Associations between left ventricular function, vascular function and measures of cerebral small vessel disease: a cross-sectional magnetic resonance imaging study of the UK Biobank

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Title: Associations between Left Ventricular Function, Vascular Function and measures of cerebral Small Vessel Disease: a Cross-Sectional Magnetic Resonance Imaging Study of the UK Biobank.

Key words: Ejection fraction, arterial stiffness, cerebral small vessel disease, magnetic resonance imaging, epidemiology

Key points:

- Ejection fraction is non-linearly and cardiac index is linearly associated with MRI derived measures of cerebral small vessel disease.
- No associations were found for arterial stiffness with cSVD measures.

Abbreviations:

AIx = augmentation index
CI = cardiac index
cSVD = cerebral small vessel disease
EF = ejection fraction
LV =left ventricular
WMH = white matter hyperintensities

Abstract

Objectives:

Impaired cardiovascular function has been associated with cognitive deterioration, however to what extent cardiovascular dysfunction plays a role in structural cerebral changes remains unclear. We studied whether vascular and left ventricular (LV) function are associated with measures of cerebral small vessel disease (cSVD) in the middle-aged general population.

Methods:

In this cross-sectional analysis of the UK-Biobank, 4,366 participants (54% female, mean age 61 years) underwent magnetic resonance imaging to assess LV function (ejection fraction[EF] and cardiac index[CI]) and cSVD measures (total brain volume, grey and white matter volumes, hippocampal volume and white matter hyperintensities[WMH]). Augmentation index (AIx) was used as a measure of arterial stiffness. Linear and non-linear associations were evaluated using cardiovascular function measures as determinants and cSVD measures as outcomes.

Results:

EF was non-linearly associated with total brain volume and grey matter volume, with the largest brain volume for an EF between 55-60% (both $p<0.001$). EF showed a negative linear association with WMH (-0.23%[-0.44; -0.02], p=0.03), yet no associations were found with white matter or hippocampal volume. CI showed a positive linear association with white matter (β 3,194 mm^3[760; 5,627], p=0.01) and hippocampal volume (β 72.5 mm^3[23.0; 122.0], p=0.004). No associations were found for CI with total brain volume, grey matter volume or WMH. No significant associations were found between AIx and cSVD measures.

Conclusions:

This study provides novel insights into the complex associations between the heart and the brain, which could potentially guide early interventions aimed at improving cardiovascular function and prevention of cSVD.

1 Introduction

The impact of cardiovascular risk on cerebrovascular dysfunction, cognitive decline and dementia in older populations is well established[1]. In the worldwide aging population, the societal and economic impact of dementia is increasing[2].

Cardiovascular function is increasingly recognised as a potential target for the preservation of cognitive function, as heart failure is a known independent risk factor for cognitive decline[3]. Chronic hypoperfusion has been suggested as a potential pathophysiological mechanism for the impact of heart failure on cognitive decline, which is supported by studies that have shown that even mild systolic left ventricular (LV) dysfunction is associated with impaired cognitive function[4]. However, the limited amount of studies investigating the impact of LV systolic function on magnetic resonance imaging (MRI) findings of cerebral small vessel disease (cSVD), including white matter hyperintensities (WMH) and brain atrophy[5], have shown conflicting results[4; 6-9].

In addition to LV systolic function, vascular stiffness has also been associated with cognitive decline. Aortic stiffness is thought to impact the brain through a propulsion increase of the pulsatile pressure to the smaller vessels of the brain leading to cSVD[10]. So far, the impact of vascular stiffness on brain structure and function has been studied mainly using pulse wave velocity. Less is known about the impact of the augmentation index (AIx) on cSVD and the results are conflicting[11; 12]. The AIx is an easily assessable measure of systemic arterial stiffness and a known independent risk factor for cardiovascular (CV) events[13; 14].

We hypothesize that systemic LV function and vascular stiffness are associated with measures of cSVD on brain imaging. To elucidate the impact of cardiovascular dysfunction on brain structure, we performed analyses in a large scale imaging study using cardiac and brain imaging in a middle aged population.

2 Methods

The UK Biobank Study (see www.ukbiobank.ac.uk for more information) is a large population-based cohort that includes 503,325 individuals aged 45 to 73 years old[15]. The participants were recruited across the United Kingdom for participation over a 5-year period beginning in 2006. The study protocol was approved by the National Research Ethics Service Committee North West–Haydock (reference 11/NW/0382). Informed consent was obtained from all participants. Questionnaire-based data were obtained on ethnicity, socioeconomic status, smoking status, alcohol consumption and history of cardiovascular disease. Serum sample collection has been previously described in detail[16]. Between 2014 and 2017 a dedicated laboratory performed serum analysis of among others, CRP, cholesterol, HbA1c and creatinine. For this study we only included data of individuals who underwent cardiac magnetic resonance imaging during the study before the 30^{th} of January 2018. A short overview and explanation of the used measures is supplied in table **S1.**

Cardiac MRI

A 20-min electrocardiographically-gated cardiac MRI protocol was performed on a 1.5 Tesla wide bore scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare)[17]. The scanner uses a 45 mT/m and 200 T/m/s gradient system with an 18 channels anterior body surface coil, jointly with 12 elements of an integrated 32 element spine coil. For the analysis of LV function (ejection fraction (EF) and cardiac index(CI)), four long axis cines were acquired (horizontal long axis, vertical long axis, and LV outflow tract cines both sagittal and coronal) together with a short axis stack of balanced steady state free precession cines (breath hold acquisitions with flip angle of 80°, repetition time 2.7 ms, echo time 1.16 ms for the long axis and 2.6 ms and 1.10 ms for the short axis respectively, long axis slice thickness of 6 mm and 8 mm for the short axis with a 2 mm gap, matrix 208 x 187 and typical field of view of 380 x 274 mm for the long axis and 380 x 252 mm for the short axis with 50 reconstructed phases). Automated image analysis was performed by the inline software provided by

the scanner to determine end-diastolic and end-systolic volumes to calculate EF, CI (cardiac output/ body surface area) and stroke volume[18].

Brain MRI

For brain imaging, participants were scanned on a 3.0-T scanner (Siemens Skyra, software VD13, Siemens Healthcare) with a 32-channel radiofrequency receiver head coil. Preprocessing was performed with the use of FSL packages (version 5.0, FMRIB Software Library). As part of the imaging processing and quality control pipeline (referred to as FBP, version 1.0; Biobank Pipeline in FMRIB) the coordinating UK Biobank research team performed imaging processing and analysis for brain volumes[19].

T1-weighted images were acquired using a magnetization-prepared 3D rapid-acquisition and a gradient-echo sequence (matrix 208 x 256 x 256; voxel size 1 x 1 x 1 mm; inversion time 880 msec; repetition time 2000 ms). T2-FLAIR was performed using a 3D-SPACE sequence (matrix 192 x 256 x 256; voxel size 1.05 x 1.0 x 1.0 mm; inversion time 1800 msec; repetition time 5000 msec). For extraction of white matter, grey matter and hippocampal volume, segmentation of T1-weigted data was first performed using FAST (version 4.1; Automated Segmentation Tool in FMRIB). The brain measures were normalized for head size. The volume of WMH's were derived from T1 and T2-FLAIR images, using BIANCA (Brain Intensity AbNormality Classification Algorithm)[20].

Augmentation Index (AIx) by Pulse Wave Analysis

The Vicorder (Skidmore Medical) device was used to digitally compute a brachial pressure wave trace from a manual sphygmomanometer inflated to a static 70 mmHg using a volume displacement technique[17]. The Vicorder software calculates the central pressure wave using a brachial-to-aortic transfer function. The central pressure waveform consists of two peaks, the first peak originates from the left ventricular output and the second peak arises from the peripheral pulse wave reflection. AIx is

the percentage increase in pulse pressure caused by the second reflected waveform[21]. Negative values have been shown to falsely distort the analysis and were therefore excluded[22].

Statistical Analysis

A complete case analysis was performed. Variables were checked for normal distribution and transformed if necessary. WMH were log-transformed to adjust for a right-skewed distribution and after analysis back-transformed for interpretation to represent the mean percentage change in WMH. Potential outliers were excluded (more than 4 times the standard deviation of the mean). Analysis of variance (ANOVA) was used to test for a significant difference in explanatory power between a linear or non-linear function describing the associations between cardiovascular function measures and cSVD measures. When ANOVA indicated a better fit of the data using a linear function, linear regression coefficients (β) with corresponding 95% confidence intervals reflecting the change in brain volumes per unit change in cardiovascular function (EF, CI, AIx) were described. In cases where ANOVA indicated a non-linear function as a better fit, polynomial splines were performed with four degrees of freedom. For EF, additional multivariate analyses were performed to test whether normal EF (≥50%) versus reduced EF (<50%), as defined in the current ESC guideline, was associated with cSVD[23]. All analyses were adjusted for age, sex, ethnicity, socioeconomic status, smoking status, alcohol use, hypertension and diabetes. As heart rate, height and mean arterial pressure are known to affect AIx, additional adjustment for these parameters was performed in analyses with AIx. Interaction terms for sex and age (dichotomised to <60 years old and ≥60 years old) were added to the analysis to test whether the associations of cardiovascular function with cSVD was stronger in either sex or age categories. Sensitivity analyses was performed by excluding participants with diabetes or a history of cardiovascular disease (ischemic heart disease and stroke). Variance inflation factors (VIF) were used to assess multicollinearity, the results are shown in the supplementary data. Multicollinearity was

considered present if VIF was above 10.[24] Analyses were performed using R (version 3.6.1) and a P-value <0.05 was considered statistically significant.

3 Results

502,617 individuals participated in the UK-biobank, of which 4,366 participants had available cardiac and brain imaging measures (Flow diagram shown in **figure 1**). An overview of the baseline characteristics is provided in **table 1**. Age of participants ranged from 45 to 73 years old with a mean of 61.1 ± 7.2 years and 54% of participants were female. Participants were slightly obese (BMI 26.4 ± 4.0 kg/m2), 61.2% had never smoked and 23% had a history of hypertension. On average, mean cardiovascular parameters were relatively normal with an EF of 56.2 ± 6.0, CI of 2.6 ± 0.5 and AIx of 21.2 ± 8.6.

Associations between systolic LV function and measures of cerebral small vessel disease

Tables 2 shows the adjusted associations between left ventricular parameters and brain parameters. Unadjusted analysis are shown in supplementary **table S2**. ANOVA indicated that a non-linear function provided the best fit for the associations between EF and total brain volume (p<0.001), and between EF and grey matter volume (p<0.001) (**figure 2b and 2c**). An EF below 55% was associated with lower total brain and grey matter volumes in non-linear function analysis (figure 2). Also in cases with an EF above 60% lower total brain and grey matter volumes were observed. A significant negative linear association was observed between EF and WHM (-0.23% [-0.44; -0.02], p=0.03), accordingly a 10% lower EF is on average associated with 2.3% more WMH. No significant associations were found between EF and white matter volume (p=0.08) or hippocampal volume (p=0.13). Similar results were found for EF dichotomized to normal (≥50%) and reduced EF (<50%), in which a reduced EF was associated with a lower total brain and grey matter volume (β -8340.0 mm^3 [-14259.4; -2420.5],

p=0.006; -6586.0 mm^3 [-10069.5; -3102.9], p<0.001 respectively). Again, no significant associations were found for white matter volume (p=0.38) and hippocampal volume (p=0.32). Reduced EF was again associated with more WMH (4.85% [0.84; 9.02], p=0.02).

We performed an additional analysis towards the association of a high EF with lower total brain volume and grey matter volume **(figure 2b and 2c)** to examine if this could be explained by a reduction in stroke volume, which can be observed in a hypertrophic and hyperdynamic LV. To delineate the impact of high EF on stroke volume in our population, EF was plotted against stroke volume, showing a rapid decline in stroke volume above an EF of 70% **(figure 3)**. Additionally, the association between EF and brain volumes was further adjusted for stroke volume, showing similar associations between EF and total brain or grey matter volume (data not shown).

For CI, ANOVA indicated that a linear association provided the best explanatory power to analyse the association between CI and white matter volume (β 3,194 mm^3 [760; 5,627], p=0.01) and hippocampal volume (β 72.5 mm^3 [23.0; 122.0], p=0.004). Per 1 L/min/m^2 change in CI, white matter volume changed with 3,194 mm^3. So in a person with 2 SD (SD=0.5L/min/m^2) higher CI, white matter volume is on average 3,194 mm^3 higher. CI was not significantly associated with total brain volume, grey matter volume or WMH (p=0.13, p=0.75 and 0.97 respectively).

Associations between vascular stiffness and measures of cerebral small vessel disease

In the adjusted analysis, none of the associations between vascular stiffness and brain volumes were significant (total brain volume p=0.51; grey matter p=0.64; white matter p=0.51; hippocampal p=0.54, WMH p=0.72) (**Table 2**).

Effect modification and sensitivity analysis

There was no significant sex or age interaction present in any of the associations between cardiovascular function and brain parameters (supplementary **table S3**).

In the sensitivity analysis, where participants with diabetes or a history of cardiovascular disease were excluded, comparable results to our main findings were found for the associations between cardiovascular function and brain parameters (supplementary **table S4**).

4 Discussion

This cross-sectional population-based study provides novel insights into the complex heart-brain axis, in which we showed that ejection fraction is non-linearly associated with cerebral small vessel disease (cSVD) measures and that lower cardiac index is linearly associated with a larger burden of cSVD. However, no associations were found for arterial stiffness with cSVD imaging measures.

Associations between systolic LV function and measures of cerebral small vessel disease

We found non-linear associations between EF and total brain and grey matter volume, showing that a higher EF is not necessarily better than lower EF. This is supported by a previous study where a high EF >65% was associated with an increased mortality risk after myocardial infarction in women[25]. An EF higher than 70%can indicate LV hypertrophy, in which situation the higher EF is compensating for the decrease in stroke volume due to a decrease in end-diastolic and end-systolic volumes[26]. Unfortunately, data on LV mass was unavailable and therefore LV hypertrophy could not be assessed. In an additional analysis, we did observe that stroke volume rapidly decreases when EF exceeds 70%, however there was no significant change in the association between EF and total and grey matter volume after additional adjustment for stroke volume.

The non-linear association of EF with total brain volume and grey matter volume also shows that a lower than normal EF is associated with total brain atrophy and grey matter atrophy, also shown by the association of reduced EF (<50%) with total brain and grey matter atrophy. The non-linear association illustrates the complexity of the interaction between EF and cSVD. In clinical practice it is good to realize that a high EF does not automatically exclude the possibility of cardiac associated cSVD. However, the largest impact of EF on cSVD in the middle-aged population is most likely still to be expected from patients with a reduced EF.

A previously proposed mechanism explaining the association of impaired LV function with brain atrophy is through a reduction in cerebral perfusion. . Under normal conditions cerebral autoregulation adequately provides steady brain perfusion even in sudden variations in blood pressure, however cerebral autoregulation is less effective in a state of chronically reduced perfusion as is the case in heart failure[27]. This is supported by previous findings showing that cerebral perfusion recovered in heart failure patients with reduced EF after heart transplantation[28]. Whether this is also applicable in patients with a very high EF is unknown.

Previous studies found no apparent linear impact of EF on total brain or grey matter volumes[4; 7; 29]. Interestingly, one study that investigated the impact of EF on markers of abnormal brain aging found U-shaped associations between EF and cognitive function tests, where the lowest and highest EF quintiles were associated with poorer cognitive function[9]. However, they found no association between EF and total brain volume. Similarly, we found a non-linear association between EF and markers of cSVD. In addition, we found a significant association between EF and total brain volume, possibly due to the larger sample size enabling us to detect subtle associations between EF and brain volumes.

Where two relatively small investigations found no association between EF and WMH[4; 7], a recent study found that EF is linearly associated with WMH in a high risk population of ischaemic stroke patients[8]. To our knowledge, our study is the first to show an association between EF and WMH in

the general population. The association of a low EF with higher volume of WMH could be explained by a low cerebral flow state. Reduced cerebral flow has been associated with a greater amount of WMH in patients with heart failure[30; 31]. As grey matter volume loss and WMH have been linked to cognitive dysfunction and Alzheimer's disease, the current findings suggest that decreased EF could contribute to cognitive decline associated with aging.[32]. In combination with the previously found U-shaped association between EF and cognitive function[9], monitoring cognitive function in patients treated for impaired cardiac function could be important.

The positive association of CI with white matter and hippocampal volume found in our study is supported by previous findings showing that lower CI corresponds to lower resting cerebral blood flow in the temporal lobes on MR-perfusion in older adults[33]. The found association between CI and hippocampal volume further supports the theory of cerebral hypoperfusion, as the hippocampus is known to be more sensitive to cerebral hypoxia as compared to other regions[34]. The fact that CI is a measure of systemic perfusion (cardiac output/ body surface area), in which situation higher is better, partly explains why CI shows a positive linear association with white matter volume as compared to the non-linear associations of EF with brain volumes.

A previous investigation has shown that CI was associated with total brain volume but not with hippocampal volume. In this study cardiac parameters were assessed 4 years after brain MRI assessment with hippocampal volume available in less than half (n=696) of the study population (n=1,504) [6]. It has been estimated that white matter volume loss due to aging between 60 and 65 years old is approximately 0.29% per year. When applied to our cohort this means that in a participant of 61 years old a 2 SD lower CI than average is associated with the equivalent of nearly 1.5 years of white matter volume aging[35]. White matter and hippocampal volume are predictors for the development of dementia,[36] where lower CI has previously been associated with lower cerebral blood flow and an increased risk of dementia[33; 37]. Our results show that CI is associated with white matter volume and hippocampal volume. Taking the previous studies into account this could suggest

that CI is associated with white matter and hippocampal atrophy via reduced cerebral perfusion, which may lead to dementia. Prospective studies are needed to test this theory and to investigate whether optimisation of cardiac function will result in a reduction of cSVD and improved cognitive function. In recent basic research sympathetic neuronal activation and inflammation have been proposed as crucial factors in an intimate heart-brain network, providing promising possibilities for combined heart-brain axis therapies in the future*[38].*

Associations between vascular stiffness and measures of cerebral small vessel disease

Vascular stiffness did not show significant associations with any of the brain volumes measured on MRI. In the relation between vascular stiffness and brain volumes, age was found to be the most important confounder. With advancing age, vascular stiffness will increase and brain volume will decrease. However, we do not know to what extent vascular stiffness lies within the causal path between age and brain volumes. Previous studies have shown significant associations between vascular stiffness and total brain volume, WMH as well as Alzheimer's disease, however these studies used a different proxy for vascular stiffness; pulse wave velocity[39]. Our findings are in line with two previous studies that used the AIx as a measure for vascular stiffness, which found no significant impact on grey and white matter volumes[12; 40]. The AIx is based on the principle of wave reflection, however in elderly patients the aorta stiffens and the wave reflection may actually reduce because of increased compliance between the stiffened aorta and the stiffer peripheral arteries. This could explain the absence of an association between AIx and brain parameters, where pulse wave velocity more consistently has shown associations with cSVD measures[39].

Limitations

This study has some limitations that need consideration. Because of the cross-sectional design, no causal effects can be determined. Additionally, no data on diastolic function or LV mass were available at the time of the study and have therefore not been assessed. Vascular stiffness was assessed by the augmentation index, which limitations have been discussed in the previous paragraph. There is also the possibility of residual confounding, where cardiac dysfunction and cSVD share many risk factors for which we aimed to adjust as much as possible while at the same time being wary for over adjustment. The population under study was mainly composed of Caucasians between 45 and 73 years old, therefore the results of this study may not be applicable to other age groups and ethnicities. An additional limitation that needs consideration is healthy volunteer bias that has been reported in the UK biobank, potentially leading to an underestimation of the impact in our study due to an underrepresentation of more severe cardiac dysfunction and brain abnormalities. However, the UK biobanks large size and heterogeneity of exposure measures provide valid scientific inferences of associations between exposures and health conditions that are generalizable to other populations[41].

5 Conclusion

This study provides novel insights into the complex associations between the heart and the brain ("cardiac-brain axis"), which could potentially guide early interventions aimed at improving cardiovascular function and prevention of cerebral small vessel disease, and thereby possibly preserving cognitive function in the long run.

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TABLES

Table 1. Baseline characteristics stratified by gender.

	Gender		Total population
	Men	**Women**	
	n = 2008	*n = 2358*	*n = 4366*
Age (years)	61.7 ± 7.2	60.5 ± 7.1	61.1 ± 7.2
Ethnicity (% whites)	1940 (96.6)	2294 (97.3)	4234 (97.0)
Townsend Deprivation Index	-2.0 (2.7)	-1.9 (2.7)	-1.9 ± 2.7
BMI (kg/m^2)	26.8 ± 3.5	26.0 ± 4.4	26.4 ± 4.0
Smoking			
- Never (%)	1140 (57.3)	1502 (64.5)	2642 (61.2)
- Former (%)	741 (37.2)	742 (31.9)	1483 (34.3)
- Current (%)	109 (5.5)	85 (3.6)	194 (4.5)
Alcohol			
- Never	112 (5.6)	160 (6.9)	272 (6.3)
- Special occasions	142 (7.1)	345 (14.8)	487 (11.2)
- 1-3x/month	166 (8.3)	327 (14.0)	493 (11.4)
- 1-2x/week	507 (25.4)	619 (26.5)	1126 (26.0)
- 3-4x/week	608 (30.5)	547 (23.4)	1155 (26.7)
- Daily	461 (23.1)	337 (14.4)	798 (18.4)
SBP (mmHg)	136.3 ± 16.6	136.7 ± 20.0	136.5 ± 18.5
DBP (mmHg)	71.5 ± 10.0	66.8 ± 11.1	69.0 ± 10.9

History of			
- Hypertension (%)	547 (27.4)	468 (20.1)	1015 (23.5)
- Diabetes (%)	110 (5.5)	79 (3.4)	189 (4.4)
- Angina (%)	46 (2.3)	31 (1.3)	77 (1.8)
- Myocardial infarction (%)	58 (2.9)	15 (0.6)	73 (1.7)
- Stroke (%)	34 (1.7)	17 (0.7)	51 (1.2)
Left ventricular:			
- Ejection fraction (%)	54.6 ± 6.2	57.6 ± 5.4	56.2 ± 6.0
- End-diastolic volume (mL)	157.6 ± 32.8	122.9 ± 24.4	138.8 ± 33.3
- End-systolic volume (mL)	71.8 ± 19.9	52.3 ± 13.3	61.3 ± 18.0
- Stroke volume (mL)	85.7 ± 18.4	70.6 ± 14.4	77.6 ± 18.0
- Cardiac output (L/min)	5.2 ± 1.1	4.4 ± 0.9	4.7 ± 1.1
- Cardiac index (L/min/m²)	2.6 ± 0.5	2.5 ± 0.5	2.6 ± 0.5
Augmentation index (%)	19.4 ± 8.0	22.7 ± 8.8	21.2 ± 8.6
Brain parameters:			
- Total brain volume (cm^3)	1496.2 ± 70.5	1520.6 ± 72.2	1509.4 ± 72.4
- Grey matter volume (cm^3)	781.5 ± 43.5	814.29 ± 44.8	799.2 ± 47.1
- White matter volume (cm^3)	714.5 ± 40.8	706.3 ± 40.9	710.1 ± 41.1
- Hippocampal (cm^3)	8.0 ± 0.9	7.6 ± 0.8	7.8 ± 0.9
- WMH (cm^3)	2.62 [1.48; 5.32]	2.11 [1.21; 4.10]	2.34 [1.30; 4.68]

Data are shown as n (%), mean ± SD or median [interquartile range]. Overweight = BMI 25-29.9 kg/m2, Obese = BMI >30 kg/m², Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, LV = left ventricular, SBP = systolic blood pressure, WMH = white matter hyperintensities.

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Table 2. Associations of vascular and LV systolic function with cSVD measures

	LV EF (%)			*LV CI (L/min/m^2)*			*AIx (%)*		
	*Regression type**	*β [95% CI]*	*p-value*	*Regression type**	*β [95% CI]*	*P-value*	*Regression type**	*β [95% CI]*	*P-value*
Total brain volume (mm^3)	Poly spline	N/A	<0.001	Linear	2940.5 (-838.6; 6719.5)	0.13	Linear	-79.8 (-318.7; 159.1)	0.51
Grey matter volume (mm^3)	Poly spline	N/A	<0.001	Linear	-360.0 (-2584.6; 1864.6)	0.75	Linear	-33.4 (-173.5; 106.7)	0.64
White matter volume (mm^3)	Linear	187.3 (-21.0; 395.5)	0.08	Linear	3193.7 (760.0; 5627.4)	0.01	Linear	-52.6 (-207.2; 102.0)	0.51
Hippocampal volume (mm^3)	Linear	3.3 (-1.0; 7.5)	0.13	Linear	72.5 (23.0; 122.0)	0.004	Linear	-1.0 (-4.1; 2.2)	0.54
WMH (%)	Linear	-0.23 (-0.44; -0.02)	0.03	Linear	-0.05 (-2.49; 2.45)	0.97	Linear	0.03 (-0.13; 0.19)	0.72

** analysis of variance was used to test best fit, linear regression or polynomial spline.* All analyses were adjusted for age, sex, ethnicity, socioeconomic status, smoking status, alcohol use, hypertension and diabetes. AIx was additionally adjusted for heart rate, height and mean arterial pressure.

Abbreviations: AIx = augmentation index, CI = cardiac index, EF = ejection fraction, LV = left ventricular, N/A = not applicable, WMH = white matter hyperintensities.

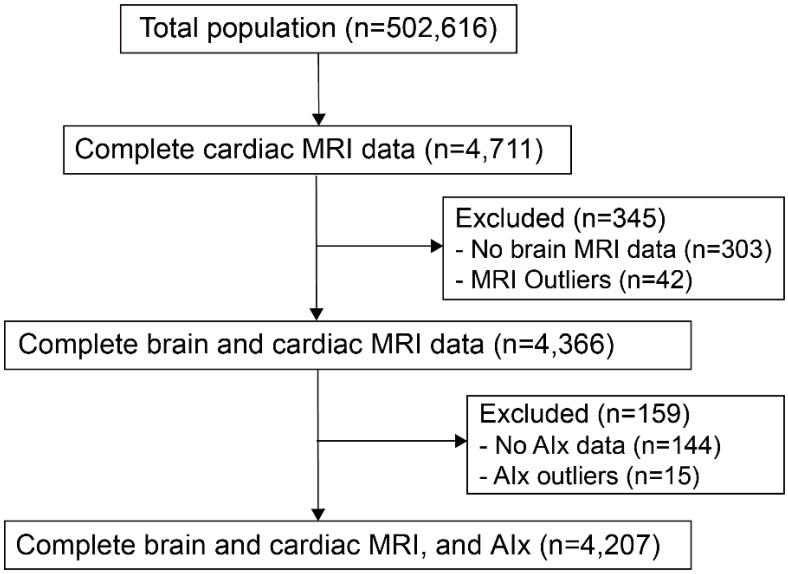
Table 3. Associations of reduced ejection fraction (<50%) with cSVD measures

	β [95% CI]	*p-value*
Total brain volume (mm^3)	-8340.0 (-14259.4; -2420.5)	0.006
Grey matter volume (mm^3)	-6586.0 (-10069.5; -3102.9)	<0.001
White matter volume (mm^3)	-1691.7 (-5508.3; 2125.0)	0.38
Hippocampal volume (mm^3)	-39.4 (-117.1; 38.4)	0.32
WMH (%)	4.85 (0.84; 9.02)	0.02

All analyses were adjusted for age, sex, ethnicity, socioeconomic status, smoking status, alcohol use, hypertension and diabetes. *Abbreviations: WMH = white matter hyperintensities.*

FIGURES

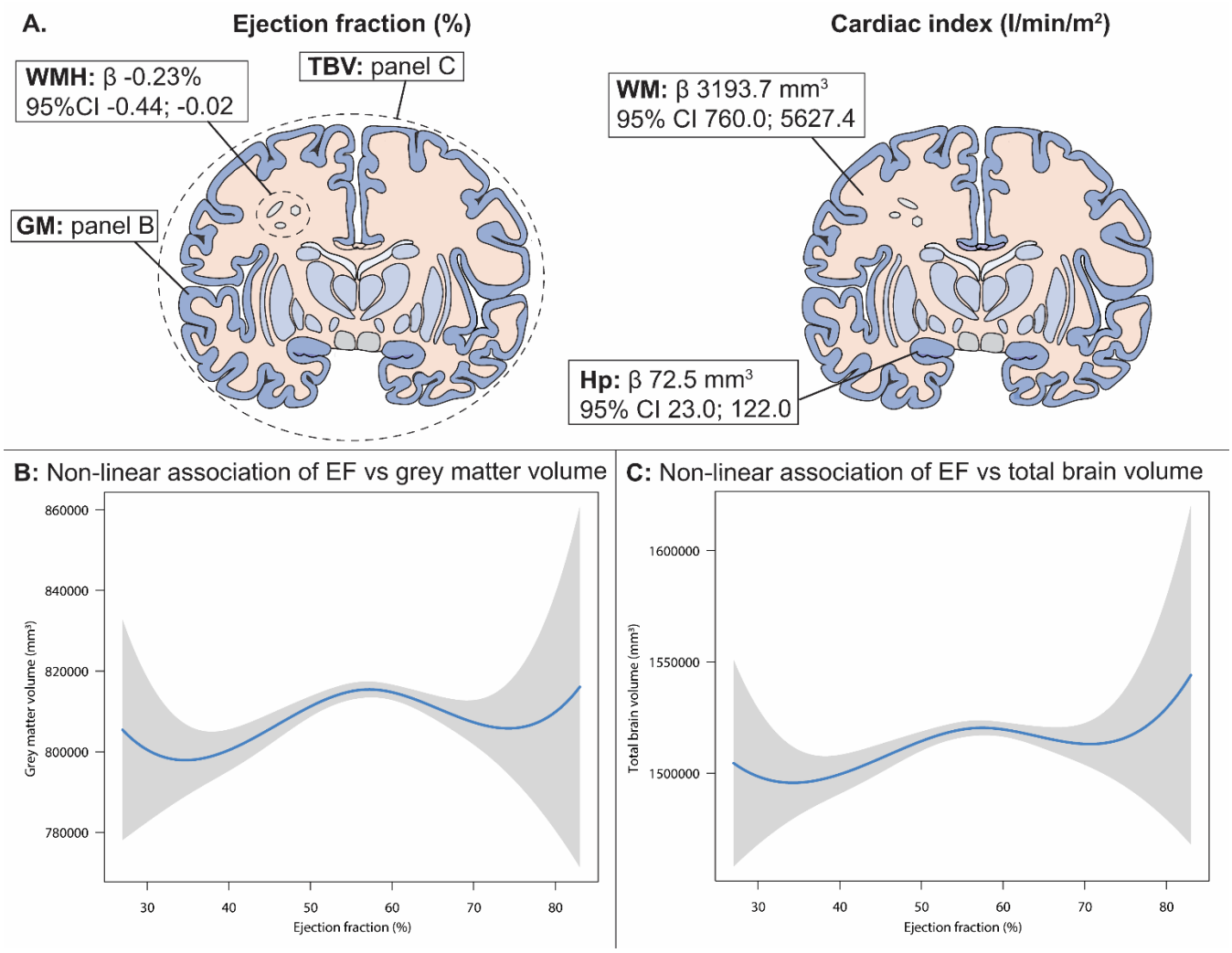
Figure 1: Flow diagram describing sample selection.



AIx: augmentation index; MRI: magnetic resonance imaging. Values more than 4 times the standard deviation of the mean were regarded as outliers, for AIx also negative values were excluded (n=11) as these cannot be regarded as true negative values[22].

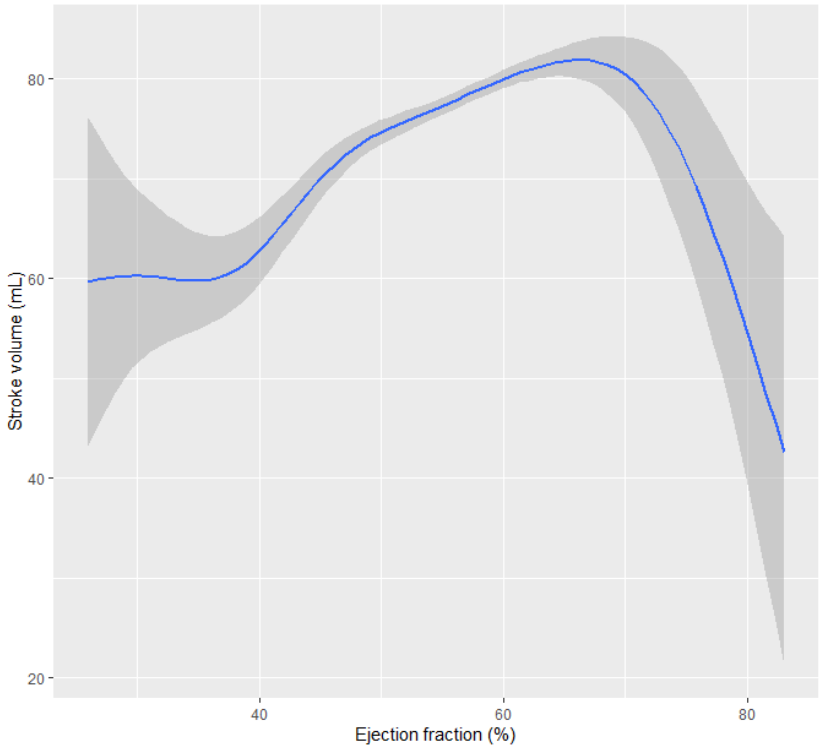
Figure 2: An overview of the main study findings.

Panel **A.** on the left shows the significant associations between EF and cSVD measures and on the right the significant associations between CI and cSVD measures. Panel **B.** shows the non-linear association between EF and grey matter volume and **C.** shows the non-linear association between EF and total brain volume.



* Panel B and C: polynomial splines performed with 4 degrees of freedom. All analyses were adjusted for age, sex, ethnicity, socioeconomic status, smoking status, alcohol use, hypertension and diabetes. Abbreviations: GM: grey matter; Hp: hippocampus; TBV: total brain volume; WM: white matter; WMH: white matter hyperintensities

Figure 3: The association of LV ejection fraction with LV stroke volume, illustrating a rapid decline in stroke volume above an EF of 70%.



SUPPLEMENTARY TABLES

Table S1. A short overview and explanation of the used measures

Measure:	***Short explanation:***
White matter hyperintensities (WMH)	Also known as leukoaraiosis, these are abnormal changes in white matter shown on MRI as increased signal intensity on MRI. WMH are part of cSVD, which are associated with cognitive impairment.
Cardiac output (CO)	CO is a measure to describe systolic cardiac function and is expressed in L/min. CO is calculated as follows: heart rate × stroke volume.
Cardiac index (CI)	CI is defined as: cardiac output/ body surface area. So the cardiac index is a measure that normalizes the cardiac output to the body size. This is important because a large person needs a higher CO as compared to a smaller person to provide adequate perfusion of all tissues. CI accounts for this by calculating the cardiac output per square meter of body surface area.
Ejection fraction (EF)	EF is a measure to describe systolic cardiac function. Unlike cardiac output, EF is not dependent on body size and therefore needs no normalization. EF is the percentage of blood ejected from the left ventricle at each heartbeat and calculated as follows: (stroke volume/ end diastolic volume) × 100%.
Pulse wave velocity (PWV)	PWV is the velocity at which the systolic pressure wave travels though the aorta and is a measure for vascular stiffness. The stiffer the aorta, the faster the pressure wave travels through the aorta.
Augmentation index (AIx)	AIx measures the percentage increase in pulse pressure caused by the reflected pressure wave at the peripheral vessels and is a measure of vascular stiffness. If the aorta is stiffer, the peripherally reflected pressure wave travels faster and arrives during pressure build-up of the next wave, thereby augmenting the pulse pressure.

Table S2. Crude associations of vascular and LV systolic function with cSVD measures

	LV EF (%)			*LV CI (L/min/m^2)*			*AIx (%)*		
	*Regression type**	*β [95% CI]*	*p-value*	*Regression type**	*β [95% CI]*	*P-value*	*Regression type**	*β [95% CI]*	*P-value*
Total brain volume (mm^3)	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001	Linear	-666.2 (-921.3; -411.1)	<0.001
Grey matter volume (mm^3)	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001
White matter volume (mm^3)	Linear	92.2 (-112.3; 296.6)	0.38	Linear	7894.0 (5459.5; 10328.6)	<0.001	Linear	-377.3 (-521.6; -233.1)	<0.001
Hippocampal volume (mm^3)	Poly spline	N/A	0.04	Poly spline	N/A	<0.001	Linear	-13.0 (-16.0; -10.0)	<0.001
WMH (%)	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001

*analysis of variance was used to test best fit, linear regression or polynomial spline. Abbreviations: AIx = augmentation index, CI = cardiac index, EF = ejection fraction, LV = left ventricular, N/A = not applicable, WMH = white matter hyperintensities.

Table S3: Sex and age interaction analysis of associations of vascular and LV systolic function with cSVD measures

	LV EF (%)			*LV CI (L/min/m^2)*			*AIx (%)*	
	p-value for sex interaction	*p-value for age interaction*		*p-value for sex interaction*	*p-value for age interaction*		*p-value for sex interaction*	*p-value for age interaction*
Total brain volume (mm^3)	0.23	0.40		0.86	0.24		0.60	0.14
Grey matter volume (mm^3)	0.23	0.46		0.75	0.31		0.21	0.07
White matter volume (mm^3)	0.65	0.43		0.89	0.31		0.77	0.54
Hippocampal volume (mm^3)	0.10	0.33		0.96	0.58		0.09	0.38
WMH (%)	0.61	0.29		0.35	0.15		0.74	0.61

Abbreviations: AIx = augmentation index, CI = cardiac index, EF = ejection fraction, LV = left ventricular, N/A = not applicable, WMH = white matter hyperintensities.

Table S4. Sensitivity analysis of associations of vascular and LV systolic function with cSVD measures

	LV EF (%)			*LV CI (L/min/m²)*			*AIx (%)*		
	*Regression type**	*β [95% CI]*	*p-value*	*Regression type**	*β [95% CI]*	*P-value*	*Regression type**	*β [95% CI]*	*P-value*
Total brain volume (mm³)	Poly spline	N/A	0.002	Linear	2576.9 (-1350.2; 6504.0)	0.20	Linear	-104.7 (-352.5; 143.2)	0.41
Grey matter volume (mm³)	Poly spline	N/A	<0.001	Linear	-717.3 (-3031.0; 1596.4)	0.54	Linear	-55.1 (-200.5; 90.2)	0.46
White matter volume (mm³)	Linear	137.7 (-81.6; 357.1)	0.22	Linear	3183.0 (641.2; 5724.8)	0.01	Linear	-56.0 (-217.5; 105.4)	0.50
Hippocampal volume (mm³)	Linear	3.0 (-1.443558; 7.44393)	0.19	Linear	61.2 (9.77; 112.68842)	0.02	Linear	-0.7 (-3.9; 2.6)	0.69
WMH (%)	Linear	-0.26 (-0.48; -0.04)	0.02	Linear	0.66 (-1.89; 3.27)	0.62	Linear	0.04 (-0.12; 0.20)	0.61

*analysis of variance was used to test best fit, linear regression or polynomial spline. Abbreviations: AIx = augmentation index, CI = cardiac index, EF = ejection fraction, LV = left ventricular, N/A = not applicable, WMH = white matter hyperintensities.

Table S5. Test for multicollinearity in the associations between ejection fraction and measures of cSVD using Variance Inflation Factors (VIF)

	Total brain volume	Grey matter volume	White matter volume	Hippocampal volume	WMH
Age	1.06	1.06	1.06	1.06	1.07
Sex	1.11	1.11	1.11	1.11	1.12
Smoking	1.04	1.04	1.04	1.04	1.04
Alcohol	1.08	1.08	1.07	1.07	1.08
Ethnicity	1.00	1.00	1.00	1.00	1.03
SES	1.04	1.04	1.04	1.04	1.04
Hypertension	1.06	1.06	1.05	1.05	1.05
Diabetes	1.03	1.03	1.03	1.03	1.03

Abbreviations: SES = socioeconomic status, WMH = white matter hyperintensities.

Table S6. Test for multicollinearity in the associations between cardiac index and measures of cSVD using Variance Inflation Factors (VIF)

	Total brain volume	Grey matter volume	White matter volume	Hippocampal volume	WMH
Age	1.10	1.10	1.10	1.10	1.11
Sex	1.05	1.05	1.05	1.05	1.05
Smoking	1.04	1.04	1.04	1.04	1.04
Alcohol	1.08	1.08	1.08	1.08	1.08
Ethnicity	1.00	1.00	1.00	1.00	1.04
SES	1.04	1.04	1.04	1.04	1.03
Hypertension	1.05	1.05	1.05	1.05	1.05
Diabetes	1.03	1.03	1.03	1.03	1.03

Abbreviations: SES = socioeconomic status, WMH = white matter hyperintensities.

Table S7. Test for multicollinearity in the associations between augmentation index and measures of cSVD using Variance Inflation Factors (VIF)

	Total brain volume	Grey matter volume	White matter volume	Hippocampal volume	WMH
Age	1.15	1.15	1.15	1.15	1.16
Sex	2.23	2.23	2.23	2.22	2.27
Smoking	1.04	1.04	1.04	1.04	1.04
Alcohol	1.08	1.08	1.08	1.08	1.09
Ethnicity	1.01	1.01	1.01	1.01	1.04
SES	1.04	1.04	1.04	1.04	1.03
Hypertension	1.11	1.11	1.11	1.11	1.11
Diabetes	1.04	1.04	1.04	1.04	1.03
Height	2.22	2.22	2.22	2.22	2.26
Heart rate	1.11	1.11	1.11	1.11	1.12
MAP	1.18	1.18	1.18	1.18	1.19

Abbreviations: MAP = mean arterial pressure, SES = socioeconomic status, WMH = white matter hyperintensities.