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

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

5 **Key points:**
6 - Ejection fraction is non-linearly and cardiac index is linearly associated with MRI derived measures
7 of cerebral small vessel disease.
8 - No associations were found for arterial stiffness with cSVD measures.

9

10 **Abbreviations:**

11 AIx = augmentation index

12 CI = cardiac index

13 cSVD = cerebral small vessel disease

14 EF = ejection fraction

15 LV =left ventricular

16 WMH = white matter hyperintensities

1 **Abstract**

2 **Objectives:**

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

7 **Methods:**

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

14 **Results:**

15 EF was non-linearly associated with total brain volume and grey matter volume, with the largest brain
16 volume for an EF between 55-60% (both $p < 0.001$). EF showed a negative linear association with
17 WMH ($-0.23\%[-0.44; -0.02]$, $p=0.03$), yet no associations were found with white matter or
18 hippocampal volume. CI showed a positive linear association with white matter (β 3,194 mm³[760;
19 5,627], $p=0.01$) and hippocampal volume (β 72.5 mm³[23.0; 122.0], $p=0.004$). No associations were
20 found for CI with total brain volume, grey matter volume or WMH. No significant associations were
21 found between AIx and cSVD measures.

22 **Conclusions:**

- 1 This study provides novel insights into the complex associations between the heart and the brain, which
- 2 could potentially guide early interventions aimed at improving cardiovascular function and prevention
- 3 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 30th 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

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

3 **Brain MRI**

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

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

18 **Augmentation Index (AIx) by Pulse Wave Analysis**

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

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

3 **Statistical Analysis**

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

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

3 **3 Results**

4 502,617 individuals participated in the UK-biobank, of which 4,366 participants had available cardiac
5 and brain imaging measures (Flow diagram shown in **figure 1**). An overview of the baseline
6 characteristics is provided in **table 1**. Age of participants ranged from 45 to 73 years old with a mean
7 of 61.1 ± 7.2 years and 54% of participants were female. Participants were slightly obese (BMI 26.4
8 ± 4.0 kg/m²), 61.2% had never smoked and 23% had a history of hypertension. On average, mean
9 cardiovascular parameters were relatively normal with an EF of 56.2 ± 6.0 , CI of 2.6 ± 0.5 and AIX of
10 21.2 ± 8.6 .

11 **Associations between systolic LV function and measures of cerebral small vessel** 12 **disease**

13 **Tables 2** shows the adjusted associations between left ventricular parameters and brain parameters.
14 Unadjusted analysis are shown in supplementary **table S2**. ANOVA indicated that a non-linear
15 function provided the best fit for the associations between EF and total brain volume ($p < 0.001$), and
16 between EF and grey matter volume ($p < 0.001$) (**figure 2b and 2c**). An EF below 55% was associated
17 with lower total brain and grey matter volumes in non-linear function analysis (figure 2). Also in cases
18 with an EF above 60% lower total brain and grey matter volumes were observed. A significant negative
19 linear association was observed between EF and WHM (-0.23% [-0.44 ; -0.02], $p = 0.03$), accordingly a
20 10% lower EF is on average associated with 2.3% more WMH. No significant associations were found
21 between EF and white matter volume ($p = 0.08$) or hippocampal volume ($p = 0.13$). Similar results were
22 found for EF dichotomized to normal ($\geq 50\%$) and reduced EF ($< 50\%$), in which a reduced EF was
23 associated with a lower total brain and grey matter volume (β -8340.0 mm³ [-14259.4 ; -2420.5],

1 p=0.006; -6586.0 mm³ [-10069.5; -3102.9], p<0.001 respectively). Again, no significant associations
2 were found for white matter volume (p=0.38) and hippocampal volume (p=0.32). Reduced EF was
3 again associated with more WMH (4.85% [0.84; 9.02], p=0.02).

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

11 For CI, ANOVA indicated that a linear association provided the best explanatory power to analyse the
12 association between CI and white matter volume (β 3,194 mm³ [760; 5,627], p=0.01) and hippocampal
13 volume (β 72.5 mm³ [23.0; 122.0], p=0.004). Per 1 L/min/m² change in CI, white matter volume
14 changed with 3,194 mm³. So in a person with 2 SD (SD=0.5L/min/m²) higher CI, white matter volume
15 is on average 3,194 mm³ higher. CI was not significantly associated with total brain volume, grey
16 matter volume or WMH (p=0.13, p=0.75 and 0.97 respectively).

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

1 **Effect modification and sensitivity analysis**

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

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

7 **4 Discussion**

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

12 **Associations between systolic LV function and measures of cerebral small vessel** 13 **disease**

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

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

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

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

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

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

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

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

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

7 **Associations between vascular stiffness and measures of cerebral small vessel** 8 **disease**

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

1 **Limitations**

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

15 **5 Conclusion**

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

20

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1 TABLES

Table 1. Baseline characteristics stratified by gender.

	Gender		Total
	Men	Women	population
	<i>n</i> = 2008	<i>n</i> = 2358	<i>n</i> = 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/m ²)	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.

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

	<i>LV EF (%)</i>			<i>LV CI (L/min/m²)</i>			<i>AIx (%)</i>		
	<i>Regression</i>	<i>β [95% CI]</i>	<i>p-value</i>	<i>Regression</i>	<i>β [95% CI]</i>	<i>P-value</i>	<i>Regression</i>	<i>β [95% CI]</i>	<i>P-value</i>
	<i>type*</i>			<i>type*</i>			<i>type*</i>		
<i>Total brain volume (mm³)</i>	Poly spline	N/A	<0.001	Linear	2940.5 (-838.6; 6719.5)	0.13	Linear	-79.8 (-318.7; 159.1)	0.51
<i>Grey matter volume (mm³)</i>	Poly spline	N/A	<0.001	Linear	-360.0 (-2584.6; 1864.6)	0.75	Linear	-33.4 (-173.5; 106.7)	0.64
<i>White matter volume (mm³)</i>	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
<i>Hippocampal volume (mm³)</i>	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
<i>WMH (%)</i>	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.

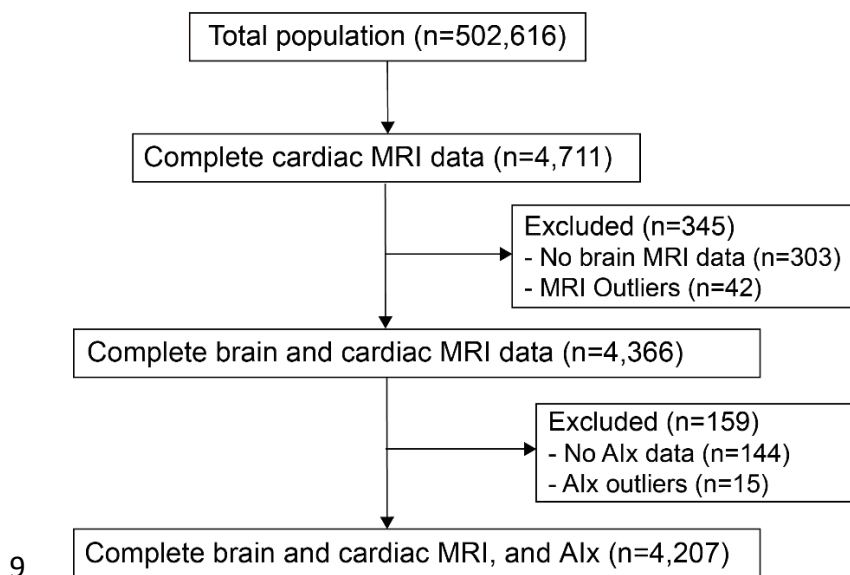
3 **Table 3.** Associations of reduced ejection fraction (<50%) with cSVD measures

	β [95% CI]	<i>p</i> -value
<i>Total brain volume (mm³)</i>	-8340.0 (-14259.4; -2420.5)	0.006
<i>Grey matter volume (mm³)</i>	-6586.0 (-10069.5; -3102.9)	<0.001
<i>White matter volume (mm³)</i>	-1691.7 (-5508.3; 2125.0)	0.38
<i>Hippocampal volume (mm³)</i>	-39.4 (-117.1; 38.4)	0.32
<i>WMH (%)</i>	4.85 (0.84; 9.02)	0.02

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

7 FIGURES

8 **Figure 1:** Flow diagram describing sample selection.

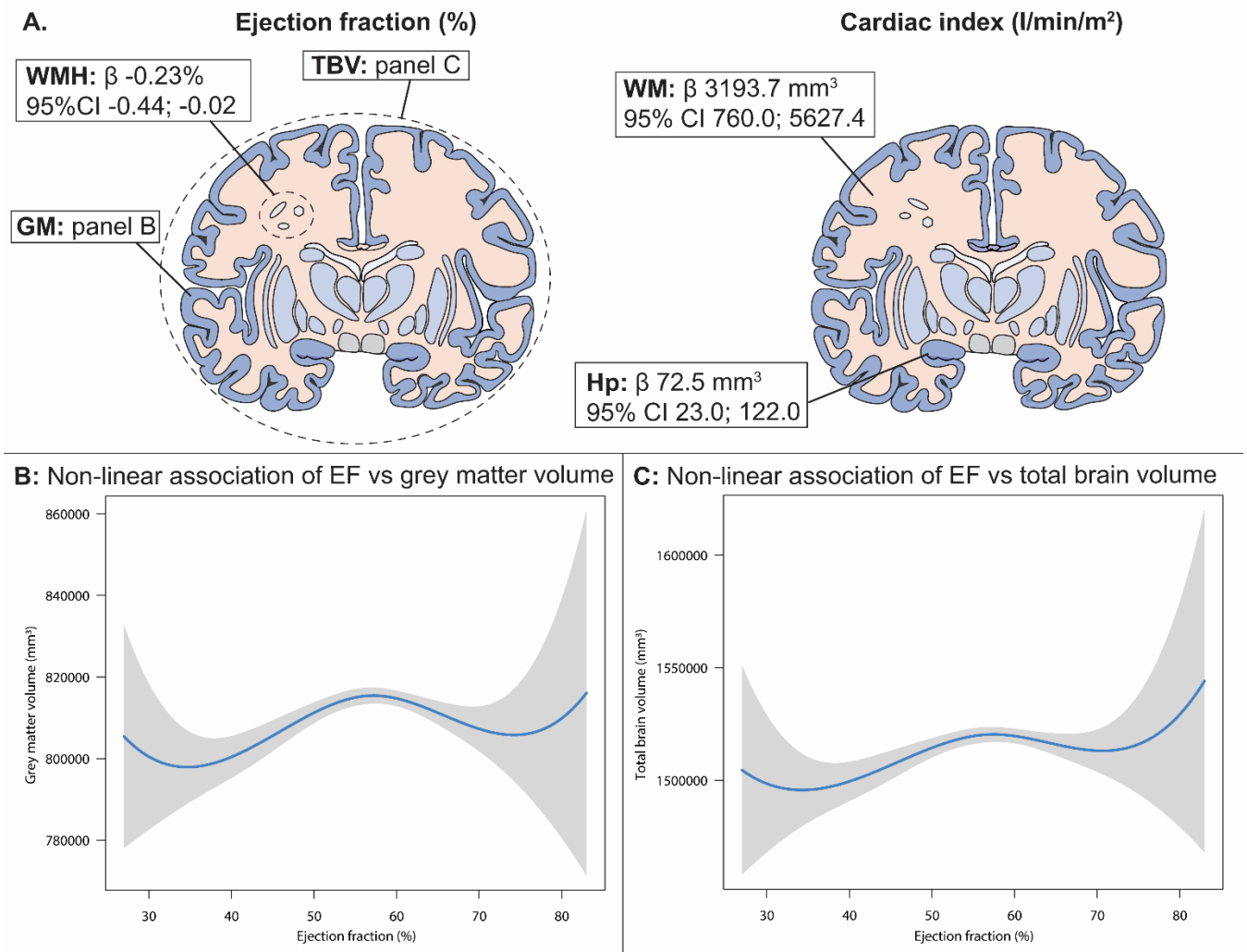


10 AIx: augmentation index; MRI: magnetic resonance imaging. Values more than 4 times the standard deviation of the mean
11 were regarded as outliers, for AIx also negative values were excluded (n=11) as these cannot be regarded as true negative
12 values[22].

13

14 **Figure 2:** An overview of the main study findings.

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

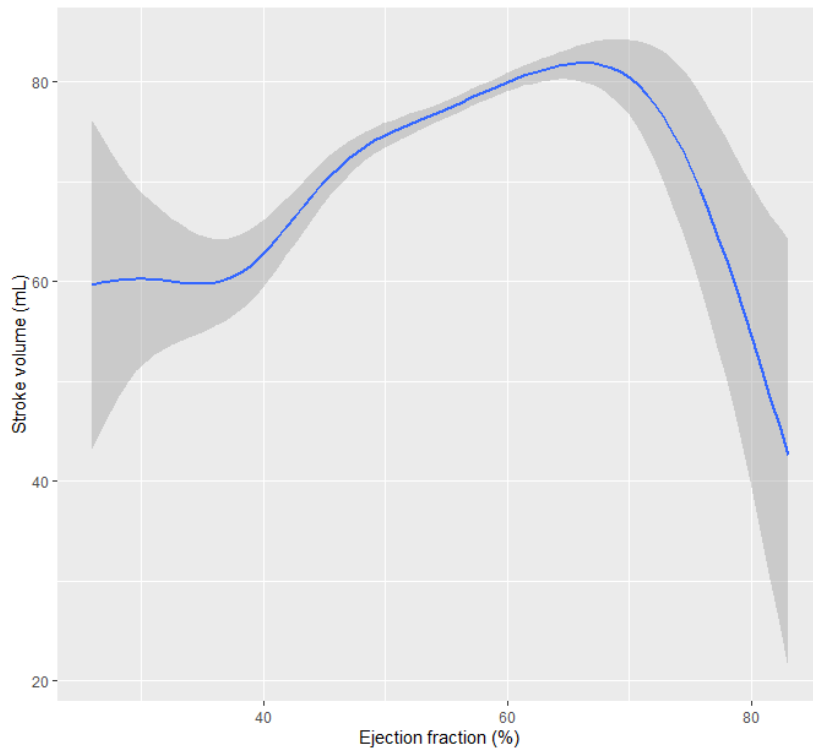


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20 * Panel B and C: polynomial splines performed with 4 degrees of freedom. All analyses were
21 adjusted for age, sex, ethnicity, socioeconomic status, smoking status, alcohol use, hypertension and
22 diabetes. Abbreviations: GM: grey matter; Hp: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

24

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



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30 **SUPPLEMENTARY TABLES**

31 **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 through the aorta and is a measure for vascular stiffness. The stiffer the aorta, the faster the pressure wave travels through the aorta.
Augmentation index (Alx)	Alx 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.

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

	<i>LV EF (%)</i>			<i>LV CI (L/min/m²)</i>			<i>AIx (%)</i>		
	<i>Regression type*</i>	<i>β [95% CI]</i>	<i>p-value</i>	<i>Regression type*</i>	<i>β [95% CI]</i>	<i>P-value</i>	<i>Regression type*</i>	<i>β [95% CI]</i>	<i>P-value</i>
<i>Total brain volume (mm³)</i>	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001	Linear	-666.2 (-921.3; - 411.1)	<0.001
<i>Grey matter volume (mm³)</i>	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001
<i>White matter volume (mm³)</i>	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
<i>Hippocampal volume (mm³)</i>	Poly spline	N/A	0.04	Poly spline	N/A	<0.001	Linear	-13.0 (-16.0; -10.0)	<0.001
<i>WMH (%)</i>	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001	Poly spline	N/A	<0.001

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

36

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

	<i>LV EF (%)</i>			<i>LV CI (L/min/m²)</i>			<i>AIx (%)</i>	
	<i>p-value for sex interaction</i>	<i>p-value for age interaction</i>		<i>p-value for sex interaction</i>	<i>p-value for age interaction</i>		<i>p-value for sex interaction</i>	<i>p-value for age interaction</i>
<i>Total brain volume (mm³)</i>	0.23	0.40		0.86	0.24		0.60	0.14
<i>Grey matter volume (mm³)</i>	0.23	0.46		0.75	0.31		0.21	0.07
<i>White matter volume (mm³)</i>	0.65	0.43		0.89	0.31		0.77	0.54
<i>Hippocampal volume (mm³)</i>	0.10	0.33		0.96	0.58		0.09	0.38
<i>WMH (%)</i>	0.61	0.29		0.35	0.15		0.74	0.61

38 Abbreviations: AIx = augmentation index, CI = cardiac index, EF = ejection fraction, LV = left ventricular, N/A = not applicable, WMH =
39 white matter hyperintensities.
40

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

	<i>LV EF (%)</i>			<i>LV CI (L/min/m²)</i>			<i>Alx (%)</i>		
	<i>Regression type*</i>	<i>β [95% CI]</i>	<i>p-value</i>	<i>Regression type*</i>	<i>β [95% CI]</i>	<i>P- value</i>	<i>Regression type*</i>	<i>β [95% CI]</i>	<i>P-value</i>
<i>Total brain volume (mm³)</i>	Poly spline	N/A	0.002	Linear	2576.9 (-1350.2; 6504.0)	0.20	Linear	-104.7 (-352.5; 143.2)	0.41
<i>Grey matter volume (mm³)</i>	Poly spline	N/A	<0.001	Linear	-717.3 (-3031.0; 1596.4)	0.54	Linear	-55.1 (-200.5; 90.2)	0.46
<i>White matter volume (mm³)</i>	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
<i>Hippocampal volume (mm³)</i>	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
<i>WMH (%)</i>	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

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

44

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

	White				
	Total brain	Grey matter	matter	Hippocampal	
	volume	volume	volume	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

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

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48

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

	White				
	Total brain	Grey matter	matter	Hippocampal	
	volume	volume	volume	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

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

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

	White				
	Total brain	Grey matter	matter	Hippocampal	
	volume	volume	volume	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

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

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56