Low Cardiac Index Is Associated With Incident Dementia and Alzheimer Disease

The Framingham Heart Study

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Background—Cross-sectional epidemiological and clinical research suggests that lower cardiac index is associated with abnormal brain aging, including smaller brain volumes, increased white matter hyperintensities, and worse cognitive performances. Lower systemic blood flow may have implications for dementia among older adults.

Methods and Results—A total of 1039 Framingham Offspring Cohort participants free of clinical stroke, transient ischemic attack, and dementia formed our sample (age, 69±6 years; 53% women). Multivariable-adjusted proportional hazard models adjusting for Framingham Stroke Risk Profile score (age, sex, systolic blood pressure, antihypertensive medication, diabetes mellitus, cigarette smoking, cardiovascular disease history, atrial fibrillation), education, and apolipoprotein E4 status related cardiac magnetic resonance imaging–assessed cardiac index (cardiac output divided by body surface area) to incident all-cause dementia and Alzheimer disease (AD). Over the median 7.7-year follow-up period, 32 participants developed dementia, including 26 cases of AD. Each 1-SD unit decrease in cardiac index increased the relative risk of both dementia (hazard ratio [HR]=1.66; 95% confidence interval [CI], 1.11–2.47; *P*=0.013) and AD (HR=1.65; 95% CI, 1.07–2.54; *P*=0.022). Compared with individuals with normal cardiac index, individuals with clinically low cardiac index had a higher relative risk of dementia (HR=2.07; 95% CI, 1.02–4.19; *P*=0.044). If participants with clinically prevalent cardiovascular disease and atrial fibrillation were excluded (n=184), individuals with clinically low cardiac index had a higher relative risk of both dementia (HR=2.92; 95% CI, 1.34–6.36; *P*=0.007) and AD (HR=2.87; 95% CI, 1.21–6.80; *P*=0.016) compared with individuals with normal cardiac index.

Conclusion—Lower cardiac index is associated with an increased risk for the development of dementia and AD. (***Circulation*. 2015;131:1333-1339. DOI: 10.1161/CIRCULATIONAHA.114.012438.**)

Key Words: Alzheimer disease ■ blood circulation ■ brain ■ cardiac output ■ dementia ■ hemodynamics

A poorly understood aspect of cognitive aging is the association between cardiac output and brain aging. Clinical and epidemiological data suggest that after vascular risk factors are accounted for, very modest reductions in cardiac output are cross-sectionally associated with worse cognitive performance,[1] smaller brain volumes,[2] white matter hyperintensities,[3] and reduced normative cerebral perfusion values in regions of white matter injury.[4] These observations may be due to subclinical systemic blood flow disrupting cerebral blood flow homeostasis, especially among older adults with compromised cerebral circulation control mechanisms.[5]

Clinical Perspective on p 1339

Given that multiple vascular risk factors[6,7] and prevalent cardiovascular disease (CVD)[8] increase the risk for dementia, examining relations between systemic hemodynamics and incident dementia may provide essential evidence for future strategies to prevent dementia. On the basis of prior cross-sectional work,[1,2,8] we hypothesized that magnetic resonance imaging–assessed

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cardiac index would be associated with incident dementia and Alzheimer disease (AD) in community-dwelling adults.

Methods

Participants

The Framingham Offspring Study design has been previously described.[9] From 1971 to 1975, 5124 participants were recruited and have been examined approximately every 4 years since. The present sample was derived from 3539 participants attending the seventh examination cycle (1998–2001), of whom 1677 consented to undergo cardiac magnetic resonance imaging between 2002 and 2006. Figure 1 summarizes the inclusion and exclusion criteria for the present study. The study protocol was approved by the local Institutional Review Board, and participants provided written informed consent before assessments.

Cardiac Index Measurement

The Framingham Heart Study cardiac magnetic resonance imaging protocol has been reported elsewhere.[2,10,11] Briefly, supine imaging was performed on a Philips 1.5-T scanner with a 5-element commercial cardiac array coil. End-expiratory breath-hold, ECG-gated, cine steady-state free-precession images were acquired in 2-chamber, 4-chamber, and contiguous short-axis orientations (temporal resolution, 39 milliseconds; repetition time, R-R interval; echo time, 9 milliseconds; flip angle, 30°; field of view, 400 mm; matrix size, 208×256; slice thickness, 10 mm; gap, 0 mm). Analyses were performed by an experienced reviewer blinded to clinical information using a clinical workstation (EasyVision 5.1, Philips Medical Systems). End-diastolic volume (EDV) was determined as the minimal cross-sectional area of a midventricular slice. EDV and end-systolic volume (ESV) were computed by the summation-of-disks method with cardiac output (L/min) calculated as follows: (EDV−ESV)×heart rate. Cardiac output was divided by body surface area to calculate cardiac index ($L \cdot min^{-1} \cdot m^{-2}$). The interrater reliability correlation coefficient for EDV was 0.95 and for ESV was 0.92. The intraobserver coefficient of variation for EDV was 2.6% and for ESV was 3.5%.[12] The interobserver coefficient of variation for EDV was 3.5% and for ESV was 4.8%.[12]

Incident Dementia and AD Case Definition

Starting at cycle examination 5 (beginning in 1991), Offspring participants have been systematically monitored at each cycle examination for the development of dementia. Such monitoring includes a cognitive concern by the participant, a family member, or a Framingham study physician or staff member (including concerns about neuropsychological performance) or a Mini-Mental State Examination[13] score below an education-based cutoff, 3 points worse than a preceding examination (after cycle examination 5), or a 5-point decrement overall (after cycle examination 5), which triggers more in-depth testing.[14,15] All available neurological examination results, neuropsychological assessment results, study records, hospital records, primary care physician records, neuroimaging records, family interview information, and autopsy results are reviewed by a panel that includes at least 1 neurologist and at least 1 neuropsychologist to adjudicate dementia cases, diagnosis dates, and subtypes. Standard diagnostic criteria are used to define dementia[16]; in addition, Framingham criteria require dementia severity to be equivalent to or greater than a Clinical Dementia Rating[17] global score of 1 and for symptoms to have been present for a minimum of 6 months. AD-type dementia is defined with the use of standard criteria and includes probable and possible AD.[18]

Covariates

Covariates were defined at the seventh examination cycle unless otherwise noted. Education was defined categorically, including no high school degree, high school degree but no college, some college but no college degree, or a college degree. The Framingham Stroke Risk Profile score included age, sex, systolic blood pressure, antihypertensive medication, diabetes mellitus, cigarette smoking, left ventricular hypertrophy, CVD history, and atrial fibrillation. Systolic blood pressure was the mean of 2 measurements obtained during the examination by a Framingham Heart Study physician. Diabetes mellitus included previous or current fasting blood glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or previous or current use of oral hypoglycemic or insulin. Current cigarette smoking (ie, yes/no within the year before examination 7) and medication use were ascertained by self-report. Prior CVD (ie, coronary heart disease, angina, coronary insufficiency, myocardial infarction, heart failure, intermittent claudication) was defined at the time of cardiac

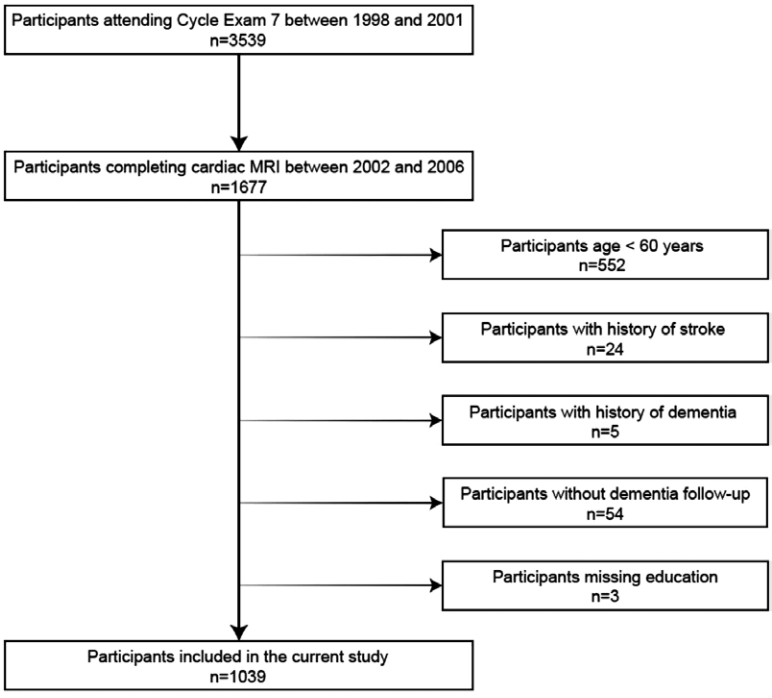

Figure 1. Participant selection details. MRI indicates magnetic resonance imaging.

magnetic resonance imaging acquisition and obtained via medical histories and Framingham Heart Study physical examinations and electrocardiograms, as well as hospitalization and physician records. A panel of 3 experienced investigators adjudicated CVD events.[19] Apolipoprotein E (APOE) genotyping was determined by polymerase chain reaction amplification and restriction isotyping.[20]

Statistical Analysis

For hypothesis testing, Cox proportional hazard regression models examined the association between cardiac index and incident dementia in 2 models that included covariates based on prior work.[21,22] Model 1 adjusted for age (years), sex, and education (categorical). Model 2 adjusted for Framingham Stroke Risk Profile (which assigns points for age by sex), education, and APOE allele 4 (APOE4) status (ie, ε4 negative versus ε4 positive[23]). Models were repeated, restricting the outcome to AD-type dementia. A second set of primary analyses repeated the models above, treating cardiac index as a categorical variable to align with clinical cut points of cardiac index. That is, models examined the relative risk of incident dementia between participants with clinically low cardiac index (defined[24,25] as <2.5 $L \cdot min^{-1} \cdot m^{-2}$) and normal cardiac index (referent). Again, models were repeated, restricting the outcome to AD-type dementia. Secondary analyses were performed on all models, excluding participants with prevalent CVD (n=145) and atrial fibrillation (n=66). These exclusions resulted in 5 fewer cases of dementia (including 4 fewer cases of AD) for analyses. Significance was set at $P<0.05$. Data were analyzed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Participant Characteristics

The mean sample age was 69±6 years (range, 60–89 years), and 53% were women. Cardiac index was normally distributed in the sample, and low cardiac index (ie, <2.5 $L \cdot min^{-1} \cdot m^{-2}$)[24] was present in 33% of participants (n=341). After the exclusion of individuals with prevalent CVD, low cardiac index was present in 31% of the sample (n=269). Over the median follow-up period of 7.7 years (range, 0–11 years), 32 participants developed dementia, including 26 AD cases. Table 1 summarizes clinical characteristic details for participants included in and excluded from the present analysis.

Table 1. Characteristics for Included and Excluded Participants

Clinical Characteristics	Current Sample (n=1039)	Excluded Attendees of the Seventh Examination Cycle ≥60 y of Age (n=86)	*P* Value
Age at examination 7, y	69±6	73±6	<0.001
Time from examination 7 to CMR, y	4.4±1.0	NA	NA
Female sex, %	53	44	NS
Systolic blood pressure, mm Hg	128±18	133±17	0.025
Education, %			0.028
No high school degree	3	9	
High school degree/no college	30	32	
Some college, no college degree	31	23	
College degree	35	37	
Diabetes mellitus, %	11	28	<0.001
Prevalent CVD, %	14	45	<0.001
Angina	7	9	NS
Coronary heart disease	10	17	0.037
Coronary insufficiency	<1	0	NS
Heart failure	1	3.5	NS
Intermittent claudication	2	7	0.011
Myocardial infarction	4	9	0.047
Atrial fibrillation, %	6	8	NS
APOE4, %	23	26	NS
CMR-assessed cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.75±0.49	2.72±0.57	NS
Low cardiac index (<2.5 $L \cdot min^{-1} \cdot m^{-2}$), %	33	38	NS

Values are mean±SD when appropriate. APOE4 indicates apolipoprotein E4 allele; CMR, cardiac magnetic resonance imaging; and CVD, cardiovascular disease. CVD does not include clinical stroke or transient ischemic attack. CVD categories are not mutually exclusive. *P*=NS indicates a nonsignificant comparison at the $P<0.05$ threshold

Continuous Cardiac Index

In models adjusting for age, sex, and education, each 1-SD unit decrease in cardiac index increased the relative risk of dementia (hazard ratio [HR]=1.71; 95% confidence interval [CI], 1.14–2.57; $P=0.01$) and AD (HR=1.71; 95% CI, 1.09–2.66; $P=0.018$). When models were adjusted for education, Framingham Stroke Risk Profile, and APOE4 status, findings were essentially unchanged (dementia: HR=1.66; 95% CI, 1.11–2.47; $P=0.013$; AD: HR=1.65; 95% CI, 1.07–2.54; $P=0.022$; Table 2). When participants with prevalent CVD and atrial fibrillation (n=184) were excluded from the analyses, cardiac index was still significantly associated with incident dementia and AD (Table 2).

Categorical Cardiac Index

In models adjusting for age, sex, and education, participants with impaired cardiac index had a higher risk of dementia (HR=2.15; 95% CI, 1.07–4.32; $P=0.032$) but not AD (HR=2.21; 95% CI, 1.02–4.81; $P=0.095$). When models were adjusted for education, Framingham Stroke Risk Profile, and APOE4 status, findings were similar in that participants with impaired cardiac index had a significantly increased risk of dementia (HR=2.07; 95% CI, 1.02–4.19; $P=0.044$) but not AD (HR=2.10; 95% CI, 0.96–4.61; $P=0.063$). Table 2 provides model details, and Figure 2 shows an illustration of categorical results using survival curves estimated from Cox regression at the mean of the covariates (age, sex, and education) for low cardiac index and normal cardiac index. When participants with prevalent CVD and atrial fibrillation were excluded, participants with impaired cardiac index had an increased relative risk of both dementia (HR=2.92; 95% CI, 1.34–6.36; $P=0.007$) and AD (HR=2.87; 95% CI, 1.21–6.80; $P=0.016$; Table 2) compared with participants with normal cardiac index.

Discussion

Among community-dwelling adults ≥60 years of age, we found that cardiac index is associated with incident

Table 2. Association Between Cardiac Index and Risk for Dementia or AD

		Dementia (n=32/1039)			Dementia, Excluding Prevalent CVD and AF (n=27/855)			AD (n=26/1039)			AD, Excluding Prevalent CVD and AF (n=22/855)		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Model 1	Cardiac index*	1.71	1.14–2.57	0.010	2.00	1.26–3.19	0.003	1.71	1.09–2.66	0.018	2.03	1.22–3.37	0.007
	Cardiac index ≥2.5 $L \cdot min^{-1} \cdot m^{-2}$		Referent			Referent			Referent			Referent	
	<2.5 $L \cdot min^{-1} \cdot m^{-2}$	2.15	1.07–4.32	0.032	2.93	1.35–6.33	0.006	2.21	1.02–4.81	0.095	2.92	1.24–6.86	0.014
Model 2	Cardiac index*	1.66	1.11–2.47	0.013	1.98	1.26–3.11	0.003	1.65	1.07–2.54	0.022	1.99	1.22–3.24	0.006
	Cardiac index ≥2.5 $L \cdot min^{-1} \cdot m^{-2}$		Referent			Referent			Referent			Referent	
	<2.5 $L \cdot min^{-1} \cdot m^{-2}$	2.07	1.02–4.19	0.044	2.92	1.34–6.36	0.007	2.10	0.96–4.61	0.063	2.87	1.21–6.80	0.016

AD indicates Alzheimer disease; AF, atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease; and HR, hazard ratio. Model 1 was adjusted for age, sex, and education, and model 2 was adjusted for education, apolipoprotein E4 status, and Framingham Stroke Risk Profile (which assigns points for age, systolic blood pressure, antihypertensive medication, diabetes mellitus, cigarette smoking, left ventricular hypertrophy, CVD history, and atrial fibrillation by sex).

*HR reported per 1-SD unit decrease in cardiac index.

dementia and AD over a median follow-up period of 7.7 years. That is, per 1-SD unit decrease in cardiac index, the relative risk of incident dementia and AD increased. When cardiac index was examined categorically, participants with clinically low cardiac index had a >2-fold increased risk of developing dementia compared with participants with normal cardiac index. When participants with prevalent CVD and atrial fibrillation were excluded, participants with clinically low cardiac index had a nearly 3-fold increased risk of developing both dementia and AD compared with the referents.

Our data are among the first to demonstrate that low cardiac index is related to an increased relative risk of incident dementia and AD in a community-based cohort. The present findings extend our prior cross-sectional research relating cardiac index to neuroimaging phenotypes of AD, including reduced total brain volume and increased lateral ventricular volume.[2] Furthermore, our secondary models suggest that prevalent CVD and atrial fibrillation do not statistically explain the significant observations in our primary models.

The mechanisms underlying our observations are unknown and likely multifactorial. Human studies suggest that autoregulation of cerebral blood velocity in the macrovasculature is preserved in acute settings of orthostatic hypotension.[26,27] However, there is limited research assessing cerebral blood flow or perfusion regulation in the setting of chronic reduction (the exception being the extreme clinical model of heart failure[28,29]). Animal research suggests that autoregulatory mechanisms for maintaining cerebral blood flow may not function reliably when cardiac output is manipulated,[30] especially in the presence of cerebrovascular injury.[31] Therefore, we speculate that one mechanism accounting for our findings is compromised cerebral autoregulation or control mechanisms whereby subtle, chronic reductions in systemic hemodynamics over time disrupt cerebral blood flow in the microvasculature. Such changes could place the brain at

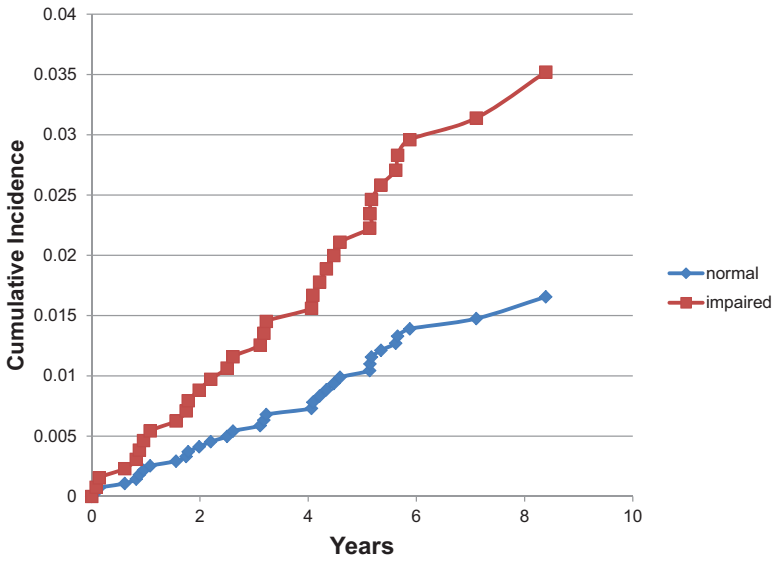

Figure 2. Cumulative incidence of dementia between individuals with normal and impaired cardiac index adjusted for age, sex, and education.

greater risk for cerebrovascular and neurodegenerative processes, especially in the presence of concomitant age-related changes in blood-brain barrier permeability[32] and vascular compliance.[33,34] Furthermore, compromised cerebrovascular health has been shown to propagate amyloid deposition,[35,36] is associated with compromised β-amyloid clearance,[37–39] and contributes to faster clinical manifestation[40,41] and trajectory[42,43] of AD. Thus, systemic hemodynamics may affect cerebral hemodynamics in those older adults who have compromised cerebral circulation control mechanisms and contribute to the pathogenesis or exacerbation of amyloid deposition and subsequent neuronal injury. That being said, we cannot rule out other possible mechanisms, an epiphenomenon not captured by our covariates, residual confounding, or chance.

Consistent with our prior work in the Framingham Heart Study,[2] it is notable that one third of our cohort had cardiac index values below a clinical threshold for abnormal cardiac function (<2.5 $L \cdot min^{-1} \cdot m^{-2}$). One explanation is that prevalent CVD may have contributed to cardiac dysfunction, resulting in lower cardiac index values. However, the prevalence of low cardiac index was similar when participants with prevalent CVD were excluded, suggesting that the low cardiac index seen in our cohort is not explained by clinical heart disease. It is plausible that age-related changes in left ventricular diastolic filling such as reduced contribution of early atrial filling, impaired left ventricular compliance, or reduced preload may have contributed to reductions in cardiac output.[44,45] Additional research is warranted to identify the mechanisms underlying lower cardiac index in ambulatory older adults, especially if future research replicates the present findings that low cardiac index is a risk factor for incident dementia and AD.

Previous work suggests that vascular risk factors modestly increase the risk of AD. For example, hypertension is related to a 1.4-fold increase in incident AD,[46] whereas diabetes mellitus is related to a 2.4-fold increased risk,[46] especially among APOE4-negative elders (HR=2.7).[7] In the present study, we report that lower cardiac index increases the relative risk of dementia and AD by ≈2-fold when we exclude people with prevalent CVD and atrial fibrillation and adjust for key demographic, environmental, and genetic risk factors related to AD, including age, sex, education, systolic blood pressure, diabetes mellitus, prevalent CVD, and APOE4 status.[6–8,21,22,46]

Our study has several strengths, including the large community-based cohort free of clinical dementia and stroke at baseline, comprehensive ascertainment of potential confounders, a precise cardiac imaging technique for quantifying cardiac output in epidemiological cohorts, stringent quality control procedures for cardiac measurement and dementia surveillance, and a core laboratory for processing measurements. However, the present findings must be tempered by several caveats. The racial makeup of the Framingham Offspring Study is white, so the generalizability to other races and ethnicities is unknown. Similarly, whether our results are relevant to individuals <60 years of age is unknown. Despite the effect size of our findings, it is imperative to highlight the very small number of incident cases as a major limitation to the present methods. There are only 26 dementia cases in total, including 21 cases of AD, which may be due to less sensitive dementia surveillance methods (eg, using impaired cross-sectional Mini-Mental State Examination performances or performance decrements over time to trigger a more in-depth assessment). It is also a noteworthy limitation that we relied on more traditional criteria for diagnosing dementia and AD rather than more recent criteria such as recommendations put forth by the National Institute on Aging and Alzheimer's Association Workgroup.[47] Our methodology also did not include neuroimaging measures of cerebral blood flow, cerebrovascular reactivity, or vascular stiffness, which limits our ability to explain the mechanism(s) underlying our observations. Finally, we cannot exclude the possibility of residual confounding or chance. The stability of associations reported here and their magnitude should be interpreted with caution until future studies can replicate our findings.

Conclusions

Resting cardiac index is associated with risk for incident dementia and AD, including individuals free of prevalent CVD and atrial fibrillation. We propose that subtle reductions in cardiac index are associated with an accelerated pathophysiology of dementia and AD in particular. Further investigation into the mechanisms underlying this increased risk is merited for identifying targets for primary prevention purposes or therapeutic interventions.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In this study, we assessed the association between lower cardiac index and both incident dementia and Alzheimer disease among older adults. More than 1000 participants from the Framingham Offspring Cohort were included in the analyses. Participants were ≥60 years of age with no history of clinical stroke, transient ischemic attack, or dementia at baseline. We related cardiac magnetic resonance imaging–assessed cardiac index to incident all-cause dementia and Alzheimer disease using multivariable-adjusted proportional hazard models. Models were adjusted for education, apolipoprotein E4 status, and Framingham Stroke Risk Profile score (ie, age, systolic blood pressure, antihypertensive medication, diabetes mellitus, cigarette smoking, cardiovascular disease, and atrial fibrillation by sex). We found that a lower cardiac index was associated with a higher relative risk of both incident dementia and Alzheimer disease over a median follow-up period of 7.7 years. When we excluded participants with clinically prevalent cardiovascular disease and atrial fibrillation (n=184), a lower cardiac index continued to be associated with a higher relative risk of both dementia and Alzheimer disease. In light of our observation that one third of the cohort had clinically low cardiac index (<2.5 $L \cdot min^{-1} \cdot m^{-2}$), our findings may have major public health relevance to Alzheimer disease and dementia risk factors and prevention strategies. Future research is necessary to understand the pathway(s) by which low cardiac index increases risk of dementia and Alzheimer disease for the purposes of informing interventions evaluating whether enhancing cardiac index can reduce unhealthy brain aging or the risk of dementia and Alzheimer disease.

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