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ORIGINAL RESEARCH

Cardiac Hypertrophy Is Associated With Advanced Brain Aging in the General Population

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BACKGROUND: Hypertrophy of the left ventricle (LV) has recently been associated with adverse changes of brain structure in older adults, notably increased burden of white matter hyperintensities (WMHs). Whether greater LV size or mass is also related to WMH burden in middle-aged adults is currently unclear. In addition, its relation with alterations in cortical thickness (CT) has not been studied to date.

METHODS AND RESULTS: Data from 1602 participants of the population-based SHIP (Study of Health in Pomerania) with LV ejection fraction >40% and no history of myocardial infarction were included (aged 21–82 years; median age, 49 years; 53% women). Participants underwent both echocardiography and magnetic resonance imaging of the head. Imaging markers of brain aging (ie, CT and WMH volume) were determined from magnetic resonance imaging scans. LV mass and diameter were associated with lower global CT and greater WMH volume, while adjusting for age, sex, body height, fat-free body mass, and intracranial volume. Moreover, thicknesses of the interventricular septum and posterior wall were also associated with lower global CT. These associations could not be explained by cardiovascular risk factors (including hypertension), inflammatory markers, or sociodemographic factors. Regional analyses showed distinct spatial patterns of lower CT in association with LV diameter and posterior wall thickness.

CONCLUSIONS: LV diameter and mass are associated with lower global and regional CT as well as greater WMH burden in the general population. These findings highlight the brain structural underpinnings of the associations of LV hypertrophy with cognitive decline and dementia.

Key Words: brain imaging ■ epidemiology ■ left ventricular hypertrophy

Greater left ventricular (LV) diameter and LV mass (LVM) are well-known risk factors for future cardiac events and mortality.[1,2] The adverse effects of cardiovascular diseases on brain structure have been studied extensively during the past decades. For example, patients with hypertension[3,4] and coronary artery disease[5] show increased rates of white matter lesions and age-related decline in gray matter volume compared with healthy individuals. The relationships of LV diameter and LVM with brain structures have only recently been explored.

In the SHS (Strong Hearth Study), LVM was associated with decreased hippocampal volume, greater white matter hyperintensities (WMHs), and impaired cognitive function after a mean follow-up time of 17 years.[6] This was confirmed by recent results from the ARIC (Atherosclerosis Risk in Communities) Study, showing that higher LVM and wall thickness are associated with greater volume of WMH and brain infarctions in elderly patients.[7] Moreover, LV hypertrophy was related to increased risk of incident dementia.[8] Similarly, greater LVM was related to compromised

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CLINICAL PERSPECTIVE

What Is New?

- Increased left ventricular diameter and mass were related to lower global and regional cortical thickness as well as greater white matter lesion burden in middle-aged adults with preserved systolic function (ejection fraction >40%) and no history of myocardial infarction.
- These associations could not be explained by traditional cardiovascular risk factors or markers of systemic inflammation.
- Our findings highlight the brain structural underpinnings of the previously reported associations of cardiac hypertrophy with cognitive decline and dementia.

What Are the Clinical Implications?

- Subclinical changes in cardiac structure may play an important role in the cause and, possibly, prevention of cognitive decline and dementia at an early stage.

Nonstandard Abbreviations and Acronyms

CT	cortical thickness
E/A	ratio of peak velocity blood flow in early diastole/peak velocity flow in late diastole
E/e'	ratio of early mitral inflow velocity/mitral annular early diastolic velocity
LVD	left ventricular diameter during diastole
LVM	left ventricular mass
LVS	left ventricular diameter during systole
PWD	posterior wall thickness during diastole
RAAS	renin-angiotensin-aldosterone system
SHIP	Study of Health in Pomerania
WMH	white matter hyperintensity

white matter microstructure in older adults with mild cognitive impairments.[9]

Evidence for the involvement of the cerebral cortex in the heart-brain axis comes from cardiac diseases (eg, Takotsubo syndrome)[10,11] or stroke-related myocardial injury.[12] Stress-induced chronic hyperactivation of the sympathetic nervous system causes dendritic atrophy in the prefrontal cortex and may render it almost completely dysfunctional in severe cases of posttraumatic stress disorder.[13,14] On the other hand, stress also causes LV hypertrophy via activation of the renin-angiotensin-aldosterone system (RAAS),[15] among others. On the basis of these findings, we hypothesized LVM and other markers of LV hypertrophy to be associated with a lower cortical thickness (CT), typically observed in accelerated brain aging and neurodegenerative diseases.[16–18] The frontal and somatosensory cortex are two candidate regions where abnormalities may be expected on the basis of the current understanding of the heart-brain axis.[19]

Our analyses were based on data from 1602 participants of SHIP-Trend (Study of Health in Pomerania Trend), a large-scale, population-based prospective cohort study in northeast Germany.[20] Participants underwent both echocardiography and magnetic resonance imaging (MRI) of the head. CT and WMH volume were determined using automated image processing methods. We first studied the associations of CT and WMH volume with cardiovascular risk factors (obesity, diabetes mellitus, hypertension, high blood pressure [BP], and smoking), markers of systemic inflammation (CRP [C-reactive protein], white blood cell count, and fibrinogen), and sociodemographic factors (living alone, income, and number of years of education). Second, we analyzed their associations with structural and functional echocardiographic parameters. Third, we assessed whether these associations could be explained by the above-mentioned risk factors.[21–23]

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to "Forschungsverbund Community Medicine" (community-medicine@unigreifswald.de).

Study Sample

SHIP (Study of Health in Pomerania) is a prospective population-based cohort of adults from West Pomerania, a northeastern region in Germany of ≈220 000 inhabitants.[20] The data used in our analyses were derived from SHIP-Trend, a cohort initiated 10 years after SHIP in the same region. In brief, from the total population of West Pomerania, a 2-stage stratified cluster sample of 8016 adults between the ages of 20 and 79 years was drawn. A total of 4420 individuals agreed to participate in the study. All participants gave written informed consent. The study was approved by the ethics committee of the University Medicine Greifswald and complies with the Declaration of Helsinki. Data used in our analyses come from the baseline examinations, which took place between 2008 and 2011.

A total of 1748 SHIP-Trend participants received an echocardiography analysis, bioelectrical impedance analysis, and MRI of the head (Figure 1). Participants with LV ejection fraction <40% (N=14), estimated

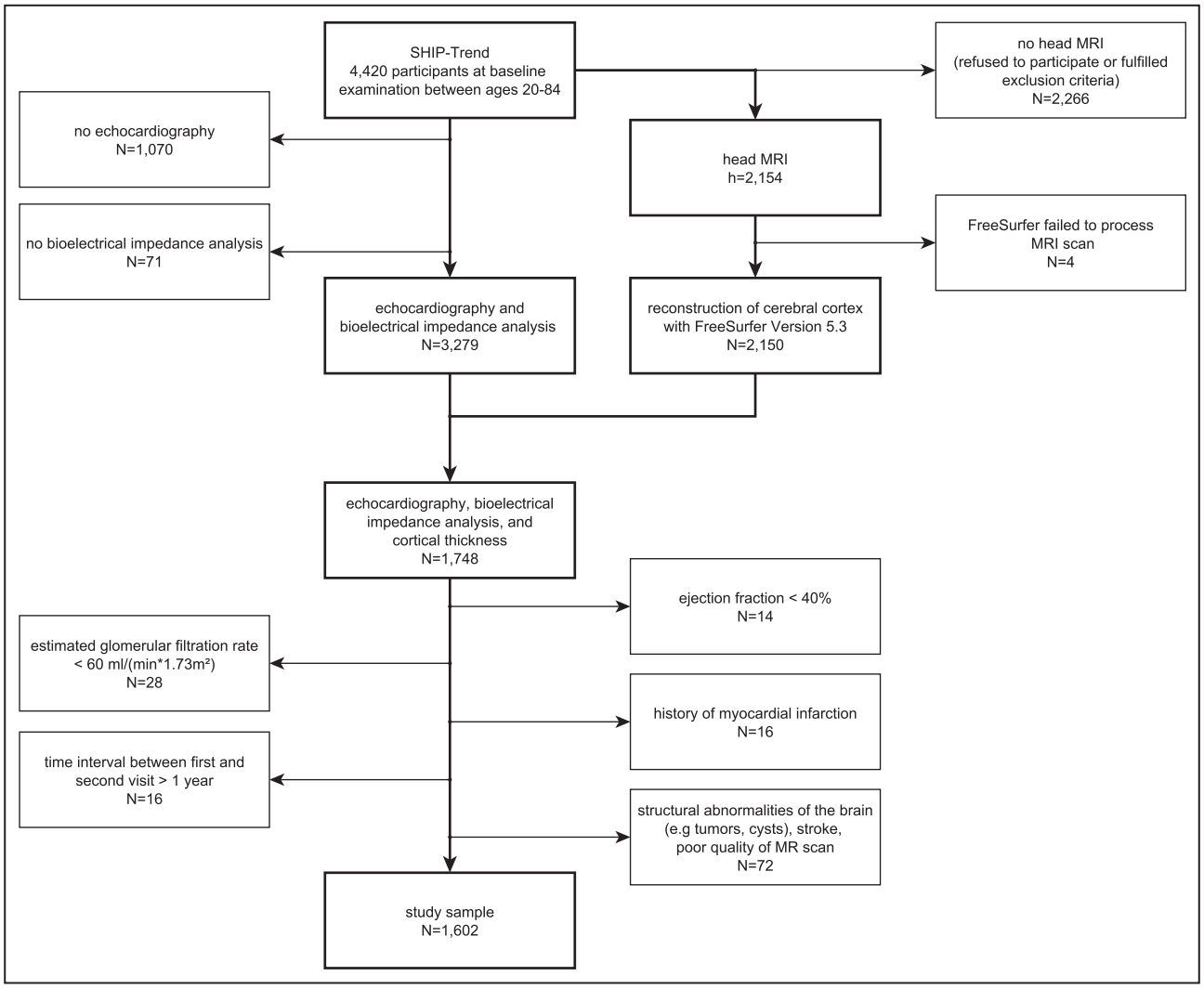

Figure 1. Flowchart showing the selection of the study sample.
The study sample is based on the SHIP (Study of Health in Pomerania)-Trend baseline examinations, which took place between 2008 and 2011. The final sample comprised 1602 adults from the population of West Pomerania, a northeastern region in Germany. MR indicates magnetic resonance; and MRI, MR imaging.

glomerular filtration rate <60 mL/(min×1.73 m^2) (N=28; calculated on the basis of serum creatinine and cystatin c[24]), and self-reported myocardial infarction (N=16) were excluded. In addition, participants who received MRI later than 1 year after echocardiography were excluded (N=16). Furthermore, an additional 78 participants were excluded because of structural abnormalities of the brain (eg, cysts and tumors), stroke, or poor scan quality after inspection by expert radiologists. The final study sample comprised data of 1602 participants. Details on data collection are provided in Data S1

Statistical Analysis

As a first analysis, the correlation matrix of all exposures, outcomes, and potentially confounding parameters was calculated using the Pearson correlation. Global CT and WMH volume were the primary outcomes of the association analyses. Associations with cardiovascular risk factors (waist circumference, diabetes mellitus, hypertension, systolic BP, diastolic BP, ever smoking, and current smoking), inflammatory markers (CRP, fibrinogen, and white blood cell count), sociodemographic factors (living alone, equalized disposable income, and number of years of education), and echocardiographic parameters (left ventricular diameter during diastole [LVD], left ventricular diameter during systole [LVS], interventricular septal thickness during systole, interventricular septal thickness during diastole, posterior wall thickness during diastole [PWD], posterior wall thickness during systole, LVM, LV ejection fraction [LVEF], ratio of early mitral inflow velocity/mitral annular early diastolic velocity [E/e′], and

ratio of peak velocity blood flow in early diastole/peak velocity flow in late diastole [E/A]) (exposures) were studied by linear ordinary least squares regressions[25] for each exposure separately, resulting in 2×23 regression models. All continuous and dichotomous variables (including the outcomes) were z-transformed to 0 mean and unit variance. As the distribution of WMH volume is right skewed, normalization was performed using a log transformation.[26] Analyses were adjusted for age, sex, body height, and fat-free mass, which are well known to be associated with echocardiographic parameters[27,28] and partly also with CT,[17] by including them as control variables in the regression models. We also included the total intracranial volume of the head, which is well known to correlate with the size of brain structures.[29] Finally, we also included the interaction of sex with age to account for differences in age-related atrophy between men and women.[30] The base models therefore comprised the control variables (age, sex, body height, fat-free body mass, total intracranial volume, and the interaction of sex with age) and a single exposure variable. Continuous control variables were modeled by restricted cubic splines with 5 knots located at the 5%, 27.5%, 50%, 72.5%, and 95% quantiles to account for possible nonlinear relationships.[25] Statistical effects of the exposures on the outcomes were assessed on the basis of the regression coefficients. In addition, we also considered Cohen f^2 as a general measure of effect size (see Cohen,[31] formula 9.2.3, page 410).

We examined whether the associations between outcomes and echocardiographic parameters can be explained by cardiovascular risk factors, inflammatory marker, or sociodemographic variables. This was done by including them in the base models as additional control variables both individually and all together (extended models). Again, continuous risk factors were modeled by restricted cubic splines (see above). We investigated changes in the regression coefficients of the exposures by applying Z-tests to the normalized differences, $z = (\beta_1 - \beta_2) / (\sigma_1^2 + \sigma_2^2)^{1/2}$ with β_1 and β_2 being the regression coefficients of the exposure within an extended model and the base model, respectively, and σ_1 and σ_2 denoting the corresponding SEs.[32]

Finally, we studied the associations of echocardiographic parameters with CT of 68 regions defined by the Desikan-Killiany atlas[33] (secondary outcomes). We used the Benjamini-Hochberg method with false discovery rate ≤5% to account for multiple testing.[34]

Fulfillment of the statistical assumptions of ordinary least squares regression was checked by visual inspection of diagnostic plots. Cases with unusually large residuals were excluded from the analyses. All statistical analyses were performed with R version 4.0.3. Figures were created with the ggplot2 package in R and the freesurfer_statsurf_scalar package in MATLAB.

RESULTS

Sample Characteristics

The characteristics of the study population are shown in Table 1. The sample comprised 1602 participants from 21 to 82 years of age, with a median age of 49 years, and 53% (N=839) being women. Median body mass index was 26.6 kg/m^2. A total of 40.4% and 35.8% were never smokers and former smokers, respectively. Hypertension and diabetes mellitus were present in 37.7% and 5.9%, respectively, of the study population.

Echocardiographic Parameters

LV diameters and wall thicknesses (ie, posterior wall thickness and width of the interventricular septum) were highly correlated among each other (eg, r=0.61 for LVD and LVS), but correlations between both groups of parameters were small (eg, r=0.14 for LVD and PWD). Structural parameters were moderately or highly correlated with LVM (r=0.43 … 0.76). LVEF was more strongly related to structural parameters during systole (eg, r=−0.81 for LVS) than during diastole (eg, r=−0.05 for LVD). Parameters of diastolic function (E/e′ and E/A) were moderately positively and inversely, respectively, correlated with wall thicknesses both during systole and diastole but not with LV diameters. The complete correlation matrix of echocardiographic parameters, among others, is shown in Figure S1. The fraction of variance in echocardiographic parameters, explained by the control variables age, sex, body height, fat-free body mass, and the interaction of sex and age, varied between 5.4% and 53% for LVEF and LVM, respectively. Adding interactions of sex with body height and fat-free mass did not significantly improve the explained variance.

Associations of Global CT and WMH Volume With Cardiovascular Risk Factors, Inflammatory Markers, and Sociodemographic Factors

Global CT varied between 1.83 and 2.71 mm and lessened on average with age by 0.05 mm per decade. After regressing global CT on the control variables of the base model, we identified 6 cases with unusually large residuals that were excluded from subsequent analyses (Figure S2). The fraction of explained variance was 38%. Adding interactions of sex with total intracranial volume, body height, and fat-free mass did not significantly improve the explained variance. Global CT was inversely associated with concentrations of CRP (β=−0.048; P=0.021), white blood cell count (β=−0.062; P=0.002), ever smoking (β=−0.056; P=0.007), and current smoking (β=−0.079; P=1.2e-4).

Table 1. Sample Characteristics (N=1602)

	Value
Clinical variables	
Women, %	52.4
Age, y	49 (40–59)
Smoking, %	
Never	40.4
Former	35.8
Current	23.8
Missing	1
Systolic blood pressure, mm Hg	125 (113–136)
Diastolic blood pressure, mm Hg	76 (70–83)
Hypertension, %	37.7
Missing	3
Diabetes mellitus, %	5.9
Body measures	
Body height, m	1.70 (1.64–1.78)
Body mass, kg	77.9 (68.0–88.7)
Body mass index, kg/m^2	26.7 (24.0–29.6)
Fat-free body mass, kg	54.5 (46.6–66.0)
Waist circumference, cm	87.3 (78.5–96.6)
Missing	2
Laboratory measurements	
CRP, mg/L	1.12 (0.60–2.28)
Missing	80
White blood cell count, 10^9 cells/L	5.49 (4.70–6.60)
Missing	2
Fibrinogen, g/L	2.9 (2.4–3.4)
Missing	14
Sociodemography	
Living alone, %	24.6
Equivalized disposable income, €	1450 (1096–1803)
Missing	60
Education, y	13 (11–15)
Missing	15
Echocardiography	
LVD, cm	4.89 (4.55–5.24)
LVS, cm	2.83 (2.54–3.15)
IVSD, cm	1.01 (0.89–1.13)
IVSS, cm	1.59 (1.38–1.81)
PWD, cm	0.95 (0.85–1.07)
PWS, cm	1.57 (1.39–1.78)
LVM, g	172 (139–210)
LVEF, %	72.3 (66.5–78.1)
E/e'	5.8 (5.0–7.0)
Missing	48
E/A	1.13 (0.94–1.41)
Missing	19
Brain imaging	
Estimated total intracranial volume, L	1.58 (1.47–1.70)
Mean cortical thickness, mm	2.36 (2.27–2.42)
White matter hyperintensity volume, mm^3	149 (57–368)
Missing	229

Values are given as percentages or medians with CIs (25% and 75% quantiles). Hypertension was classified according to International Society of Hypertension–World Health Organization 1999 (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or intake of antihypertensive drugs). Diabetes mellitus was defined on the basis of self-report, intake of antidiabetic medication (anatomical therapeutic chemical: A10), glycated hemoglobin ≥6.5%, or blood glucose levels ≥11.1 mmol/L. CRP indicates C-reactive protein; E/A, ratio of peak velocity blood flow in early diastole/peak velocity flow in late diastole; E/e′, ratio between early mitral inflow velocity/mitral annular early diastolic velocity; IVSD, intraventricular septum thickness during diastole; IVSS, intraventricular septum thickness during systole; LVD, left ventricular diameter during diastole; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVS, left ventricular diameter during systole; PWD, posterior wall thickness during diastole; and PWS, posterior wall thickness during systole.

Global CT was positively associated with number of years of education (β=0.074; *P*=3.5e-4) and equalized disposable income (β=0.052; *P*=0.014) while adjusting for the control variables of the base model. Regression coefficients and CIs are shown by Table 2. Combining the 2 dichotomous smoking variables into a single one (never/former/current) yielded an overall effect of f^2=1.0%. Number of years of education exhibited the second strongest effect on global CT (f^2=0.8%).

The distribution of WMH volume was right skewed, and a log transformation was applied for normalization. About 36% of WMH variance was explained by the control variables of the base model. Three cases were excluded from the subsequent analyses because of unusually large residuals (Figure S2). Adding interactions of sex with total intracranial volume, body height, and fat-free mass did not significantly improve the explained variance. WMH volume was positively associated with hypertension (β=0.065; *P*=0.009), systolic BP (β=0.058; *P*=0.028), and ever smoking (β=0.049; *P*=0.027). Regression coefficients and CIs are shown by Table 3. The effect size of smoking status (never/former/current) was f^2=0.4%. Hypertension exhibited the strongest effect on WMH volume (f^2=0.5%). Results of sex-stratified analyses are provided in Tables S1 and S2.

Associations of Global CT and WMH Volume With Echocardiographic Parameters

Global CT was inversely associated with LVD (β=−0.055; *P*=0.025), LVS (β=−0.046; *P*=0.036), interventricular septal thickness during systole (β=−0.051; *P*=0.030), PWD (β=−0.090; *P*=1.6e-4), and LVM (β=−0.12; *P*=3.9e-5) while adjusting for the control variables of the base model. There were no significant

Table 2. Associations of Global CT With Echocardiographic Parameters, Cardiovascular Risk Factors, Inflammatory Markers, and Sociodemographic Variables

Variable	Exposure	Base model			Extended model		
		β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
Cardiovascular risk factors	Waist circumference	−0.021	(−0.092 to 0.049)	5.45E-01	…	…	…
	Diabetes mellitus	−0.019	(−0.059 to 0.021)	3.43E-01	…	…	…
	Hypertension	−0.028	(−0.074 to 0.018)	2.20E-01	…	…	…
	Systolic blood pressure	−0.017	(−0.065 to 0.031)	4.83E-01	…	…	…
	Diastolic blood pressure	0.012	(−0.032 to 0.057)	5.81E-01	…	…	…
	Ever smoking	−0.056	(−0.097 to −0.015)	6.70E-03†	…	…	…
	Current smoking	−0.079	(−0.120 to −0.038)	1.21E-04‡	…	…	…
Inflammatory markers	CRP	−0.048	(−0.089 to −0.007)	2.08E-02*	…	…	…
	White blood cell count	−0.062	(−0.102 to −0.022)	1.81E-03†	…	…	…
	Fibrinogen	−0.042	(−0.085 to 0.002)	5.43E-02	…	…	…
Sociodemographics	Living alone	−0.037	(−0.078 to 0.003)	6.74E-02	…	…	…
	Equivalized disposable income	0.052	(0.010 to 0.095)	1.39E-02*	…	…	…
	Years of education	0.074	(0.033 to 0.115)	3.57E-04‡	…	…	…
Echocardiography	LVD	−0.055	(−0.103 to −0.007)	2.47E-02*	−0.058	(−0.109 to −0.006)	2.91E-02*
	LVS	−0.046	(−0.089 to −0.003)	3.63E-02*	−0.026	(−0.073 to 0.020)	2.71E-01
	IVSD	−0.027	(−0.072 to 0.018)	2.34E-01	−0.008	(−0.057 to 0.040)	7.33E-01
	IVSS	−0.051	(−0.098 to −0.005)	2.95E-02*	−0.051	(−0.100 to −0.002)	4.23E-02*
	PWD	−0.090	(−0.137 to −0.044)	1.57E-04‡	−0.057	(−0.109 to −0.006)	2.89E-02*
	PWS	−0.032	(−0.078 to 0.014)	1.68E-01	−0.016	(−0.065 to 0.033)	5.11E-01
	LVM	−0.119	(−0.175 to −0.062)	3.93E-05‡	−0.095	(−0.157 to −0.032)	2.89E-03†
	LVEF	0.019	(−0.021 to 0.059)	3.40E-01	−0.005	(−0.048 to 0.037)	8.03E-01
	E/e′	0.001	(−0.045 to 0.046)	9.82E-01	0.025	(−0.024 to 0.074)	3.18E-01
	E/A	0.006	(−0.044 to 0.056)	8.09E-01	0.018	(−0.039 to 0.075)	5.30E-01

Standardized regression coefficients with 95% CIs are given. Results are adjusted for age, sex, body height, fat-free body mass, total intracranial volume, and the interaction of sex with age (base model). In addition, associations with echocardiographic parameters were also adjusted for all cardiovascular risk factors, inflammatory markers, and sociodemographic variables (extended model). CRP indicates C-reactive protein; CT, cortical thickness; E/A, ratio of peak velocity blood flow in early diastole/peak velocity flow in late diastole; E/e′, ratio between early mitral inflow velocity/mitral annular early diastolic velocity; IVSD, intraventricular septum thickness during diastole; IVSS, intraventricular septum thickness during systole; LVD, left ventricular diameter during diastole; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVS, left ventricular diameter during systole; PWD, posterior wall thickness during diastole; and PWS, posterior wall thickness during systole.

Significance levels: *P<0.05, †P<0.01, ‡P<0.001.

associations of global CT with any functional cardiac parameter. Regression coefficients and CIs are shown in Table 2. Global CT was most strongly associated with LVM (f^2=1.1%) followed by PWD (f^2=0.9%). Additional adjustment for cardiovascular risk factors, inflammatory markers, and sociodemographic factors, both individually and all together (extended models), did not significantly modify these associations (Z-tests; |z|<0.94; Figure S3). Inclusion of CRP did weaken the association with PWD and therefore also with LVM marginally (z=−0.46 and z=−0.26, respectively). The association between global CT and LVS was marginally weaker when including income (z=−0.33). When adjusting for all risk factors together, the associations of global CT with LVD, interventricular septal thickness during systole, PWD, and LVM remained significant.

WMH volume was positively associated with LVD (β=0.067; P=0.013) and LVM (β=0.071; P=0.027), and inversely associated with E/A (β=0.057; P=0.043), while adjusting for the control variables of the base model. Regression coefficients and CIs are shown in Table 3. WMH volume was most strongly associated with LVD (f^2=0.45%). Additional adjustment for cardiovascular risk factors, inflammatory markers, and sociodemographic factors, both individually and all together (extended models), did not significantly modify these associations (Z-tests; |z|<0.51; Figure S4). The association with LVM and E/A became nonsignificant when adjusting for all risk factors (z=−0.07 and z=−0.03, respectively). Results of sex-stratified analyses are provided in Tables S1 and S2.

Table 3. Associations of WMH Volume With Echocardiographic Parameters, Cardiovascular Risk Factors, Inflammatory Markers, and Sociodemographic Variables

Variable	Exposure	Base model			Extended model		
		β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
Cardiovascular risk factors	Waist circumference	−0.0381	(−0.117 to 0.041)	3.33E-01	…	…	…
	Diabetes mellitus	0.0056	(−0.040 to 0.051)	8.07E-01	…	…	…
	Hypertension	0.0653	(0.015 to 0.116)	9.71E-03†	…	…	…
	Systolic blood pressure	0.0585	(0.005 to 0.112)	2.81E-02*	…	…	…
	Diastolic blood pressure	0.0318	(−0.018 to 0.081)	2.00E-01	…	…	…
	Ever smoking	0.0498	(0.005 to 0.095)	2.76E-02*	…	…	…
	Current smoking	0.0320	(−0.013 to 0.077)	1.58E-01	…	…	…
Inflammatory markers	CRP	−0.0109	(−0.054 to 0.032)	6.15E-01	…	…	…
	White blood cell count	0.0154	(−0.027 to 0.058)	4.70E-01	…	…	…
	Fibrinogen	0.0225	(−0.025 to 0.070)	3.46E-01	…	…	…
Sociodemographics	Living alone	0.0171	(−0.028 to 0.062)	4.48E-01	…	…	…
	Equivalized disposable income	−0.0109	(−0.057 to 0.036)	6.41E-01	…	…	…
	Years of education	−0.0452	(−0.091 to 0.001)	5.01E-02	…	…	…
Echocardiography	LVD	0.067	(0.014 to 0.121)	1.31E-02*	0.080	(0.021 to 0.138)	7.69E-03†
	LVS	0.040	(−0.008 to 0.089)	1.04E-01	0.030	(−0.023 to 0.083)	2.71E-01
	IVSD	−0.010	(−0.060 to 0.040)	6.91E-01	−0.023	(−0.079 to 0.033)	4.16E-01
	IVSS	−0.011	(−0.062 to 0.041)	6.84E-01	−0.016	(−0.072 to 0.040)	5.77E-01
	PWD	0.040	(−0.012 to 0.092)	1.33E-01	0.024	(−0.034 to 0.083)	4.17E-01
	PWS	0.034	(−0.017 to 0.084)	1.96E-01	0.029	(−0.026 to 0.085)	2.99E-01
	LVM	0.071	(0.008 to 0.134)	2.71E-02*	0.067	(−0.004 to 0.138)	6.43E-02
	LVEF	−0.012	(−0.056 to 0.033)	5.99E-01	0.005	(−0.043 to 0.054)	8.31E-01
	E/e′	0.010	(−0.040 to 0.060)	6.94E-01	0.001	(−0.054 to 0.057)	9.60E-01
	E/A	0.057	(0.002 to 0.112)	4.30E-02*	0.057	(−0.006 to 0.121)	7.70E-02

Standardized regression coefficients with 95% CIs are given. Results are adjusted for age, sex, body height, fat-free body mass, total intracranial volume, and the interaction of sex with age (base model). In addition, associations with echocardiographic parameters were also adjusted for all cardiovascular risk factors, inflammatory markers, and sociodemographic variables (extended model). CRP indicates C-reactive protein; E/A, ratio of peak velocity blood flow in early diastole/peak velocity flow in late diastole; E/e′, ratio between early mitral inflow velocity/mitral annular early diastolic velocity; IVSD, intraventricular septum thickness during diastole; IVSS, intraventricular septum thickness during systole; LVD, left ventricular diameter during diastole; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVS, left ventricular diameter during systole; PWD, posterior wall thickness during diastole; PWS, posterior wall thickness during systole; and WMH, white matter hyperintensity.

Significance levels: *P<0.05, †P<0.01.

Associations of Regional CT With Echocardiographic Parameters

We found consistent inverse associations of regional CT with LV structural parameters while adjusting for the control variables of the base model. Figure 2A shows a map of the cortical regions of the right hemisphere. In general, LVD was more strongly associated with thickness of the parietal, temporal, and occipital lobes, whereas PWD was more strongly related to thickness of the frontal lobe and cingulate cortex (Figure S5). LVM was most strongly related to regional CT, with significant associations in 50 of 68 regions after correction for multiple testing (false discovery rate ≤5%). There were no significant associations of regional CT with any functional cardiac parameter.

When additionally adjusting for all cardiovascular risk factors, inflammatory markers, and sociodemographic variables, we found significant associations of LVD and PWD with CT of the right postcentral gyrus (β=−0.103; $P_{adjusted}$=0.029) and right pars triangularis (β=−0.096; $P_{adjusted}$= 0.045), respectively. LVM was most strongly related to regional CT, with significant associations in 13 of 64 regions, notably with the right pars triangularis (β=−0.151; $P_{adjusted}$=7.3e-4) and right postcentral gyrus (β=−0.125; $P_{adjusted}$=0.015) (Figure 2B). Again, there were no significant associations with any functional cardiac parameter.

Maps of regression coefficients for all echocardiographic parameters and both hemispheres are shown in Figures S5 and S6.

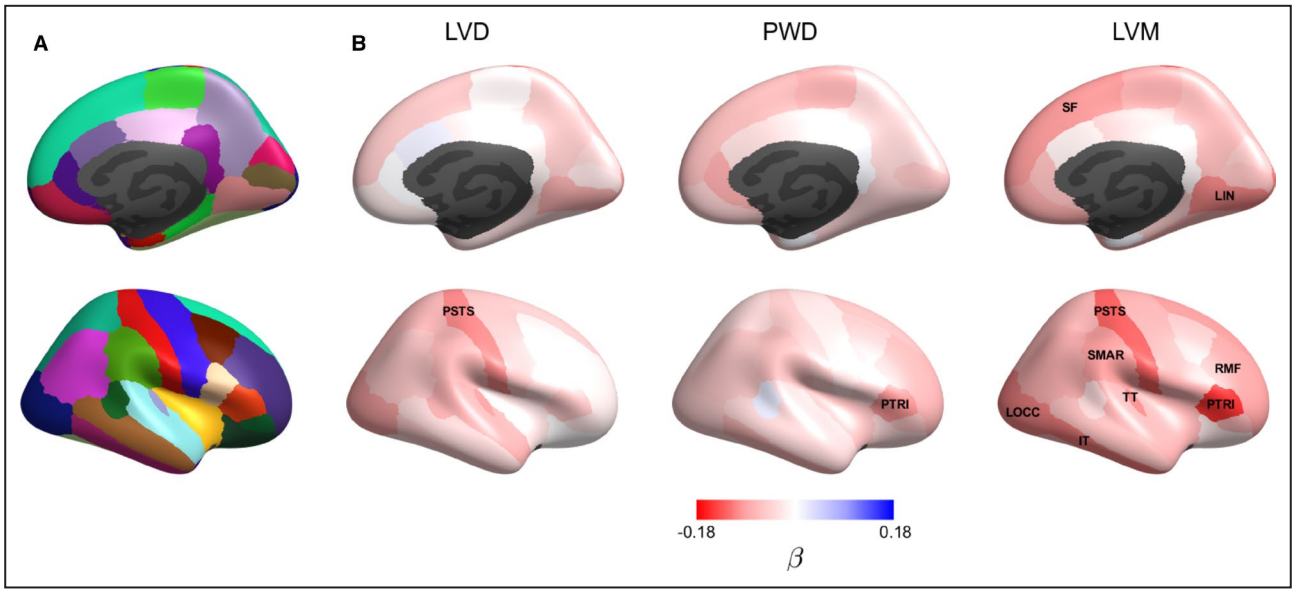

Figure 2. Associations of regional cortical thickness with left ventricular diameter during diastole (LVD), posterior wall thickness during diastole (PWD), and left ventricular mass (LVM) while adjusting for cardiovascular risk factors, inflammatory markers, and sociodemographic factors (extended model; right hemisphere only).
A, Each participant's cerebral cortex was parceled into 34 regions per hemisphere, according to the gyral-based Desikan-Killiany atlas. **B**, In addition to the control variables of the base model, we included cardiovascular risk factors (including hypertension), markers of systemic inflammation, and sociodemographic variables into the regression models of each cortical region. Standardized regression coefficients are shown. Labels are shown for those regions where associations remained significant after correction for multiple testing with the Benjamini-Hochberg method (false discovery rate ≤5%). IT indicates inferior temporal gyrus; LIN, lingual cortex; LOCC, lateral occipital cortex; PSTS, postcentral gyrus; PTRI, pars triangularis; RMF, rostral middle frontal gyrus; SF, superior frontal gyrus; SMAR, supramarginal gyrus; and TT, transverse temporal cortex.

DISCUSSION

LV hypertrophy is ever more being recognized as a risk factor for cognitive decline and dementia in elderly patients. Specifically, several previous studies have found that LV hypertrophy was associated with lower global and domain-specific cognitive performance and a greater risk for dementia, independent of hypertension.[8,35–37] Cognitive decline during normal aging and in neurodegenerative diseases is a consequence of adverse changes in brain structure.[38–40] We therefore hypothesized echocardiographic markers of LV hypertrophy to be related with CT and WMH burden in the general population. Although some previous studies found gray matter atrophy in association with greater LVM (eg, in the hippocampus),[6] its associations with global and regional CT have not been investigated to date.

In accordance with previous studies, LV mass and diameter were positively associated with greater WMH volume in our general population sample.[7,41] Moreover, we found consistent inverse associations of LV structural but not functional echocardiographic parameters with both global and regional CT. LVM was most strongly associated with global CT, followed by PWD and LVD. LVD was more strongly associated with regions of the occipital, temporal, and parietal lobes, whereas PWD was more strongly associated with regions of the frontal and cingulate cortex. This is in line with previous studies reporting independent effects of concentric (ie, large LVM but normal diameter) and eccentric (ie, large LVD but normal mass) hypertrophy on incident dementia and cognitive function.[36,42] Recently, the association of increased LVM with compromised white matter microstructure in older adults free of dementia and heart failure has been reported.[9] Fractional anisotropy was reduced in the right inferior frontal gyrus, among others. This not only supports our finding of spatially specific associations of LVM with CT but also matches the region that was most strongly associated with LVM in our analyses. In addition, both the somatosensory cortex (which is located in the postcentral gyrus) and the frontal cortex are hypothesized to play pivotal roles in neural control of the cardiovascular system.[19]

We examined the roles of various cardiovascular risk factors, inflammatory markers, and sociodemographic factors. Associations of echocardiographic parameters with global CT and WHM volume could not be explained by any of these risk factors. For instance, LVM is generally driven by increased systolic BP.[43] Yet, neither BP nor hypertension did significantly modify the association between LVM and global CT. Moreover, the associations were not significantly modified when

additionally adjusting for smoking status and inflammatory markers, although they were strongly associated with CT themselves[22,44] (Figure 2B). This was also the case when controlling for all risk factors, thereby potentially suggesting an independent association of LVM with both global CT and WMH volume. We would like to highlight that the effect size of smoking status on global CT was about the same as the ones of LVD and PWD ($f^2 \approx 1\%$).

We did not find an association of CT with systolic and diastolic cardiac function. This is in discrepancy with previous studies reporting inverse associations of systolic function with total brain volume in samples of older individuals.[45,46] There may be two reasons for this. First, none of the previous studies examined volume or thickness of the cerebral cortex in particular. Second, our sample comprised of middle-aged individuals with preserved systolic function (LVEF >40%) and no history of myocardial infarction. Furthermore, one may assume that the adverse effects of poor cardiac function on the cerebral cortex become only apparent in older individuals or in individuals with impaired cardiac systolic function. This is supported by the fact that other studies in healthy individuals also have failed to find an association of LVEF with cognitive decline or risk of dementia in individuals free of cardiovascular disease and dementia.[36]

The potential biological mechanisms underlying the observed association between LV hypertrophy and thinner cerebral cortex are complex and remain to be fully understood. In general, the relation between the heart and the brain is bidirectional, with the brain influencing the heart (eg, in broken-heart syndrome/Takotsubo cardiomyopathy), as well as the heart effecting the brain (eg, in embolic stroke).[47] The strong association of LVM with CT in healthy middle-aged adults observed herein might reflect a subclinical neurocardiological syndrome caused by stress-induced chronic hyperactivation of the sympathetic nervous system. The latter is known to impair top-down function of the prefrontal cortex because of catecholamine-induced dendritic atrophy, with signs of prefrontal dysfunction in posttraumatic stress disorder.[14] On the other hand, stress-induced chronic hyperactivation of the sympathetic nervous system is also known to increase LVM via activation of the RAAS.[15] The RAAS plays a pivotal role in maintaining circulatory homeostasis. Aldosterone release from the adrenal cortex is stimulated by angiotensin II. This mineralocorticoid hormone induces greater renal sodium and water reabsorption, thereby influencing BP. Although the peripheral effects of the RAAS are well understood, there may also be other means of how the brain and the heart are connected through this system. For instance, salt-sensitive rats develop hypertension when aldosterone is infused intracerebroventricularly, whereas the injection of spironolactone (mineral corticoid receptor antagonist) reverses this phenotype.[48] Hyperaldosteronism is often present in depressed patients. Hence, the RAAS may partly explain why this patient group not only exhibits less CT but also has a greater risk for cardiovascular diseases.[49,50] Overall, previous studies highlight the important role of the RAAS as a potential link between LV hypertrophy and cortical thinning.

The present study has several limitations that need to be considered when interpreting the findings. First, echocardiography and MRI were assessed in a cross-sectional setting. Consequently, causation cannot be implied. Second, although we adjusted for a variety of confounding factors, residual confounding attributable to other unmeasured factors cannot be ruled out. Third, our study included middle-aged White Europeans, and results cannot be generalized to other age groups or races/ethnicities. Fourth, we would like to highlight that the individuals who participated in the MRI examination were not randomly drawn from the initial sample (n=4420) and were selected on the basis of examination-specific inclusion criteria (eg, abdominal circumference not exceeding the MRI bore size). Nonetheless, the strengths of our study are the large study population and the inclusion of a variety of potential confounding variables.

In summary, we report associations of markers of LV hypertrophy with CT and WMH burden, independent from a wide range of cardiovascular risk factors, inflammatory markers, and sociodemographic factors. Our findings are clinically relevant as they highlight that previously reported associations of LV hypertrophy with adverse changes in brain structure in elderly patients are already present in healthy middle-aged adults.

ARTICLE INFORMATION

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Supplementary Material

Data S1
Tables S1–S3
Figures S1–S6

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Supplemental Material

Data S1.

Supplemental Methods

Data Collection

Medical history and socio-demographic variables were assessed by standardized questionnaires during a computer-assisted face-to-face interview. Blood pressure (BP), body height, body weight, and waist circumference were measured during subsequent medical examinations. BP was measured three times from the right brachial artery after a 10-minute rest in a supine position and the average of the second and third measurement was considered. Fat-free body mass was measured by bioelectrical impedance analysis using the NutriGuard M device (Data Input, Pöcking, Germany). Hypertension was defined according ISH-WHO 1999 (either systolic BP ≥ 140mmHg, or diastolic BP ≥ 90mmHg, or intake of antihypertensive medications). Diabetes was defined either based on self-report, intake of anti-diabetic medication (ATC code A10), glycated hemoglobin ≥ 6.5% (International Expert Committee 2009), or blood glucose ≥ 11.1 mmol/l (IDF-WHO 2006). Both echocardiography and collection of blood samples were performed during the day of the interview. MRI of the head was performed during a second visit with a median time interval of 18 days (max. 347 days).

Ultrasound measurements

Two-dimensional, M-Mode, and Doppler echocardiography were performed using the Vivid-I system (GE Medical Systems, Waukesha, USA). Measurements of the LV end-diastolic and end-systolic diameter (LVD and LVS, in cm), interventricular septal thickness during diastole and systole (IVSD and IVSS, in cm), as well as posterior wall thickness during diastole and systole (PWD and PWS, in cm) were performed according to the guidelines of the American Society of Echocardiography (25). Left ventricular mass (LVM, in g) was calculated according to the formula $LVM=0.8\cdot1.04((LVD+IVSD+PWD)^3–LVD^3)+0.6$ as described by Devereux et al. (26). LV ejection fraction (LVEF) was calculated following the formulas according to the guidelines of the American Society of Echocardiography (25). Transmitral pulsed-wave Doppler was used to record early (E) and late (A) wave ventricular filling velocities. Ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e’), and ratio of peak velocity blood flow in early diastole to peak velocity flow in

late diastole (E/A) were calculated. Certification examinations for inter-observer variations revealed an agreement of more than 90%.

Magnetic Resonance Imaging

T_1-weighted and fluid-attenuated inversion recovery (FLAIR) scans of the head were obtained using a 1.5T Siemens Magnetom Avanto scanner (Siemens, Erlangen, Germany) (27). The following parameters were used: T_1: orientation=axial plane, TR=1,900ms, TE=3.37ms, flip angle 15°, slice thickness=1mm, and resolution 1mm x 1mm, FLAIR: orientation=axial plane, TR=5,000ms, TE=325ms, slice thickness=3mm, and resolution 0.9mm × 0.9mm.

Cortical Thickness

T_1-weighted MRI scans were processed with the image-processing pipeline FreeSurfer version 5.3 which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu). The processing includes segmentation of the cerebral cortex, calculation of mean CT of each hemisphere as well as regional CT according the Desikan-Killiany atlas. The Desikan-Killiany atlas comprises 34 gyral-based regions per hemisphere and has been successfully applied in a wide range of imaging studies in the past (28). The underlying method has been shown to give anatomically valid and reliable results (29). The list of all cortical regions can be found in Table S3. Global CT was defined as the mean thickness of left and right hemisphere.

CT but not cortical volume or surface area was considered because it is weaker associated with body size and sex (30), thereby minimizing the nuisance variation shared with structural cardiac measurements. Moreover, CT has been found to be a more sensitive measure of neurodegeneration in Alzheimer's disease (31,32). FreeSurfer also gives an estimate of the total intracranial volume (TIV) of the head which can be used to account for some of the variability of CT between the study participants.

White Matter Hyperintensities

After preprocessing and coregistration of T_1-weighted and FLAIR scans WMH lesions were segmented using a support vector machine-based method (33). Quality of segmentations were assessed by visual inspection, and total WMH volumes and counts were determined. Minimum WMH volume was set to 5 mm^3. For details we refer to Habes et al. (34).

Inflammatory Markers

Blood samples were taken from the cubital vein of the participants in supine position. White blood cell count (WBC) was determined using the Sysmex XT 2000, XE 5000 or SE 9000 analyzers (Sysmex, Kobe, Japan) or the Advia 2120i (Siemens Healthcare Diagnostics,

Eschborn, Germany). Concentrations of C-reactive protein (CRP) were determined in serum by nephelometry on the Dimension VISTA (Siemens Healthcare Diagnostics, Eschborn, Germany). Fibrinogen concentrations were measured in citrate plasma according to Clauss using the BCS or the BCS XP system (Siemens Healthcare Diagnostics, Eschborn, Germany).

Socio-Demographic Variables

Living alone was defined as not sharing the home with a partner (neither married nor unmarried). Equalized disposable income was defined as the ratio of the winsorized household income in Euro (ranging from 333.33€ to 5,066.67€) and the square root of the number of household members (35). The number of years of education was calculated as the sum of years of scholastic and occupational education with values ranging from 8 (e.g. completed lower secondary school and no professional qualification) to 17 (university degree) years.

Table S1. Associations of global cortical thickness (a) and white matter hyperintensity volume (b) with echocardiographic parameters, cardiovascular risk factors, inflammatory markers, and socio-demographic variables in females (N=839).

(a) Global cortical thickness, females

		Base model				*Extended model*			
	Exposure	*β*	95% CI	*P*		*β*	95% CI	*P*	
Cardiovascular Risk Factors	Waist circumference	-0.034	(-0.122, 0.054)	4.34E-01		-	-	-	
	Diabetes	-0.014	(-0.069, 0.042)	6.28E-01		-	-	-	
	Hypertension	-0.054	(-0.117, 0.009)	8.87E-02	.	-	-	-	
	Systolic Blood Pressure	-0.022	(-0.085, 0.041)	4.90E-01		-	-	-	
	Diastolic Blood Pressure	-0.018	(-0.076, 0.040)	5.36E-01		-	-	-	
	Ever Smoking	-0.024	(-0.082, 0.033)	3.98E-01		-	-	-	
	Current Smoking	-0.050	(-0.107, 0.008)	8.43E-02	.	-	-	-	
Inflammatory Markers	C-reactive Protein	-0.063	(-0.122, -0.004)	3.27E-02	*	-	-	-	
	White Blood Cell Count	-0.046	(-0.101, 0.010)	1.00E-01		-	-	-	
	Fibrinogen	-0.035	(-0.093, 0.023)	2.32E-01		-	-	-	
Socio-demographics	Living Alone	-0.022	(-0.078, 0.035)	4.42E-01		-	-	-	
	Equiv. Disp. Income	0.048	(-0.010, 0.107)	1.00E-01		-	-	-	
	Years of Education	0.006	(-0.052, 0.063)	8.45E-01		-	-	-	
Echocardiography	LVD	-0.055	(-0.118, 0.008)	8.08E-02	.	-0.046	(-0.116, 0.023)	1.83E-01	
	LVS	-0.030	(-0.089, 0.029)	3.07E-01		-0.021	(-0.085, 0.043)	5.11E-01	
	IVSD	-0.044	(-0.104, 0.015)	1.39E-01		-0.028	(-0.094, 0.038)	3.91E-01	
	IVSS	-0.069	(-0.130, -0.009)	2.22E-02	*	-0.050	(-0.117, 0.017)	1.33E-01	
	PWD	-0.075	(-0.136, -0.014)	1.46E-02	*	-0.044	(-0.112, 0.024)	1.93E-01	
	PWS	-0.018	(-0.079, 0.044)	5.70E-01		0.004	(-0.064, 0.073)	8.96E-01	
	LVM	-0.113	(-0.182, -0.043)	1.21E-03	**	-0.084	(-0.164, -0.005)	3.37E-02	*
	LVEF	0.001	(-0.056, 0.058)	9.75E-01		-0.006	(-0.068, 0.055)	8.36E-01	
	E/e'	-0.003	(-0.068, 0.063)	9.36E-01		0.017	(-0.054, 0.088)	6.25E-01	
	E/A	0.033	(-0.041, 0.106)	3.78E-01		0.028	(-0.053, 0.110)	4.89E-01	

(b) White matter hyperintensity volume, females

		Base model				*Extended model*			
	Exposure	*β*	95% CI	*P*		*β*	95% CI	*P*	
Cardiovascular Risk Factors	Waist circumference	-0.0286	(-0.127, 0.069)	5.59E-01		-	-	-	
	Diabetes	0.0137	(-0.047, 0.074)	6.53E-01		-	-	-	
	Hypertension	0.0450	(-0.024, 0.114)	1.92E-01		-	-	-	
	Systolic Blood Pressure	0.0242	(-0.046, 0.094)	4.89E-01		-	-	-	
	Diastolic Blood Pressure	0.0168	(-0.048, 0.081)	6.02E-01		-	-	-	
	Ever Smoking	0.0573	(-0.007, 0.121)	7.32E-02	.	-	-	-	
	Current Smoking	0.0538	(-0.009, 0.116)	8.55E-02	.	-	-	-	
Inflammatory Markers	C-reactive Protein	-0.0215	(-0.084, 0.041)	4.91E-01		-	-	-	
	White Blood Cell Count	0.0024	(-0.057, 0.062)	9.35E-01		-	-	-	
	Fibrinogen	0.0261	(-0.038, 0.090)	4.17E-01		-	-	-	
Socio-demographics	Living Alone	0.0110	(-0.051, 0.073)	7.21E-01		-	-	-	
	Equiv. Disp. Income	0.0061	(-0.058, 0.070)	8.49E-01		-	-	-	
	Years of Education	-0.0250	(-0.087, 0.037)	4.22E-01		-	-	-	
Echocardiography	LVD	0.067	(-0.003, 0.138)	5.63E-02	.	0.098	(0.019, 0.177)	1.32E-02	*
	LVS	0.029	(-0.036, 0.094)	3.75E-01		0.029	(-0.044, 0.101)	4.32E-01	
	IVSD	-0.018	(-0.084, 0.049)	5.93E-01		-0.047	(-0.122, 0.028)	2.07E-01	
	IVSS	0.002	(-0.064, 0.069)	9.46E-01		-0.008	(-0.082, 0.067)	8.39E-01	
	PWD	0.030	(-0.038, 0.098)	3.79E-01		0.020	(-0.057, 0.096)	6.08E-01	
	PWS	0.039	(-0.030, 0.108)	2.55E-01		0.024	(-0.053, 0.101)	5.29E-01	
	LVM	0.054	(-0.022, 0.131)	1.56E-01		0.057	(-0.032, 0.146)	1.97E-01	
	LVEF	-0.002	(-0.065, 0.061)	9.50E-01		0.012	(-0.057, 0.082)	7.22E-01	
	E/e'	0.017	(-0.055, 0.088)	6.43E-01		0.021	(-0.058, 0.101)	5.90E-01	
	E/A	0.089	(0.009, 0.169)	2.70E-02	*	0.097	(0.007, 0.187)	3.14E-02	*

Standardized regression coefficients with 95% confidence intervals are given. Results are adjusted for age, sex, body height, fat-free body mass, total intracranial volume, and the interaction of sex with age (base model). In addition, associations with echocardiographic parameters were also adjusted for all cardiovascular risk factors, inflammatory markers, and socio-demographic variables (extended model).

Table S2. Associations of global cortical thickness (a) and white matter hyperintensity volume (b) with echocardiographic parameters, cardiovascular risk factors, inflammatory markers, and socio-demographic variables in males (N=763).

(a) Global cortical thickness, males

		Base model				*Extended model*			
	Exposure	*β*	95% CI	*P*		*β*	95% CI	*P*	
Cardiovascular Risk Factors	Waist circumference	-0.003	(-0.095, 0.090)	9.53E-01		-	-	-	
	Diabetes	-0.025	(-0.084, 0.035)	4.11E-01		-	-	-	
	Hypertension	-0.008	(-0.075, 0.060)	8.16E-01		-	-	-	
	Systolic Blood Pressure	-0.015	(-0.078, 0.048)	6.32E-01		-	-	-	
	Diastolic Blood Pressure	0.034	(-0.031, 0.100)	2.89E-01		-	-	-	
	Ever Smoking	-0.085	(-0.144, -0.026)	4.06E-03	**	-	-	-	
	Current Smoking	-0.109	(-0.169, -0.048)	3.32E-04	***	-	-	-	
Inflammatory Markers	C-reactive Protein	-0.036	(-0.097, 0.024)	2.32E-01		-	-	-	
	White Blood Cell Count	-0.087	(-0.145, -0.028)	3.09E-03	**	-	-	-	
	Fibrinogen	-0.040	(-0.103, 0.024)	2.12E-01		-	-	-	
Socio-demographics	Living Alone	-0.051	(-0.113, 0.010)	9.64E-02	.	-	-	-	
	Equiv. Disp. Income	0.052	(-0.011, 0.116)	1.00E-01		-	-	-	
	Years of Education	0.139	(0.079, 0.199)	4.77E-06	***	-	-	-	
Echocardiography	LVD	-0.047	(-0.110, 0.015)	1.32E-01		-0.056	(-0.124, 0.013)	1.04E-01	
	LVS	-0.057	(-0.118, 0.004)	6.34E-02	.	-0.027	(-0.095, 0.040)	4.13E-01	
	IVSD	-0.009	(-0.071, 0.052)	7.62E-01		0.011	(-0.057, 0.079)	7.41E-01	
	IVSS	-0.030	(-0.093, 0.033)	3.40E-01		-0.043	(-0.109, 0.024)	2.01E-01	
	PWD	-0.084	(-0.147, -0.021)	7.55E-03	**	-0.041	(-0.111, 0.029)	2.46E-01	
	PWS	-0.040	(-0.103, 0.024)	2.10E-01		-0.030	(-0.098, 0.038)	3.78E-01	
	LVM	-0.089	(-0.156, -0.022)	8.19E-03	**	-0.068	(-0.142, 0.007)	7.17E-02	.
	LVEF	0.036	(-0.023, 0.096)	2.25E-01		-0.006	(-0.071, 0.059)	8.59E-01	
	E/e'	-0.005	(-0.072, 0.062)	8.82E-01		0.031	(-0.043, 0.106)	4.05E-01	
	E/A	-0.019	(-0.093, 0.054)	5.96E-01		0.000	(-0.089, 0.089)	9.99E-01	

(b) White matter hyperintensity volume, males

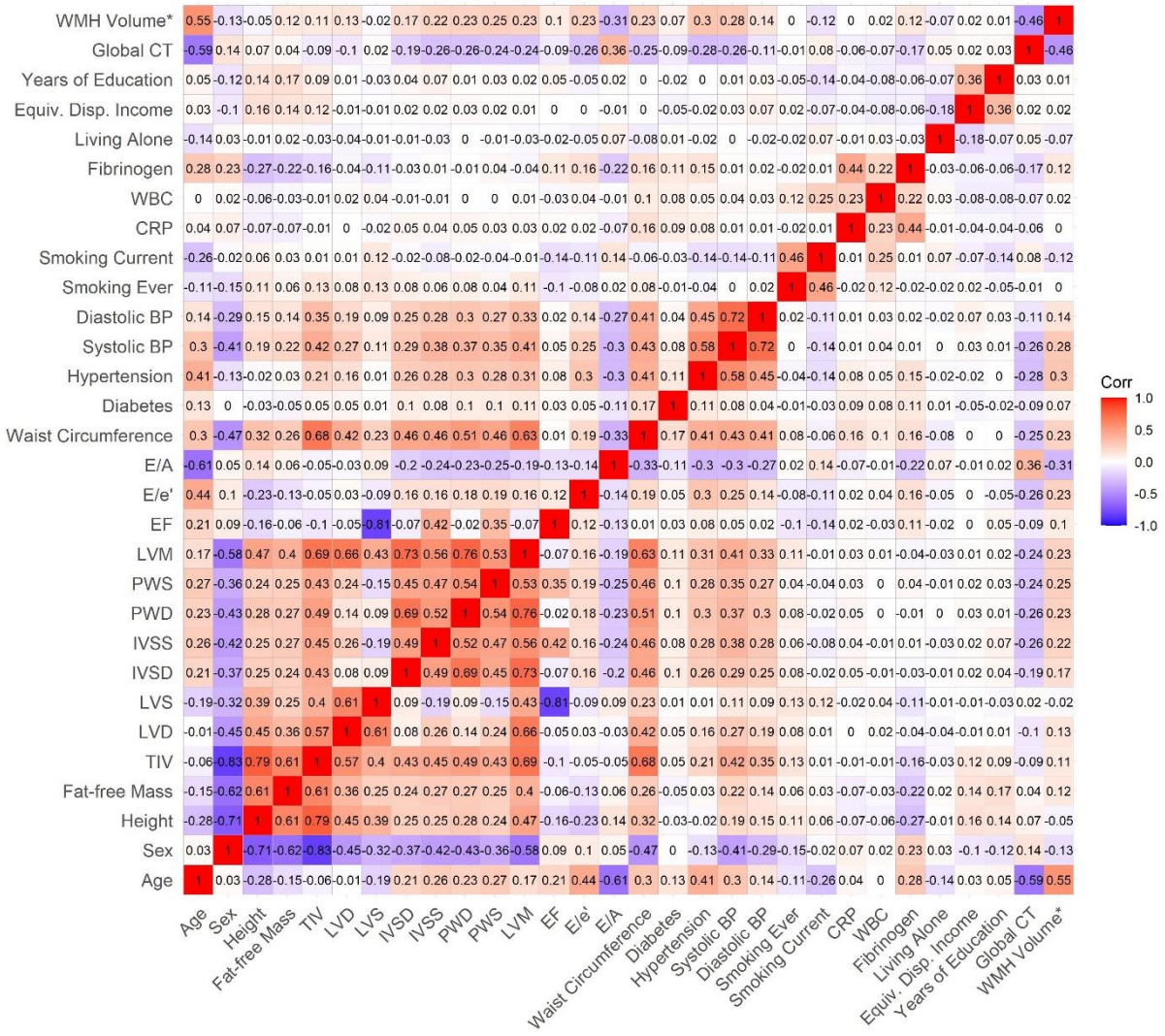
		Base model				*Extended model*		
	Exposure	*β*	95% CI	*P*		*β*	95% CI	*P*
Cardiovascular Risk Factors	Waist circumference	-0.0470	(-0.150, 0.056)	3.63E-01		-	-	-
	Diabetes	-0.0177	(-0.089, 0.054)	6.20E-01		-	-	-
	Hypertension	0.0822	(0.008, 0.156)	2.70E-02	*	-	-	-
	Systolic Blood Pressure	0.0863	(0.018, 0.155)	1.22E-02	*	-	-	-
	Diastolic Blood Pressure	0.0417	(-0.029, 0.113)	2.39E-01		-	-	-
	Ever Smoking	0.0359	(-0.028, 0.100)	2.61E-01		-	-	-
	Current Smoking	0.0093	(-0.058, 0.076)	7.81E-01		-	-	-
Inflammatory Markers	C-reactive Protein	-0.0014	(-0.063, 0.060)	9.63E-01		-	-	-
	White Blood Cell Count	0.0443	(-0.019, 0.108)	1.63E-01		-	-	-
	Fibrinogen	0.0122	(-0.057, 0.082)	7.25E-01		-	-	-
Socio-demographics	Living Alone	0.0329	(-0.035, 0.100)	3.30E-01		-	-	-
	Equiv. Disp. Income	-0.0280	(-0.097, 0.041)	4.16E-01		-	-	-
	Years of Education	-0.0689	(-0.138, 0.000)	4.64E-02	*	-	-	-
Echocardiography	LVD	-0.018	(0.118, 1.457)	1.46E-01		0.044	(-0.032, 0.121)	2.48E-01
	LVS	-0.019	(0.117, 1.455)	1.46E-01		0.035	(-0.042, 0.113)	3.63E-01
	IVSD	-0.063	(0.074, 0.151)	8.80E-01		-0.001	(-0.080, 0.078)	9.77E-01
	IVSS	-0.092	(0.046, -0.669)	5.04E-01		-0.040	(-0.117, 0.038)	3.05E-01
	PWD	-0.023	(0.115, 1.334)	1.83E-01		0.034	(-0.047, 0.115)	4.01E-01
	PWS	-0.050	(0.089, 0.567)	5.71E-01		0.033	(-0.044, 0.110)	3.88E-01
	LVM	-0.010	(0.137, 1.740)	8.24E-02	.	0.055	(-0.031, 0.140)	2.02E-01
	LVEF	-0.093	(0.038, -0.832)	4.06E-01		-0.013	(-0.088, 0.061)	7.18E-01
	E/e'	-0.077	(0.072, -0.067)	9.46E-01		-0.030	(-0.118, 0.057)	4.89E-01
	E/A	-0.053	(0.105, 0.650)	5.16E-01		0.037	(-0.064, 0.139)	4.64E-01

Standardized regression coefficients with 95% confidence intervals are given. Results are adjusted for age, sex, body height, fat-free body mass, total intracranial volume, and the interaction of sex with age (base model). In addition, associations with echocardiographic parameters were also adjusted for all cardiovascular risk factors, inflammatory markers, and socio-demographic variables (extended model).

Table S3. Regions of the cerebral cortex considered in this study (according Desikan et al. (33)).

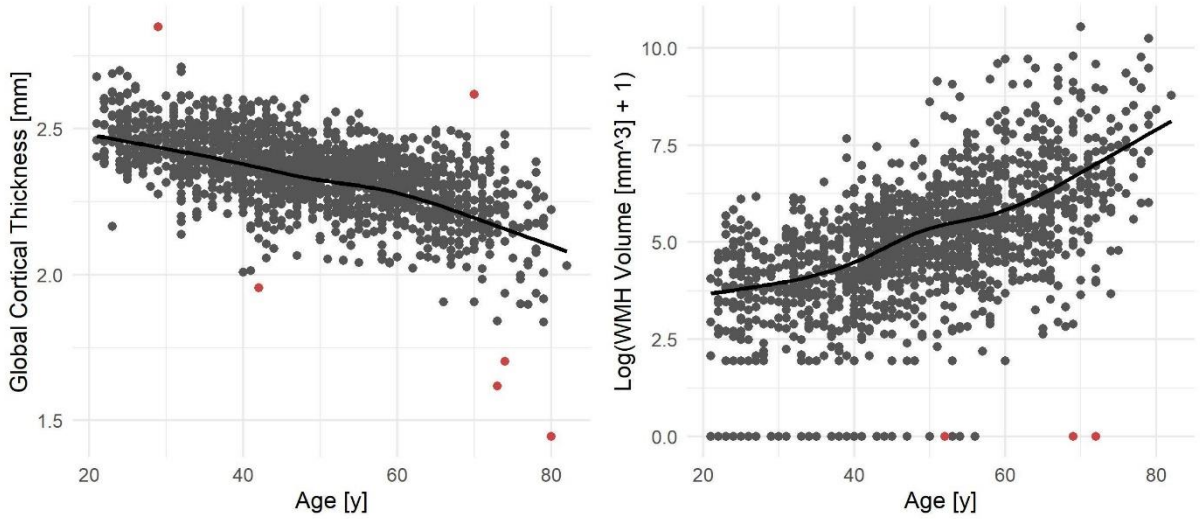
BSTS	banks of the superior temporal sulcus
CAC	caudal anterior cingulate cortex
CMF	caudal middle frontal gyrus
CUN	cuneus cortex
ENT	entorhinal cortex
FUS	fusiform gyrus
INFP	inferior parietal cortex
IT	inferior temporal gyrus
ISTC	isthmus of cingulate gyrus
LOCC	lateral occipital cortex
LORB	lateral orbitofrontal cortex
LIN	lingual cortex
MORB	medial orbitofrontal cortex
MT	middle temporal gyrus
PARH	parahippocampal gyrus
PARC	paracentral lobule
POPE	pars opercularis
PORB	pars orbitalis
PTRI	pars triangularis
PCAL	pericalcarine cortex
PSTS	postcentral gyrus
PC	posterior cingulate cortex
PREC	precentral gyrus
PCUN	precuneus cortex
RAC	rostral anterior cingulate cortex
RMF	rostral middle frontal gyrus
SF	superior frontal gyrus
SP	superior parietal cortex
ST	superior temporal gyrus
SMAR	supramarginal gyrus
FP	frontal pole
TP	temporal pole
TT	transverse temporal cortex
INS	insula

Figure S1. Correlation matrix of basic control variables, echocardiographic parameters, cardiovascular risk factors, inflammatory markers, sociodemographic variables, and the two primary outcomes, i.e. global cortical thickness (CT) and white matter hyperintensity (WMH) volume (SHIP-Trend; N=1,602).



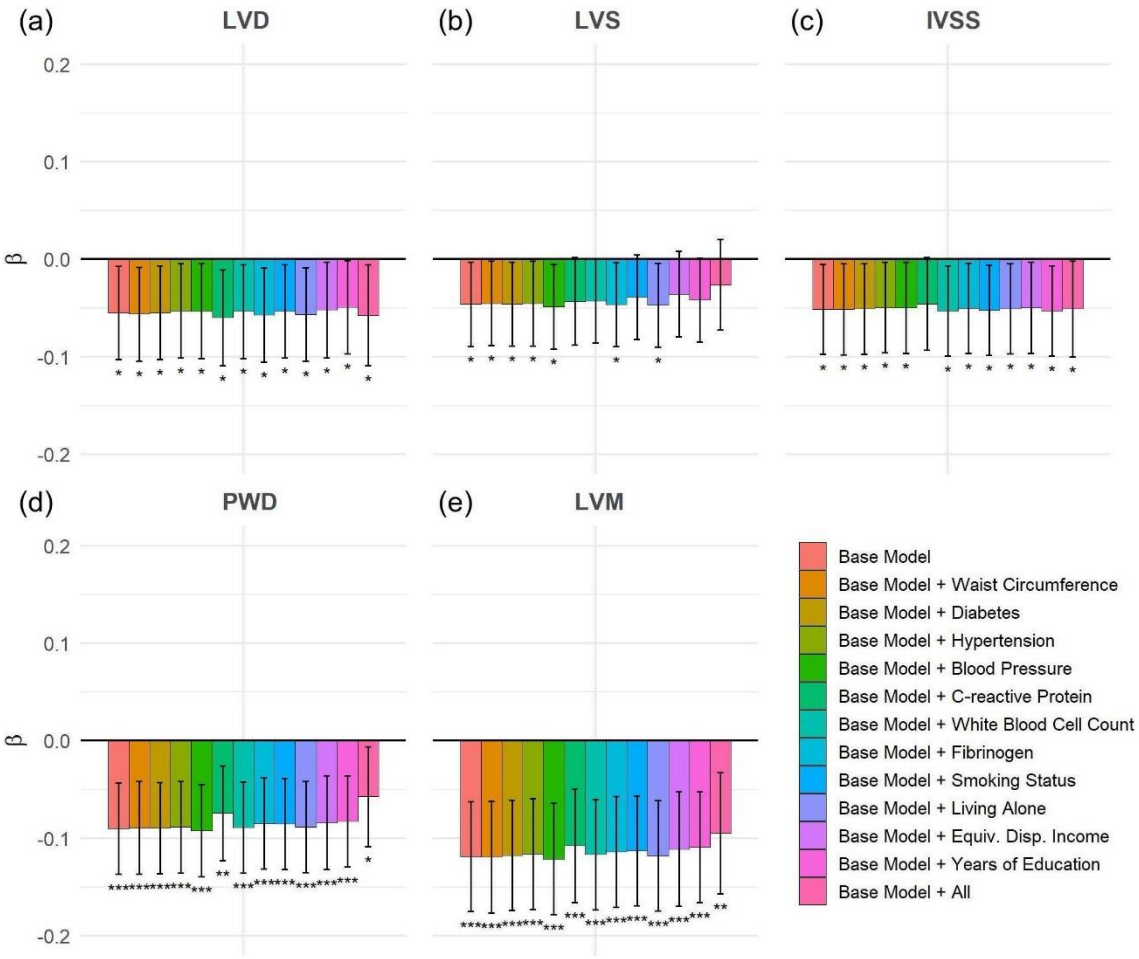
* = log transformed

Figure S2. Global cortical thickness (left) and volume of white matter hyperintensities (right) plotted against chronological age.



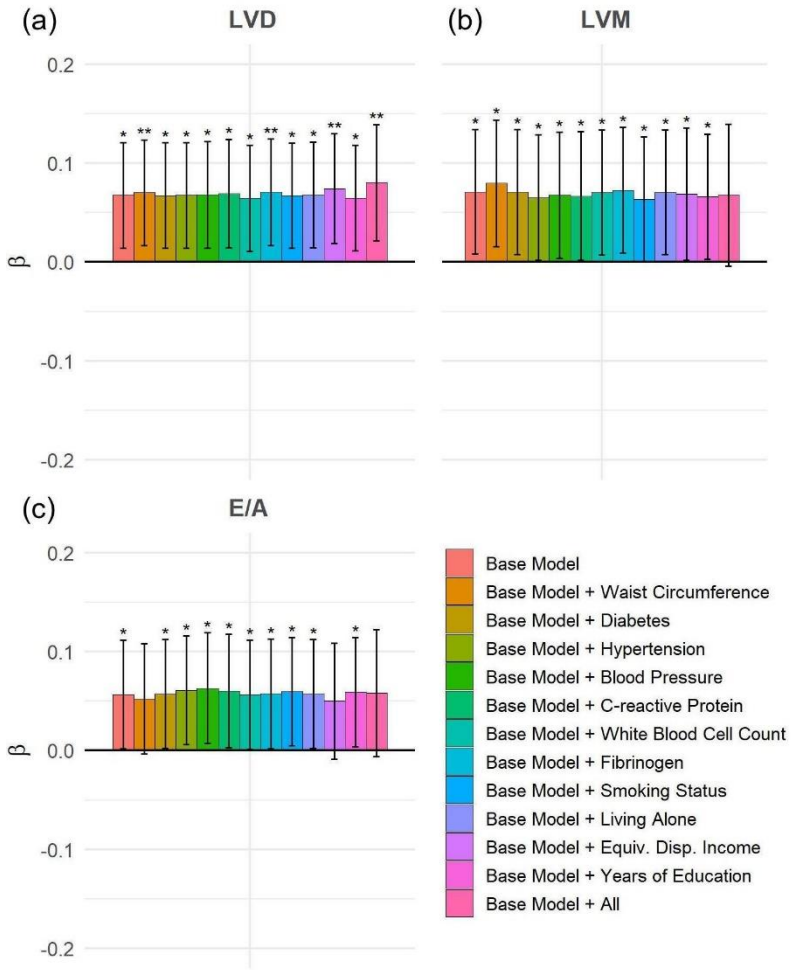
After regressing both outcomes on the control variables of the base model there were six and three cases, respectively, with unusually residual values (marked with red) which were excluded from the analyses. Solid lines represent the best fits by restricted cubic splines with five knots located at the 5%, 27.5%, 50%, 72.5%, and 95% quantiles.

Figure S3. Sensitivity analyses of associations of global cortical thickness with structural and functional echocardiographic parameters.



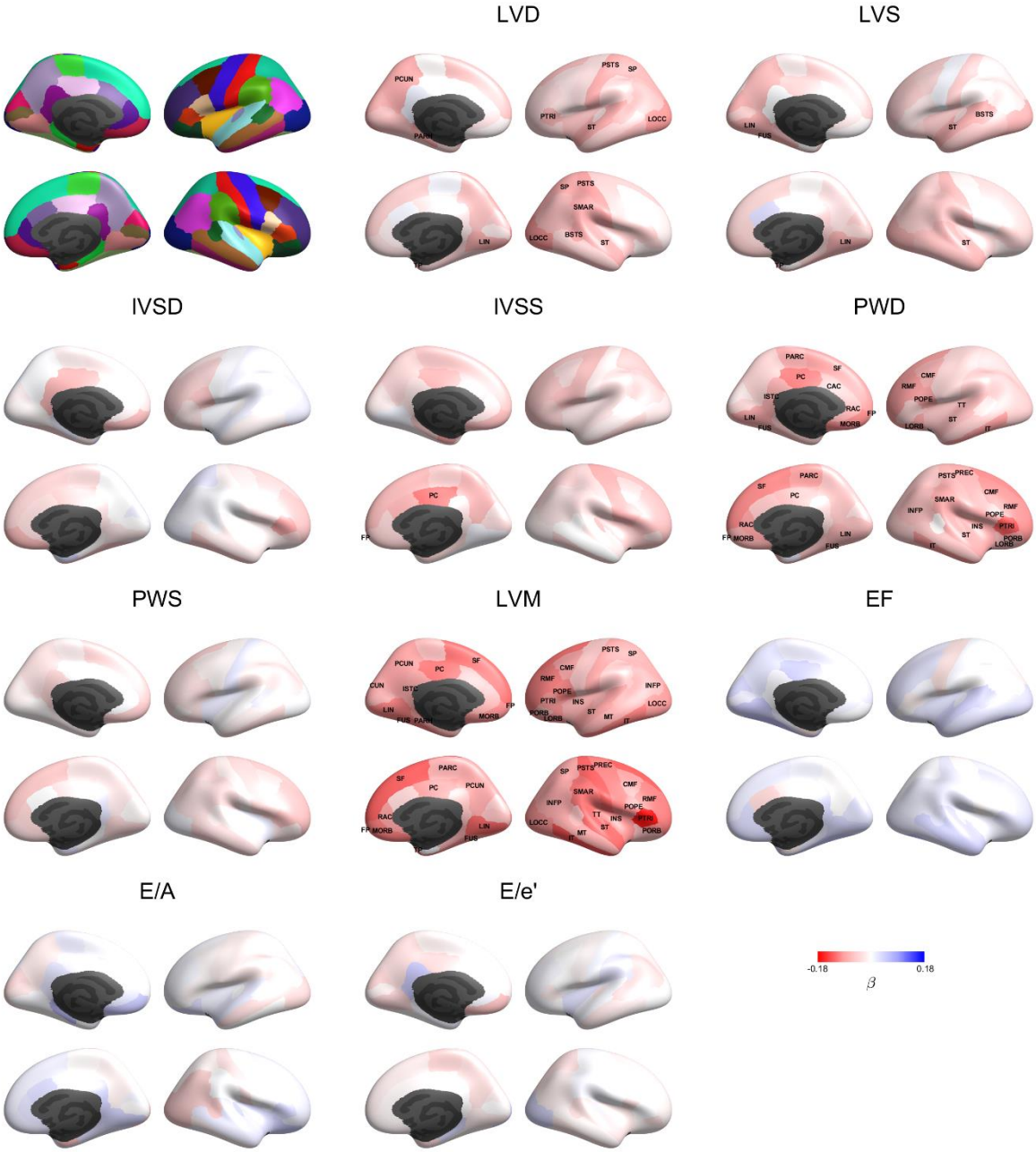
Regression coefficients of left ventricular diameter during diastole (LVD, A) and systole (LVS, B), interventricular septal thickness during systole (IVSS, C), posterior wall thickness during diastole (PWD, D) and left ventricular mass (LVM, E) did not change significantly when additionally controlling for waist circumference, diabetes, hypertension, systolic and diastolic blood pressure, C-reactive protein, white blood cell count, fibrinogen, smoking status, living alone, equivalised disposable income, or years of education both individually and all together (Z-tests, $|z|<0.94$). Continuous control variables were modelled with restricted cubic splines with 5 knots. Significance levels: * p<.05, ** p<.01, *** p<.001

Figure S4. Sensitivity analyses of associations of white matter hyperintensity volume with echocardiographic parameters.



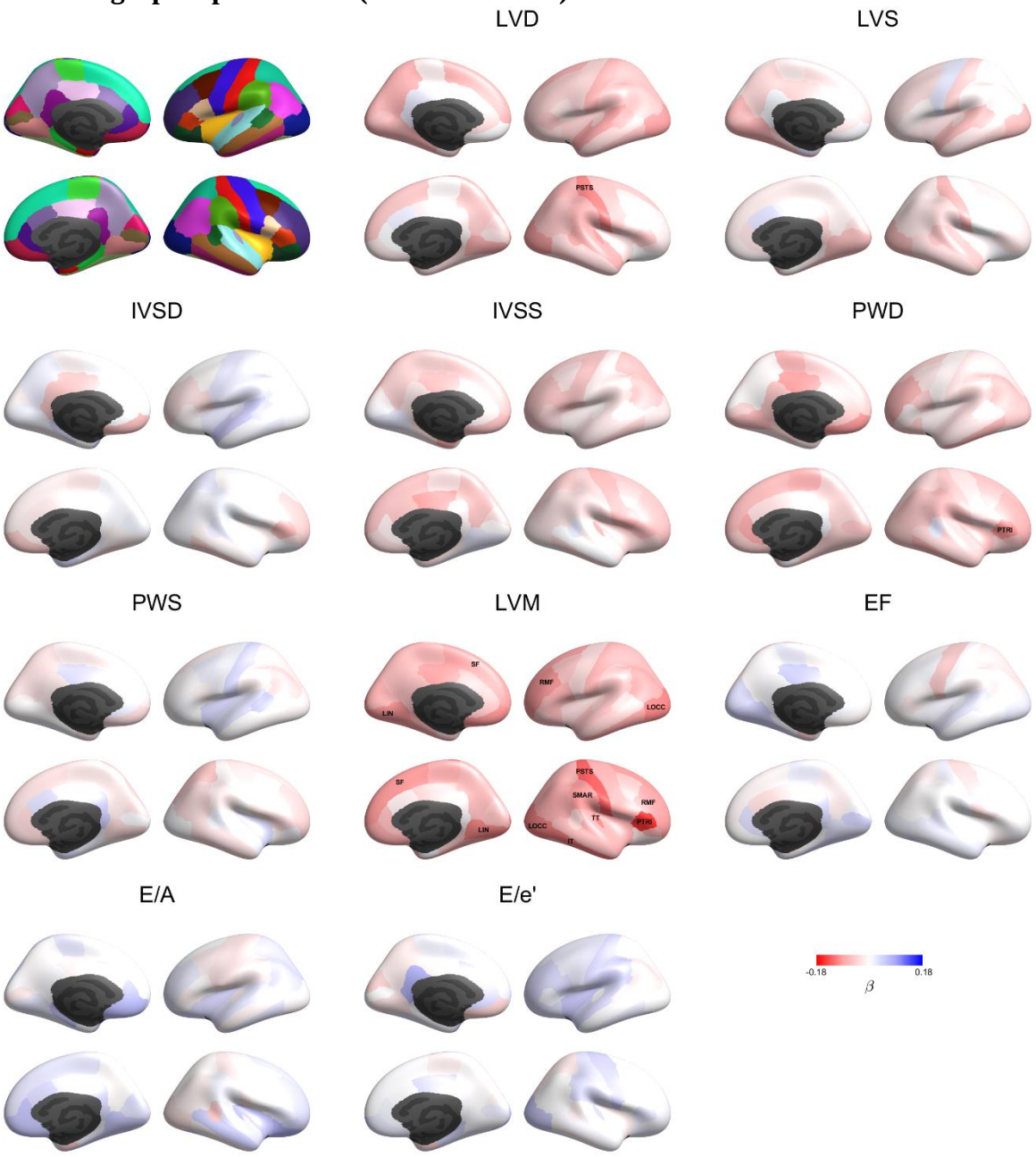
Regression coefficients of left ventricular diameter during diastole (LVD, a) left ventricular mass (LVM, b), and ratio of peak velocity blood flow in early diastole to peak velocity flow in late diastole (E/A, c) did not change significantly when additionally controlling for waist circumference, diabetes, hypertension, systolic and diastolic blood pressure, C-reactive protein, white blood cell count, fibrinogen, smoking status, living alone, equivalised disposable income, or years of education both individually and all together (Z-tests, $|z|<0.51$. Continuous control variables were modelled with restricted cubic splines with 5 knots. Significance levels: * p<.05, ** p<.01, *** p<.001

Figure S5. Associations of regional cortical thickness with structural and functional echocardiographic parameters (base model).



Analyses were adjusted for age, sex, body height, fat-free mass, total intracranial volume, and the interaction of sex with age. Labels are shown for those regions where associations remained significant after correction for multiple testing (Benjamini-Hochberg method, FDR ≤ 5%). For the abbreviations see Table S3.

Figure S6. Associations of regional cortical thickness with structural and functional echocardiographic parameters (extended model).



In addition to the control variables of the base model, analyses were adjusted for cardiovascular risk factors (waist circumference, diabetes, hypertension, systolic and diastolic blood pressure, smoking), inflammatory markers (white blood cell count, fibrinogen, and C-reactive protein), and socio-demographic variables (living alone, equivalised disposable income, and years of education). Labels are shown for those regions where associations remained significant after correction for multiple testing (Benjamini-Hochberg method, FDR ≤ 5%). For the abbreviations see Table S3.