±10	66±9	0.06
Sex, % female	53	53	52	0.89
Education, years	16±3	16±2	17±3	0.56
Race, % non-Hispanic White	81	80	82	0.70
Cognitive diagnosis, % MCI	17	15	21	0.10
FSRP score ^a	9.6±5	9.5±5	9.7±5	0.85
Cardiac output, L/min	5.0±1.4	5.0±1.3	5.1±1.5	0.62
Plasma p-tau ₂₃₁ , ng/mL	6.8±4.2	6.2±3.8	7.9±4.7	<0.001

Note. Values are denoted as mean±standard deviation or frequency. Bold font indicates p-value<0.05. *APOE*=apolipoprotein E; CBF=cerebral blood flow; CVD=cardiovascular disease; FSRP=Framingham Stroke Risk Profile; MCI=mild cognitive impairment, p-tau=phosphorylated tau. ^aA modified FSRP score excluded points assigned to age was used in statistical models. ^bKruskal-Wallis' test was used for continuous variables and Pearson's chi-square test was used for categorical variables.

Figure 1. Main Effect of Baseline Cardiac Output on Longitudinal CBF

Figure 2. *APOE*-ε4 *x* Cardiac Output Interaction on Longitudinal CBF

Figure 3. Plasma p-tau₂₃₁ *x* Cardiac Output Interactions on Longitudinal CBF

Note. Lower baseline cardiac output interacts with plasma p-tau₂₃₁ on longitudinal CBF trajectory in A) whole brain (p=0.04) and B) frontal lobe gray matter (p=0.01). Shading represents the 95% confidence interval.

Results

- Longitudinal models revealed lower baseline cardiac output was associated with a faster decline in CBF in the frontal lobes (β=0.14, p=0.05), temporal lobes (β=0.11, p=0.04), and whole brain gray matter (β=0.13, p=0.05). See **Figure 1**.
- APOE*-ε4 status modified the association between baseline cardiac output and longitudinal CBF decline in the frontal lobes (p=0.03, **Figure 2**).
- Among *APOE*-ε4 non-carriers only, lower baseline cardiac output related to faster decline of CBF in the whole brain (β=0.19, p=0.01), temporal lobes (β=0.13, p=0.03), parietal lobes (β=0.19, p=0.03), and frontal lobes (β=0.22, p=0.01, **Figure 2**).
- In plasma p-tau₂₃₁ *x* cardiac output interaction models, plasma p-tau₂₃₁ strengthened the association between cardiac output and CBF decline in the whole brain (p=0.04) and frontal lobe gray matter (p=0.01). See **Figure 3**.

Conclusions

- We found lower cardiac output at study entry related to a faster decline in longitudinal CBF, independently of preserved CVR.
- Associations between lower cardiac output and longitudinal CBF decline were strongest among *APOE*-ε4 non-carriers and strengthened by the presence of plasma p-tau₂₃₁.
- Subtle reductions in cardiac function hold important implications for cerebral hemodynamics over time, particularly in the context of AD pathology.
- These findings highlight the need for primary prevention targets or therapeutic interventions to target cardiovascular integrity in older adults.
- Future studies should investigate the mechanisms linking cardiac output and cerebral autoregulation to delineate how AD pathological burden interacts with cardiac health to affect brain aging, particularly in middle-aged individuals with no genetic risk.

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