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CLINICAL RESEARCH
Imaging

Left ventricular geometry, brain architecture, and cognition: an observational study

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Abstract

Background and Aims Cardiovascular (CV) diseases and dementia share common risk factors and often coexist in older adults. Understanding the CV–brain interaction is essential for tackling their interconnected burden. This study investigated the link between CV phenotypes, brain architecture, and cognition.

Methods Overall, 15 519 UK Biobank participants without neurodegenerative diseases or stroke (median age 64 years, 49% female) were analysed. Confirmatory factor analysis aggregated 18 CV magnetic resonance imaging (MRI) biomarkers into latent variables for left ventricular systolic function (gSyst), diastolic (gDiast) function, and geometry (gGeom); arterial compliance was measured by aortic distensibility (AoD). Multivariable linear regression models evaluated associations with brain MRI phenotypes, including grey matter volume, white matter hyperintensities, MRI diffusion white matter microstructure, and hippocampal volume. Models were adjusted for age, body mass index, height, mean blood pressure, and CV risk factors. Exploratory mediation models evaluated whether hippocampal volume accounted for associations between CV phenotypes and cognition.

Results gGeom, reflecting greater myocardial mass, wall thickness, and ventricular volumes, showed the strongest association with hippocampal volume [$\beta = 0.082$ (0.048–0.117) in females; $\beta = 0.039$ (0.006–0.071) in males] and was the only CV phenotype associated with better cognition, including higher fluid intelligence and faster reaction time. Hippocampal volume significantly accounted for the positive relationship between gGeom and cognition across sexes. In contrast, gSyst, gDiast, and AoD demonstrated weaker and less consistent associations with brain structure and were unrelated to cognition.

Conclusions Ventricular geometry emerged as the CV phenotype most strongly associated with brain architecture and cognition. Hippocampal volume may help explain this association, but further studies are needed to investigate causality.

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Structured Graphical Abstract

Key Question

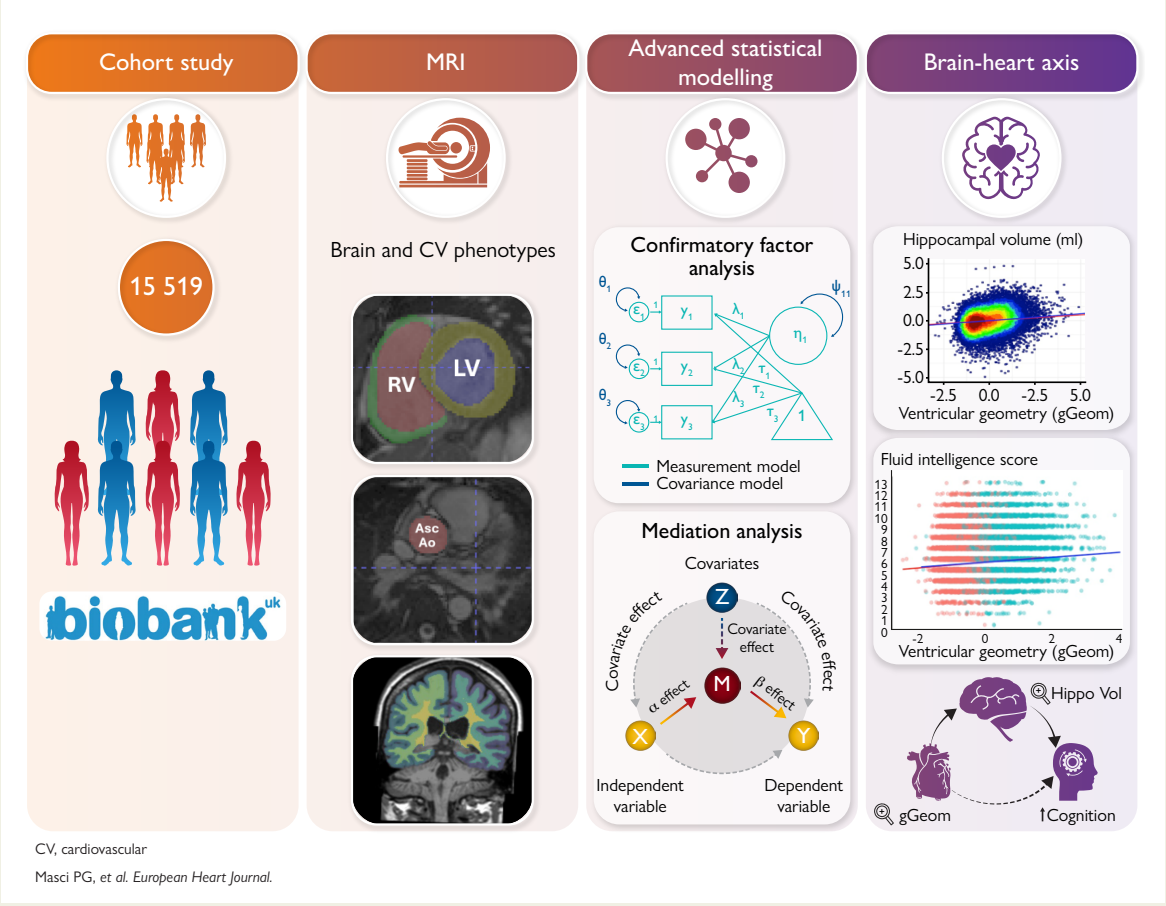
What are the most important cardiovascular phenotypes associated with brain architecture and cognition?

Key Finding

In this cohort study in participants without neurodegenerative diseases ventricular geometry, reflecting greater myocardial mass and ventricular volumes, emerged as the strongest correlate of brain structure and was linked to better cognition, explained in part by larger hippocampal volume. In contrast, ventricular systolic and diastolic function and arterial compliance showed weaker, less consistent associations with brain structure and were unrelated to cognition.

Take Home Message

These findings offer physicians and researchers a novel perspective on cardiovascular-brain interactions by challenging the current hemodynamic-arterial paradigm and emphasizing the pivotal role of ventricular geometry in shaping brain architecture and cognition.



Main components of the study. Asc Ao, ascending aorta; gGeom, latent variable for ventricular geometry; Hippo, hippocampus; LV, left ventricle; MRI, magnetic resonance imaging; RV, right ventricle.

Keywords Cardiac magnetic resonance imaging • Heart–brain axis • Ventricular geometry

Introduction

Cardiovascular (CV) diseases and dementia share common risk factors and overlapping pathobiological mechanisms, frequently coexisting in older adults, with deleterious consequences for patients, healthcare systems, and society.[1–3] These challenges are exacerbated by an aging population[4] and the lack of effective, safe, and accessible treatments for dementia, along with the continuing dismal prognosis of CV diseases.[5] Advancing our understanding of the CV–brain interaction is therefore critical for developing effective therapeutic and preventive strategies to mitigate the burden of these interconnected conditions.

Emerging evidence has linked CV diseases, such as overt heart failure and severe left ventricular (LV) dysfunction, to neurobiological and cognitive changes, including neurovascular dysfunction, reduced grey matter volume, white matter microstructural derangements, and cognitive

decline.[6–10] The prevailing hypothesis suggests that key haemodynamic abnormalities—characterized by low cardiac output, impaired cerebral blood flow autoregulation, and decreased arterial compliance—drive chronic cerebral hypoperfusion, neurodegeneration, and ultimately dementia.[6–10]

In contrast, the CV–brain relationship in individuals without overt heart failure or LV dysfunction remains less well defined. While some studies have linked subclinical cardiac dysfunction[11–13] and decreased arterial compliance[14,15] to structural brain changes and cognitive deficits, others have reported conflicting results.[16–19] These discrepancies reflect significant challenges in conducting large-scale studies that integrate robust CV and brain phenotypes with cognitive assessment. Additionally, the relationship between CV phenotypes and the hippocampus, a key subcortical region implicated in cognition, remains poorly explored.[19] Addressing these gaps is pivotal for advancing our understanding of the complex interplay between CV and brain health. By identifying causal pathways and biological targets of neurodegeneration, these can inform the development of innovative preventive and therapeutic strategies to tackle CV diseases and dementia.

To address these challenges, we leveraged the UK Biobank, one of the largest and most comprehensively phenotyped cohort studies in middle-aged and older adults, combining CV and brain magnetic resonance imaging (MRI) phenotypes with demographic, clinical, environmental, and cognitive data. To streamline the analysis and facilitate the interpretation of CV–brain interactions, we employed confirmatory factor analysis[20] to aggregate multiple CV MRI biomarkers into three latent variables, representing ventricular systolic function, diastolic function, and geometry. Arterial compliance was measured separately by ascending aorta distensibility (AoD).[21,22]

Methods

Study population

We utilized data from the UK Biobank, a large population-based prospective cohort study of ~500 000 individuals aged 40 and over.[23] For our investigation, we included participants with no history of neurodegenerative diseases or stroke and with complete data on demographics, anthropometric CV risk factors, CV and brain MRI biomarkers, and cognitive assessments.[24,25] Subjects with extreme outlying MRI biomarkers [further than ±4 standard deviations (SDs) from the mean] were excluded (*Figure 1*). Given established sex differences in cardiac and brain structure and function across the lifespan, analyses were stratified by sex to account for potential biological variation.[26,27] This study complied with the UK Biobank ethical approval from the National Health Service on 17 June 2021 (Ref: 11/NW/0382) and the subsequent extension on 18 June 2021 (Ref: 21/NW/0157).

Anthropometric, demographic, and cardiovascular risk factors and other covariates

Demographic and anthropometric characteristics were collected at the time of MRI. The age of each participant was calculated as the number of years from birth to the MRI date, while sex was self-reported. Weight (kg), height (cm), and body mass index (kg/m^2) were recorded immediately before MRI scans. Prevalent CV risk factors, along with brain and CV conditions, were identified based on self-reported questionnaires, hospital episode statistics, and first-occurrence categories[23] (see Supplementary data online, *Table S1*).

Cardiovascular magnetic resonance imaging

The CV MRI protocol has been previously described.[24] In brief, images were acquired using clinical wide bore 1.5-T scanners (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare). The scan protocol consisted of

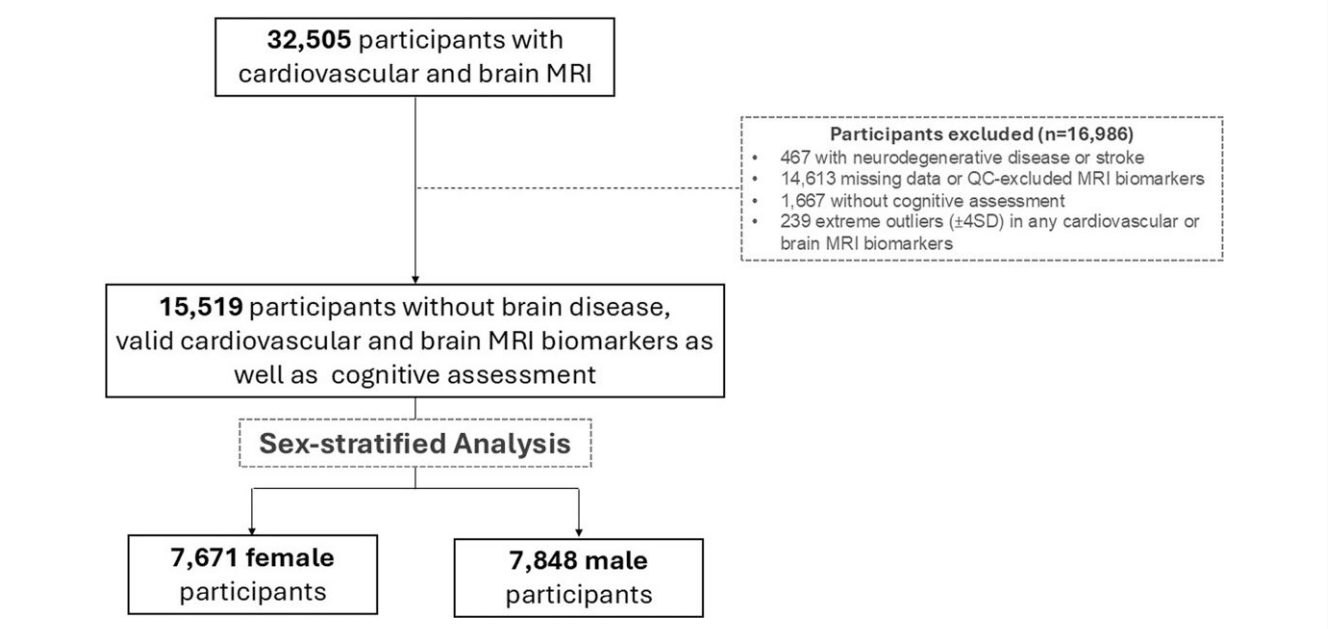


Figure 1 Study flow chart. We first identified participants with available cardiovascular and brain magnetic resonance imaging and then excluded those with prevalent neurodegenerative diseases or stroke. We also excluded subjects missing any demographic, anthropometric, cardiovascular risk factors, blood pressure, cognitive test (fluid intelligence or reaction time) data, or magnetic resonance imaging–derived biomarkers relevant to the study. Finally, we omitted subjects in whom the automatic quality-controlled pipeline identified unreliable magnetic resonance imaging biomarkers and extreme outliers (±4 SD from the mean value). MRI, magnetic resonance imaging; QC, quality control; SD, standard deviation.

cardiac short-axis, long-axis, and ascending aorta cine images using a balanced steady-state free precession sequence. Structural and functional biomarkers of both left cardiac chambers and ascending aorta were automatically extracted using our quality-controlled machine learning pipeline.[28,29] In total, 19 CV MRI biomarkers were derived, encompassing four distinct left heart pathophysiological domains, namely, systolic function ($n = 7$), diastolic function ($n = 6$), geometry ($n = 5$), and ascending AoD ($n = 1$) (see Supplementary data online, *Tables S2–S5*). Aside from AoD, confirmatory factor analysis[20] was employed to coalesce 18 CV biomarkers into domain-specific latent variables encompassing ventricular systolic function (gSyst), ventricular diastolic function (gDiast), and ventricular geometry (gGeom). The rationale for using confirmatory factor analysis, rather than exploratory approaches, was grounded on prior literature which reported associations between individual CV MRI biomarkers and brain phenotypes and cognition.[8–19] The constructed latent variables aggregated the covariance of original CV biomarkers, providing a more comprehensive and parsimonious representation of the pathological processes than any single biomarker.[20] The strength and the direction of the relationship between the constructed latent variable and the original biomarkers are determined by the factor loading, enabling good interpretability of the study analyses (see Supplementary data online, *Methods* and *Tables S2–S5*).

Brain magnetic resonance imaging

All brain MRI data were acquired using 3T scanners (Skyra, Siemens Healthcare) based on a previously described protocol.[30] In brief, brain data were acquired using a standard Siemens 32-channel head coil. T1-weighted magnetization-prepared rapid acquisition gradient echo and T2-weighted fluid-attenuated inversion recovery volumes were attained in the sagittal orientation. Diffusion MRI consisted of spin-echo echo-planar sequences with 10 T2-weighted baseline volumes and 100 distinct diffusion-encoding directions.

Global tissue volumes and tract-averaged diffusion indexes of white matter were processed by the UK Biobank team and were made available to researchers.[25,30,31] These metrics included total brain volume, grey matter volume, white matter hyperintensity (WMH) volume, hippocampal volume (and other subcortical region volumes), tract-averaged fractional anisotropy (FA), and mean diffusivity (MD) of white matter tracts. Hippocampal and other subcortical region volumes were calculated by averaging the volumes of the corresponding left and right hemispheric regions.[30,31] All brain volumetric phenotypes were corrected for head size. Confirmatory factor analysis was employed to derive latent variables for FA (gFA) and MD (gMD) to capture the shared covariance of diffusion metrics across bilateral white matter tracts in a single metric as previously reported.[25,31]

Cognitive function

Based on prior evidence, we selected fluid intelligence and reaction time from the cognitive assessment. Fluid intelligence measures unbiased logic and reasoning which is largely independent of prior knowledge and experience,[32] while reaction time measures how rapidly a subject perceives, processes, and reacts to information, therefore capturing cognitive processing capacity.[32,33] These measures have shown to provide a comprehensive assessment of cognitive function in a robust, reliable, and reproducible manner[32,33] and have been prospectively associated with incident dementia.[34]

Statistical analysis

Continuous variables were expressed as mean ± SD for normally distributed data, median (interquartile range) for non-normally distributed data, while categorical variables were reported as number (%). The WMH volume was log-transformed to approximate a normal distribution. Cardiovascular latent variables (gSyst, gDiast, gGeom) and diffusion MRI white matter tract latent variables (gFA and gMD) were derived using confirmatory factor analysis ('lavaan' package in R). For interpretability, gDiast values were multiplied by −1, so higher values indicated better LV diastolic function.

Brain MRI phenotypes were regressed onto CV phenotypes (gSyst, gDiast, gGeom, and AoD) using multivariable linear regression models. Two model types were employed: 'single' models, where each CV phenotype was introduced individually, and 'simultaneous' models, where all CV phenotypes were included together. Both models were adjusted for major confounders, including age, quadratic age (age^2), CV phenotype-by-age interaction terms (in 'single' models), body mass index, height, CV risk factors (hypertension, diabetes, dyslipidaemia, and smoking), and mean blood pressure.[35] In the 'single' models, when the interaction between CV phenotype and age was statistically significant, models were stratified by age group (<65 vs ≥65 years) and re-run without introducing the interaction term, while retaining all other covariates. 'Single' models were also utilized to investigate the associative measures between cognitive performance (fluid intelligence and reaction time) and the CV phenotypes, along with the association between brain phenotypes and each single CV MRI biomarker. Model diagnostics confirmed low multicollinearity (variance inflation factor <5) and no evidence of heteroscedasticity, as assessed by inspecting residuals-vs-fitted-values plots. Model results were presented as standardized β coefficients with 95% confidence intervals (CIs), allowing for effect size comparison.[36] Finally, meditation analysis ('mediate' package in R) was implemented to assess the causal effect of gGeom ('exposure') on cognitive function ('outcome'), with hippocampal volume being assumed as the 'mediator'.[37] Sensitivity analyses were conducted by including all participants to assess the impact of extreme MRI biomarkers on the study findings. Statistical significance was set at $\alpha = 0.05$, and all analyses were corrected for multiple comparisons by the Bonferroni's or Benjamini–Hochberg procedures, controlling for false discovery rate ('p.adjust' in R). All analyses were conducted in R (v4.1.2) using RStudio-IDE Version 2024.04.1 (Posit Software PBC).

Results

Study population

We identified 15 519 subjects [median age: 64; interquartile range: 58–70 years; 7671 (49%) female] fulfilling the study requirements (*Figure 1*). Anthropometrics, demographics, CV risk factors, and CV and brain MRI biomarkers are summarized in *Table 1*.

Association between cardiovascular phenotypes, general brain health, and hippocampal volume

Associations between brain phenotypes and CV structure and function, stratified by sex, are reported in *Table 2* and *Figure 2* and Supplementary data online, *Table S6*. Total brain volume was not associated with CV phenotypes in either sex. However, distinct patterns emerged when examining grey and white matter compartments, as well as hippocampal volume.

In women, greater grey matter volume was associated with enhanced ventricular diastolic function (higher gDiast) and lower ventricular geometry (lower gGeom), suggesting a link between preserved cortical integrity and favourable structural and functional ventricular remodelling. The WMH burden, a marker of cerebral small vessel disease, was consistently associated with CV phenotypes in both sexes. In detail, higher WMH volume correlated with reduced ventricular systolic function (lower gSyst), decreased arterial compliance (lower AoD), and greater ventricular geometrical remodelling (higher gGeom), pointing towards a shared trajectory of impaired ventricular–arterial coupling and cerebral microcirculatory abnormalities.

Diffusion MRI underscored that healthier white matter microstructure, reflected by higher gFA and lower gMD, was associated with more favourable CV profiles. In women, white matter integrity was associated with enhanced ventricular diastolic function (higher gDiast)

Table 1 Baseline characteristics

	Female ($n = 7671$)	Male ($n = 7848$)
Baseline characteristics		
Age (years)	63 ± 7	64 ± 8
Weight (kg)	68 ± 12	83 ± 12
Height (cm)	164 ± 6	177 ± 6
Body mass index (kg/m^2)	25.8 ± 4.5	26.8 ± 3.9
Systolic blood pressure (mmHg)	133 ± 19	140 ± 17
Diastolic blood pressure (mmHg)	79 ± 10	83 ± 10
Mean blood pressure (mmHg)	97 ± 12	102 ± 11
Heart rate (b.p.m.)	63 ± 9	67 ± 7
Prior or active smoking, *n* (%)	2512 (33%)	3134 (40%)
Diabetes, *n* (%)	205 (3%)	464 (6%)
Hypertension, *n* (%)	1693 (22%)	2562 (33%)
Dyslipidaemia, *n* (%)	1402 (18%)	2285 (29%)
Ischaemic heart disease, *n* (%)	241 (3%)	601 (8%)
Cardiac rhythm abnormalities, *n* (%)	277 (4%)	441 (6%)
Cardiovascular MRI		
Ventricular systolic function		
LV stroke volume (mL)	79 ± 14	98 ± 19
LV ejection fraction (%)	63 ± 6	60 ± 6
LV peak longitudinal systolic strain two-chamber (%)	−21.0 ± 2.9	−19.5 ± 2.3
LV peak longitudinal systolic strain four-chamber (%)	−27.6 ± 7.9	−24.7 ± 7.3
LV mitral annulus systolic excursion two-chamber (mm)	16.2 ± 2.8	16.2 ± 2.9
LV mitral annulus systolic excursion four-chamber (mm)	9.2 ± 1.9	9.4 ± 2.2
LV peak ejection rate (mL. s^{-1})	331 ± 74	450 ± 96
Ventricular diastolic function		
LA maximum volume (mL)	67 ± 17	77 ± 22
LA minimum volume (mL)	23 ± 10	28 ± 12
LA reservoir volume (mL)	21 ± 7	23 ± 8
LA pump volume (mL)	21 ± 6	25 ± 8
LA ejection fraction (%)	66 ± 8	65 ± 9
LV peak filling rate (mL s^{-1})	306 ± 80	347 ± 101
Ventricular geometry		
LV end-diastolic volume (mL)	127 ± 21	166 ± 30
LV end-systolic volume (mL)	48 ± 12	67 ± 17
LV mass (g)	76 ± 12	110 ± 18
LV average wall thickness (mm)	5.8 ± 0.5	6.8 ± 0.7
Basal septum wall thickness (mm)	5.9 ± 1.2	7.0 ± 1.4
Arterial stiffness		
Ascending aorta distensibility (10^{-3} mmHg^{-1})	0.002 ± 0.001	0.002 ± 0.001

Continued

Table 1 *Continued*

	Female ($n = 7671$)	Male ($n = 7848$)
Brain MRI		
Global brain health		
Total brain volume (mL)	1507 ± 73	1485 ± 70
Grey matter volume (mL)	808 ± 46	779 ± 43
WMH volume (mL)	4.3 [1.4–4.9]	5.1 [1.6–6.0]
Subcortical regions		
Hippocampus volume (mL)	3.7 ± 0.4	4.0 ± 0.5
Thalamus volume (mL)	7.4 ± 0.6	8.8 ± 0.7
Accumbens volume (mL)	0.4 ± 0.1	0.5 ± 0.1
Caudatus volume (mL)	3.3 ± 0.4	3.6 ± 0.4
Pallidus volume (mL)	1.7 ± 0.2	1.9 ± 0.2
Putamen volume (mL)	4.6 ± 0.5	5.1 ± 0.6
Amygdala volume (mL)	1.2 ± 0.2	1.3 ± 0.2

All brain volumetric phenotypes were corrected for head size.
gFA, latent factor of white matter fractional anisotropy; gMD, latent factor of white matter mean diffusivity; LA, left atrium; LV, left ventricular; MRI, magnetic resonance imaging; RA, right atrium; RV, right ventricular; WMH, white matter hyperintensity.

and greater arterial compliance (greater AoD). In men, healthier white matter microstructure associated with better ventricular function, while in both sexes, preserved white matter integrity inversely correlated with ventricular geometry. These findings collectively suggest that better ventricular performance, more favourable remodelling, and enhanced arterial compliance support better brain connectivity.

Hippocampal volumes showed sex-specific association with CV phenotypes. In women, a larger hippocampus was unexpectedly associated with reduced arterial compliance (lower AoD), while in males, it correlated with enhanced ventricular systolic function (higher gSyst). Surprisingly, in both sexes, greater hippocampal volume was positively associated with increased ventricular geometry. Overall, these findings point towards complex neurotrophic and adaptative processes underlying the CV–brain axis.

All associations were confirmed in sensitivity analyses, including individuals with outlier MRI measures (see Supplementary data online, *Table S7*).

A significant interaction between age and CV phenotypes emerged exclusively among women (see Supplementary data online, *Figure S2*). In women aged 65 years or older, the positive association between WMH burden and ventricular geometry was stronger, suggesting that the relationship between gGeom and cerebral small vessel disease intensifies with advancing age. Similarly, the link between healthier white matter microstructure (higher gFA and lower gMD) and ventricular geometry was more pronounced in the older women, suggesting a steeper age-related decline in brain connectivity with adverse ventricular remodelling.

Comparative relevance of the relationships between brain and cardiovascular phenotypes

To assess the relative contribution of CV phenotypes to brain structure, we first compared the standardized β coefficients from the 'single' models. We then examined the independent associations using 'simultaneous' models by adjusting for all CV phenotypes (*Table 2*; Supplementary data online, *Table S6*).

In females, ventricular geometry (gGeom) showed the strongest and most consistent associations across brain phenotypes. Higher gGeom was associated with lower grey matter volume (standardized $\beta = -0.041$, 95% CI −0.069 to −0.013), greater WMH burden ($\beta = 0.066$, 95% CI 0.036–0.096), and impaired white matter microstructure, as indicated by lower gFA ($\beta = -0.051$, 95% CI −0.085 to −0.017) and higher gMD ($\beta = 0.090$, 95% CI 0.058–0.123). Paradoxically, higher gGeom was associated with greater hippocampal volume ($\beta = 0.082$, 95% CI 0.048–0.117). Moreover, increased arterial compliance, as reflected by higher AoD, emerged as the second most relevant CV phenotype. Greater AoD was associated with lower WMH volume ($\beta = -0.045$, 95% CI −0.074 to −0.015), enhanced white matter integrity (gFA: $\beta = 0.034$, 95% CI 0.002–0.068; gMD: $\beta = -0.063$, 95% CI −0.095 to −0.031), but smaller hippocampal volume ($\beta = -0.052$, 95% CI −0.086 to −0.018).

In males, gGeom was again the CV phenotype most strongly and consistently associated with brain structure. Higher gGeom correlated with higher WMH burden ($\beta = 0.062$, 95% CI 0.031–0.092), poor white matter integrity (gFA: $\beta = -0.083$, 95% CI −0.112 to −0.051; gMD: $\beta = 0.114$, 95% CI 0.083–0.145). Similar to females, greater gGeom was paradoxically associated with greater hippocampal volume ($\beta = 0.039$, 95% CI 0.006–0.071). However, unlike in females, in males, systolic function (gSyst) was the second strongest CV phenotype associated with brain phenotypes. Increased gSyst was associated with lower WMH volume ($\beta = -0.038$, 95% CI −0.064 to −0.013), healthier white matter microstructure (gFA: $\beta = 0.043$, 95% CI 0.016–0.071; gMD: $\beta = -0.025$, 95% CI −0.051 to −0.011), and greater hippocampal volume ($\beta = 0.028$, 95% CI 0.001–0.055).

Of importance, in either sex, the strength, direction, and significance of the associations between gGeom and brain phenotypes remained

Table 2 Associative measures of brain phenotypes with cardiovascular phenotypes

	LV systolic function (gSyst)			LV diastolic function (gDiast)			LV geometry (gGeom)			Aortic distensibility (AoD)		
	β	95% CI	*P*-value	*β*	95% CI	*P*-value	*β*	95% CI	*P*-value	*β*	95% CI	*P*-value
Females												
Brain Vol[a]	−0.002	−0.026; 0.021	.999	0.012	−0.013; 0.037	.904	0.017	−0.012; 0.046	.571	0.015	−0.013; 0.043	.676
Brain Vol[b]	0.001	−0.023; 0.024	.999	0.015	−0.011; 0.042	.569	0.022	−0.009; 0.052	.303	0.019	−0.008; 0.046	.322
GM Vol[a]	−0.022	−0.045; 0.001	.061	0.031	0.007; 0.055	.004	−0.041	−0.069; −0.013	<.001	0.008	−0.019; 0.035	.999
GM Vol[b]	−0.020	−0.043; 0.003	.121	0.015	−0.010; 0.040	.563	−0.038	−0.068; −0.009	.004	0.012	−0.014; 0.038	.999
WMH Vol[a]	−0.027	−0.051; −0.002	.028	−0.003	−0.029; 0.023	.999	0.066	0.036; 0.096	<.001	−0.045	−0.074; −0.015	<.001
WMH Vol[b]	−0.025	−0.49; 0.001	.051	0.012	−0.015; 0.039	.999	0.073	0.041; 0.104	<.001	−0.040	−0.068; −0.001	.001
gFA[a]	0.024	−0.004; 0.052	.125	0.016	−0.013; 0.046	.645	−0.051	−0.085; −0.017	<.001	0.034	0.002; 0.068	.039
gFA[b]	0.025	−0.003; 0.054	.106	0.008	−0.023; 0.039	.999	−0.050	−0.086; −0.001	.002	0.030	−0.002; 0.062	.084
gMD[a]	−0.015	−0.042; 0.012	.709	−0.030	−0.058; −0.002	.030	0.090	0.058; 0.123	<.001	−0.063	−0.095; −0.031	<.001
gMD[b]	−0.013	−0.040; 0.014	.999	−0.008	−0.038; 0.022	.999	0.090	0.055; 0.125	<.001	−0.060	−0.090; −0.029	<.001
Hippo Vol[a]	−0.005	−0.034; 0.023	.999	−0.029	−0.058; 0.001	.057	0.082	0.048; 0.117	<.001	−0.052	−0.086; −0.018	<.001
Hippo Vol[b]	−0.002	−0.031; 0.027	.999	−0.007	−0.039; 0.024	.999	0.078	0.041; 0.115	<.001	−0.045	−0.077; −0.012	.002
Males												
Brain Vol[a]	0.004	−0.021; 0.028	.999	−0.014	−0.039; 0.011	.677	0.017	−0.012; 0.047	.543	0.018	−0.009; 0.044	.371
Brain Vol[b]	0.003	−0.022; 0.028	.999	−0.008	−0.036; 0.019	.999	0.014	−0.017; 0.045	.999	0.013	−0.013; 0.039	.822
GM Vol[a]	−0.003	−0.025; 0.022	.999	−0.002	−0.025; 0.022	.999	−0.003	−0.031; 0.025	.999	0.017	−0.008; 0.042	.359
GM Vol[b]	−0.001	−0.025; 0.023	.999	−0.004	−0.030; 0.022	.999	−0.005	−0.035; 0.025	.999	0.017	−0.008; 0.043	.355
WMH Vol[a]	−0.038	−0.064; −0.013	<.001	−0.002	−0.028; 0.024	.999	0.062	0.031; 0.092	<.001	−0.032	−0.059; −0.004	.015
WMH Vol[b]	−0.040	−0.066; −0.015	<.001	0.099	−0.019; 0.037	.999	0.069	0.037; 0.101	<.001	−0.027	−0.054; 0.001	.054
gFA[a]	0.043	0.016; 0.071	<.001	0.036	0.007; 0.064	.007	−0.083	−0.112; −0.051	<.001	0.000	−0.030; 0.030	.999
gFA[b]	0.051	0.023; 0.079	<.001	0.018	−0.012; 0.050	.504	−0.076	−0.111; −0.041	<.001	−0.001	−0.300; 0.039	.999
gMD[a]	−0.025	−0.051; −0.011	.023	−0.044	−0.071; −0.018	<.001	0.114	0.083; 0.145	<.001	−0.025	−0.053; 0.003	.115
gMD[b]	−0.033	−0.059; −0.007	.007	−0.018	−0.047; 0.011	.484	0.106	0.074; 0.139	<.001	−0.026	−0.054; 0.002	.087
Hippo Vol[a]	0.028	0.001; 0.055	.038	−0.018	−0.045; 0.010	.462	0.039	0.006; 0.071	.011	−0.024	−0.054; 0.005	.147
Hippo Vol[b]	0.030	0.023; 0.057	.026	−0.006	−0.036; 0.024	.999	0.038	0.003; 0.073	.023	−0.031	−0.060; 0.002	.094

Standardized beta (*β*) coefficients, 95% CIs, and *P*-value for multivariable linear regression models in which each brain phenotype was regressed onto a [a]single or [b]simultaneous cardiovascular phenotypes (latent variables and AoD) and adjusted for age, age^2, hypertension, diabetes, dyslipidaemia, active smoking, body mass index, height, and mean blood pressure. Bonferroni's correction was applied to 95% CIs and *P*-value. All brain volumetric phenotypes were corrected for head size.
AoD, aortic distensibility; Brain Vol, brain volume; CI, confidence interval; GM Vol, grey matter volume; gFA, latent variable for white matter anisotropy; gMD, latent variable for white matter diffusivity; Hippo Vol, hippocampus volume; LV, left ventricular; WMH Vol, white matter hyperintensity volume.

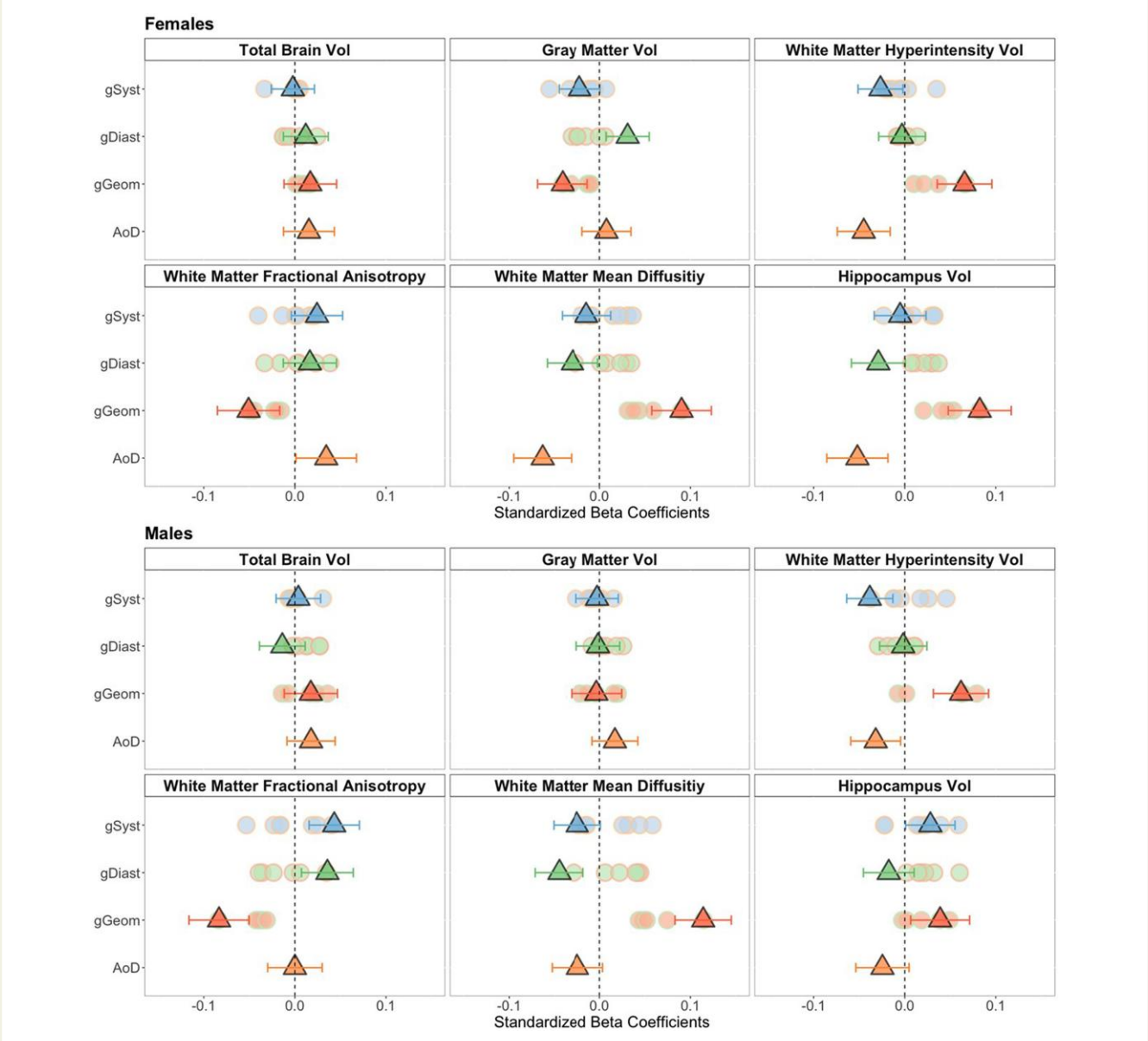


Figure 2 Association between brain phenotypes and cardiovascular phenotypes (latent variables and aortic distensibility). Standardized β coefficients (▲) and 95% confidence intervals (error bars) are shown for individual multivariable linear regression models where brain phenotypes (response variables) were regressed onto cardiovascular phenotypes (gSyst, gDiast, gGeom, AoD), with adjustment for age, age^2, hypertension, diabetes, dyslipidaemia, active smoking, body mass index, height, mean blood pressure, and the interaction term between the cardiovascular phenotype and age. Additionally, white matter fraction anisotropy and mean diffusivity correspond to the latent variables gFA and gMD, respectively (please see the main text for further details). Standardized β coefficients (◯) for each cardiovascular biomarker corresponding to the respective cardiovascular latent variable are depicted and further detailed in the Supplementary data (Supplementary data online, *Tables S10* and *S11*). Bonferroni's correction for multiple comparisons was applied to the 95% confidence intervals . AoD, aortic distensibility; gDiast, latent variable for ventricular diastolic function; gFA, latent variable for white matter anisotropy; gGeom, latent variable for ventricular geometry; gMD, latent variable for white matter diffusivity; gSyst, latent variable for ventricular systolic function; Vol, volume.

consistent when all CV phenotypes were introduced in the 'simultaneous' models, highlighting a robust independent link between ventricular remodelling and brain phenotypes.

Associations between subcortical region volumes and cardiovascular phenotypes

While ventricular geometry (gGeom) was consistently associated with phenotypes of poor brain health, it was unexpectedly linked to larger hippocampal volume. To investigate this finding further, we examined the relationships between other subcortical regions and CV phenotypes using the 'single' and 'simultaneous' models developed for our primary analysis. Similarly for the hippocampus, greater gGeom was the CV phenotype most strongly associated with larger subcortical region volumes across both models (see Supplementary data online, *Table S8*). The strongest associations were observed between gGeom and thalamic volume in both females and males.

Influence of birth weight on ventricular geometry and brain phenotypes

Given that birth weight is a known determinant of LV mass,[17,38] the primary contributor to gGeom construction, we investigated the relationship between birth weight and gGeom by regressing gGeom onto birth weight. Even after adjusting for age, body mass index, height, and CV risk factors at the time of MRI, higher birth weight was significantly associated with greater gGeom in females (standardized $\beta = 0.116$, 95% CI 0.093–0.140) and males ($\beta = 0.088$, 95% CI 0.062–0.115).

To further explore the discordant associations between gGeom and brain phenotypes, we examined the relationship between birth weight and brain phenotypes by regressing brain phenotypes onto birth weight. After adjusting for age, body mass index, height, and CV risk factors, no associations were found between birth weight and phenotypes of general brain health, such as grey matter volume, WMH burden, and white matter microstructure (gFA and gMD). However, greater birth weight was consistently linked to larger hippocampal volume in females (standardized $\beta = 0.086$, 95% CI 0.060–0.111) and males ($\beta = 0.076$, 95% CI 0.048–0.104) and an increased size of the other subcortical regions (see Supplementary data online, *Table S9*).

Cognitive performance and cardiovascular phenotypes

In female participants, higher fluid intelligence (standardized $\beta = 0.042$, 95% CI 0.013–0.071) and shorter reaction time (standardized $\beta = -0.034$, 95% CI −0.061 to −0.006), denoting better cognitive performance, were significantly associated with greater gGeom. In contrast, fluid intelligence or reaction time was not associated with gSyst, gDiast, or AoD.

Similarly, in male participants, greater fluid intelligence (standardized $\beta = 0.060$, 95% CI 0.032–0.088) and shorter reaction time (standardized $\beta = -0.033$, 95% CI −0.060 to −0.006) were linked to greater gGeom. Similarly, no association was observed between cognitive performance and gSyst, gDiast, or AoD. No interaction with age was found in either sex.

Mediation analysis

We found that hippocampal volume accounted for part of the relationship between gGeom and both fluid intelligence and reaction time in both female and male participants. Specifically, hippocampal volume explained 21% of the association of gGeom on fluid intelligence in females and 6% in males. Similarly, hippocampal volume explained 11% of the association of gGeom on reaction time in females and 10% in males. These values reflect the indirect effect—the proportion of the total association between gGeom and fluid intelligence or reaction time that operates through hippocampal volume—while the direct effect reflects the remaining association not explained by the hippocampus (*Figure 3*). These exploratory findings suggest that hippocampal integrity may partially underlie the relationship between gGeom and cognition, although causality cannot be inferred.

Discussion

This study investigated the associations between brain structure, CV phenotypes (i.e. latent variables and AoD), and cognitive function in a large, population-based cohort of middle-aged and older adults free from neurodegenerative diseases and stroke. The key findings are as follows. Firstly, ventricular geometry (gGeom), the latent variable encapsulating myocardial mass, ventricular volumes, and wall thickness, emerged as the CV phenotype most strongly associated with hippocampal and subcortical region volumes and, unlike other CV phenotypes, was linked to better cognition (*Structured Graphical Abstract*). Second, despite its associations with larger hippocampal volume and enhanced cognition, gGeom also demonstrated paradoxical associations with markers of compromised brain health, including reduced grey matter volume, increased WMH burden, and diminished white matter microstructural integrity. Third, latent variables representing systolic (gSyst) and diastolic (gDiast) function, along with arterial compliance (AoD), exhibited weaker and less consistent relationships with general brain health, as well as with hippocampal and subcortical region volumes. Importantly, none of these CV phenotypes was significantly associated with cognitive performance. Collectively, these findings underscore the complex interplay between CV and brain health, highlighting gGeom as an important determinant in brain structure and function.

Unlike previous studies which focused on a single CV biomarker,[8–19] we adopted a comprehensive approach by aggregating multiple CV MRI measures into highly informative domain-specific latent variables. This method, using confirmatory factor analysis,[20] aims to provide a more accurate representation of underlying pathophysiological processes than individual biomarkers, while preserving interpretability through factor loadings that indicate the direction and strength of relationships between biomarkers and their latent construct. We then employed multivariable linear regression to assess the associations between brain phenotypes and CV phenotypes. These models were adjusted for key confounders, including age, body mass index, height, and well-established CV risk factors. We evaluated the individual contribution of each CV phenotype in the 'single' models and their independent contribution to brain phenotype variance in 'simultaneous' models that included all CV phenotypes.

In conducting these analyses, ventricular geometry (gGeom) emerged as the CV phenotype most strongly and independently associated with hippocampal and subcortical region volumes, both in 'single' and 'simultaneous' models. gGeom was also the sole CV phenotype associated with better cognition, a well-established predictor of incident dementia.[34] Importantly, LV mass demonstrated the greatest loading (i.e. relationship) to gGeom, indicating that this single biomarker contributed the most to the gGeom construction. Smaller studies have shown conflicting results regarding LV mass, neurodegeneration, and cognition.[39–43] In hypertensive patients with severe LV hypertrophy and dysfunction,[39–41] increased risks of cognitive decline or dementia have been documented, whereas the association of uncomplicated LV hypertrophy with brain health and cognition[42,43] remain less clear, particularly in population-based studies.[17–19,43–45] Recent reports have linked LV mass and volumes to larger subcortical regions,[18,19] yet their functional implications for cognition remained unexplored. Other studies have linked cognitive performance with larger LV volumes and mass without, however, specifically addressing the association with the hippocampus or other subcortical regions.[17] Bai *et al.*[17] reported that approximately one-quarter of the positive association between LV mass and fluid intelligence was explained by greater brain volume. To our knowledge, this study is the first to demonstrate a consistent association between increased ventricular geometry, larger hippocampus, and better cognitive performance. Notably, we found that the positive association between ventricular geometry and cognition was partially explained by larger hippocampal volume across both sexes. Specifically, in females, a larger hippocampus accounted for more than one-fifth of the association between greater gGeom and fluid

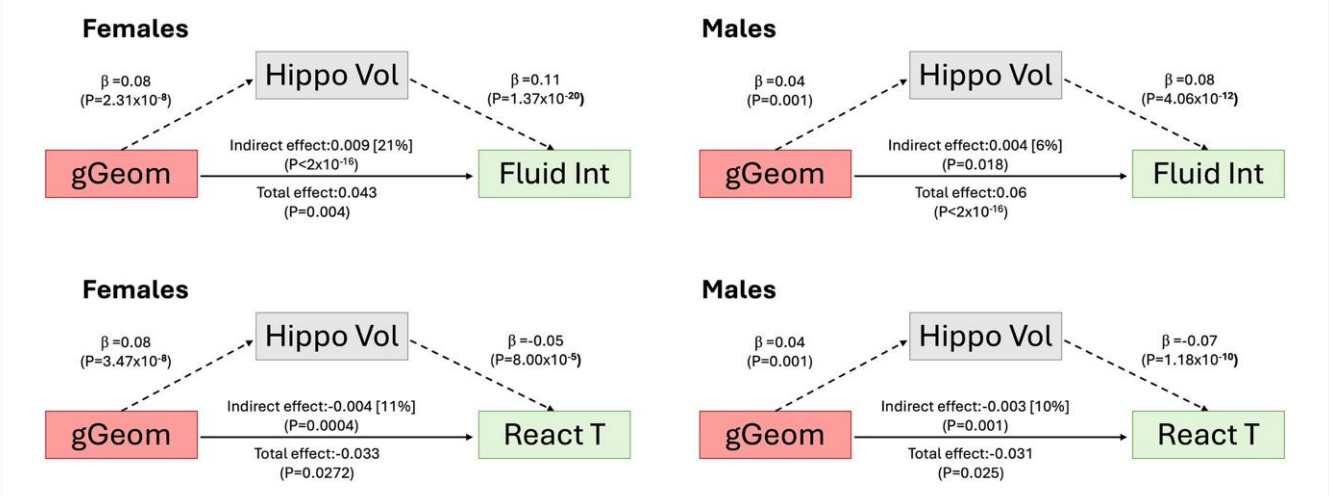


Figure 3 Mediation analysis of ventricular geometry, hippocampal volume, fluid intelligence, and reaction time. The figure shows standardized β coefficients and *P*-values for models examining the associations between gGeom (ventricular geometry; 'exposure'), hippocampal volume ('mediator'), and fluid intelligence or reaction time ('outcome') in female and male participants. All models were adjusted for key baseline confounders as detailed in the statistical methods. The indirect effect represents the proportion of the total effect of gGeom on fluid intelligence or reaction time that is mediated by hippocampal volume. gGeom, latent variable for ventricular geometry; Hippo Vol, hippocampal volume; Fluid Int, fluid intelligence; React T, reaction time.

intelligence. These findings suggest that gGeom may enhance cognitive reserve through its association with hippocampal integrity, although causation cannot be inferred.

Despite its favourable associations with hippocampal volume and cognition, gGeom was paradoxically linked to neurodegenerative markers, including increased WMH burden, reduced white matter integrity, and compromised connectivity, which have been repeatedly associated with cognitive decline and dementia.[46,47] Specifically, higher gGeom correlated with reduced fractional anisotropy and increased mean diffusivity, which are indicative of poor white matter integrity. In females, greater gGeom was associated with lower grey matter volumes, while in both sexes, it was linked to higher WMH volume—a hallmark of cerebral small vessel disease and a contributor to cognitive decline (*Figure 2* and *Table 2*). Moreover, older women exhibited increased vulnerability to neurodegeneration in response to greater ventricular geometry (gGeom), suggesting a sex- and age-specific modulation of the CV–brain axis, potentially driven by post-menopausal hormonal changes, reduced cerebrovascular resilience, and higher cumulative CV risk exposure in elderly women.[26,48]

Overall, these findings suggest that while gGeom may confer cognitive benefits via hippocampal and subcortical region preservation, its association with neurodegenerative changes highlights a complex relationship between adaptive and maladaptive processes. One possible explanation for this intriguing duality is that genetic, epigenetic, and early-life factors may have contributed to the favourable development of both ventricular geometry (mass and volumes) and subcortical brain structures, while later-life environmental factors (e.g. CV risk factors) likely influenced maladaptive changes, including LV hypertrophy and dilatation, increased WMH burden, and disruption of white matter microstructure. We observed that birth weight—a well-stablished proxy for intrauterine conditions and organogenesis—was positively and specifically associated with greater gGeom, along with larger hippocampal and subcortical region volumes in later life. This finding is consistent with the developmental origins of the health and disease hypothesis, which posits that early-life factors are key in shaping long-term trajectories of CV and neurovascular systems.[49] Mechanistically, vascularization is a critical regulator of neurogenesis during embryonic and early postnatal development, particularly in subcortical regions.[50] The hippocampus, uniquely among brain structures, retains neuroplasticity into adulthood, making it especially sensitive to vascular cues and perivascular microvascular signalling.[51] It can therefore be speculated that a well-developed CV system (i.e. high gGeom) during intrauterine and early postnatal life may enhance neurogenesis and maturation of hippocampal and subcortical structures through enriched vascularization.[50] Furthermore, emerging evidence supports shared genetic and epigenetic determinants influencing both ventricular geometry and hippocampus, lending further credence to the hypothesis of a common developmental basis underlying the observed associations between gGeom and subcortical structure volumes.[52]

We also observed a consistent positive association between ventricular geometry and subcortical regions beyond the hippocampus. Emerging evidence highlights the importance of the thalamus, putamen, and other nuclei in cognitive and memory functions, primarily through their roles in integrated spatial coding and information processing.[53] In particular, lesions affecting the rostral and anterior thalamic nuclei have been shown to elicit deficits in spatial and non-spatial cognitive tasks comparable to those observed resulting from hippocampal damage, underscoring the critical role of interconnected subcortical circuits in cognitive processing.[54]

Future research should prioritize longitudinal investigations leveraging the repeated imaging, cognitive, and genomic data available in the UK Biobank and similar cohorts. Specifically, tracking changes over time in gGeom, the hippocampus and other subcortical brain structures, along with cognitive performance, will be crucial to disentangle the temporal sequence and directionality of these associations. This approach may help clarify whether beneficial early-life CV phenotypes (e.g. higher gGeom) confer enduring neuroprotection and, by contrast, to what extent later-life maladaptive CV remodelling contributes to neurodegeneration. Additionally, integrating genome-wide association studies and polygenic risk scores could uncover shared

genetic architecture linking ventricular geometry, brain structure, and cognition, thus helping to distinguish genetic and developmental pathways from environmentally driven processes. Finally, these longitudinal and genetically informed studies may support precision medicine strategies by identifying individuals at heightened risk for dual CV–brain vulnerability and therefore guiding the timing and nature of preventive interventions.

We acknowledge that, in general, the effect size of the associative measures and mediation analyses were small according to Cohen's metric,[36] typically accounting for approximately 1% of the variance in brain structure or cognitive outcomes. However, the precision afforded by our large, well-characterized cohort ensures robust and informative estimates, offering valuable guidance for researchers and clinicians in the design of future studies and interventions. In this direction, these study findings challenge the long-held haemodynamic-arterial hypothesis, which states that reduced LV systolic performance—indicated by reduced stroke volume or cardiac index—and decreased arterial compliance, as reflected by low AoD, are the main drivers of chronic cerebral hypoperfusion, cerebral microvessel damage (e.g. high WMH burden), and neurodegenerative changes, eventually leading to cognitive decline and dementia.[11–15] While we observed an association between reduced arterial compliance (i.e. low AoD) and greater WMH burden in both sexes, the effect size of these associative measures was substantially lower than that found with ventricular geometry (gGeom). In females, decreased arterial compliance was also linked to compromised white matter microstructure and connectivity. However, these associations were not replicated in males in whom ventricular systolic function (gSyst) emerged as the second most important CV phenotype, after gGeom, associated with white matter integrity. Importantly, unlike ventricular geometry, neither gSyst, gDiast, nor AoD showed significant associations with cognitive function. Collectively, these findings highlight the relatively modest contribution of these CV phenotypes to brain structure and cognition, underscoring the dominant role of ventricular geometry.

From a clinical perspective, our study findings reinforce the importance of identifying and targeting maladaptive LV remodelling (e.g. increased gGeom) in mid-to-late life to benefit both CV and brain health. Preventive and early intervention strategies aimed at reducing LV hypertrophy and dilatation may therefore extend well beyond CV protection, potentially mitigating neurodegenerative abnormalities and lowering the risk of dementia. Our results may also have implications for patients with impaired CV development (e.g. reduced gGeom), such as those with congenital heart disease. In these individuals, abnormal heart development is known to affect neurodevelopment,[55,56] and we found that such early-life abnormalities may confer reduced resilience to neurodegenerative disease later in life, underscoring the importance of long-term monitoring and tailored preventive strategies.

Limitations

This study has several limitations. First, the cohort comprised mainly older adults of European ancestry (54% women) and residing in relatively affluent regions across the UK. The relatively healthy CV profile of the UK Biobank cohort, characterized by preserved LV systolic function, may have also limited the detection of associations between gSyst or gDiast with brain phenotypes and cognitive outcomes. Additionally, our final sample included only participants with complete data on CV imaging, cognition, and all covariates, resulting in the exclusion of 16 986 individuals. This approach may have introduced further selection bias, potentially enriching the cohort for healthier and more cognitively intact individuals. As such, our findings may not generalize to other ethnic groups, younger populations, or individuals with overt CV diseases, including heart failure. Future studies in more diverse and clinically heterogeneous populations are warranted to evaluate the broader applicability of these study findings. Second, the confirmatory factor analyses used to construct latent variables showed modest to moderate fit indices (e.g. the comparative fit index ranged from 0.406 for gDiast to 0.699 for gFA). However, the latent constructs were explicitly based on predefined groupings of CV or brain biomarkers sharing structural and functional significance. This approach was central to our analytical framework and dictated the model structure, prioritizing conceptual and pathophysiological coherence over statistical optimization. Third, our analyses were cross-sectional, and therefore, no conclusions can be drawn regarding lifelong trajectories or causality in CV–brain interactions. This limitation also applies to the mediation analysis, where the assumed directional pathways are inherently constrained by the study's cross-sectional design. Fourth, we identified only 33 cases of incident all-cause dementia in our cohort which prevented us to conduct any reliable survival analysis in our sample. Fifth, although birth weight was associated with gGeom as well as hippocampal and other subcortical region volumes, unmeasured confounders—such as childhood socioeconomic status, early-life nutrition, or perinatal exposures—were not accounted for, warranting caution in interpreting these associations. Sixth, the absence of cortical microinfarct data in our study precluded investigation of their potential mediating role in the relationship between CV and brain phenotypes with cognitive outcomes.[57] Seventh, we were unable to adjust our models for physical activity and other key lifestyle factors due to the limited availability of these data in the imaging cohort. As such, we cannot exclude the possibility of residual confounding from unmeasured behaviours such as exercise, diet, or sleep. Finally, we applied a uniform ±4 SD threshold to identify potential outliers across MRI biomarkers as previously reported.[17,18,25] While this approach helped minimize the impact of technical artefacts, it may have inadvertently excluded some physiological extreme values by not accounting for the specific distribution of each biomarker. However, the sensitivity analysis, which included participants with outlier MRI measures, confirmed the study results.

Conclusions

Our study findings offer physicians and researchers a novel perspective on the CV–brain interaction by challenging the current haemodynamic–arterial paradigm and emphasizing the important role that ventricular geometry plays in shaping brain architecture and cognition. These exploratory insights may have potentially far-fetching implications for the prevention of CV and neurodegenerative diseases, as well as the identification of genetic and early-life factors contributing to long-term CV and brain health.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

P.-G.M. was a consultant at the Perspectum Diagnostics Ltd (Oxford, UK)—consultancy ended November 2022. A.P.K. and E.P.-A. have received royalties/licenses from Perspectum Diagnostics Ltd (Oxford, UK) within the last 36 months. R.R. is currently the Chief Executive Officer of Fraiya Ltd (London, UK).

Data Availability

The data underpinning this study will be shared on reasonable request by the corresponding author.

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Ethical Approval

This study complied with the UK Biobank ethical approval from the National Health Service on 17 June 2021 (ref: 11/NW/0382) and the subsequent extension on 18 June 2021 (ref: 21/NW/0157).

Pre-registered Clinical Trial Number

None supplied.

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