Structural brain changes and all-cause mortality in the elderly population—the mediating role of inflammation

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Abstract While MRI brain changes have been related to mortality during ageing, the role of inflammation in this relationship remains poorly understood. Hence, this study aimed to investigate the impact of MRI changes on all-cause mortality and the mediating role of cytokines. All-cause mortality was evaluated in 268 community dwelling elderly (age 65–83 years) in the MEMO study (Memory and Morbidity in Augsburg elderly). MRI markers of brain atrophy and cerebral small vessel disease (SVD), C-reactive protein (CRP) and a panel of cytokines in serum were assessed. Cox proportional hazard models were used to estimate the association of MRI changes with survival over 9 years. Regression models were used to assess the hypothesis

that inflammation is mediating the relationship between MRI-brain changes and mortality. In total, 77 (29 %) deaths occurred during a mean follow up of 9 years. After adjusting for confounders, the degree of global cortical atrophy and the level of the cytokines CRP, TNF- α and IL-8 were of higher significance in study participants who had died at follow-up in comparison to survivors. In Cox proportional hazard models, higher degrees of global cortical atrophy (HR 1.56, $p = 0.003$) and regional atrophy of the temporal lobe (HR 1.38, $p = 0.011$) were associated with a significantly increased risk of mortality. Mediation analyses revealed a partial mediation by IL-6 and IL-8 of the effects of global cortical atrophy on mortality. Global cortical brain atrophy is a significant indicator of survival in the elderly. Our study supports a possible role for inflammation in the atrophy pathogenesis. If replicated in other samples, IL-6 and IL-8 level assessment may improve risk prognosis for mortality.

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Introduction

The identification of factors related to survival in age group 65 years and older is important in order to further improve primary prevention strategies. Small vessel disease (SVD) is an incidental but frequent finding on brain scans of elderly individuals (Vermeer et al. 2003; Pantoni 2010). SVD can be visualized on magnetic

resonance tomography (MRI) by the brain imaging markers white matter lesions (WML) and lacunar infarcts (LI). While brain MRI has become a frequently used diagnostic tool, also in population-based epidemiologic studies, only few studies have examined the impact of structural brain changes on survival in elderly populations (Briley et al. 2000; Bokura et al. 2006; Kuller et al. 2007; Ikram et al. 2009; Staff et al. 2010; Olesen et al. 2011; Conijn et al. 2011). In these studies, global vascular brain lesions and brain atrophy were associated with an increased risk of mortality in the elderly. The underlying mechanisms of these structural brain changes remain poorly understood, but blood-brain barrier damage (Wardlaw et al. 2003), endothelial dysfunction and inflammation have been discussed (Pantoni 2010).

Inflammation has already been identified as a key component in neurodegenerative (Amor et al. 2010) and cerebrovascular diseases (Sullivan et al. 2000; van Dijk et al. 2005; Mitaki et al. 2016). Some supporting studies on the potential correlation between inflammation and the all-cause death rate in elderly population samples have been conducted in recent years (Bruunsgaard and Pedersen 2003; Bruunsgaard et al. 2003; Störk et al. 2006). In particular, associations have been found between circulating inflammatory proteins like IL-6 and CRP and stroke and cardiovascular death (Störk et al. 2006). Little is known, however, about the relation of inflammation and small vessel disease of the brain. This raises the question if inflammation contributes to explaining the association between brain atrophy and shorter survival. The aims of our study were the following: (1) to investigate the predictive role of brain imaging markers on mortality in a population based cohort of the elderly in the course of a 9-year-follow-up period and (2) to investigate the mediating role of inflammation in the relationship between imaging markers and mortality.

Methods

Study participants

The MEMO study (Memory and Morbidity in Augsburg elderly) (Schmidt et al. 2004) is a follow-up project of the 1989/1090 World Health Organization (WHO) Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) survey Augsburg,

Germany (Keil et al. 1998). For the initial MONICA survey, a random sample aged 20–74 years of the population of Augsburg, a city in southern Germany, was drawn from the office of registration. Participants aged 65 years and older living in the city of Augsburg or two neighbouring suburbs were reinvented to participate in MEMO in 1997/98. The main aim of MEMO was to examine cognitive function and risk factors for neurodegenerative diseases in the elderly. The overall response rate among those legitimates was 60.6 % ($N = 635$) with a sample size of 385. The study was authorized by the Local Ethics Board of the University of Muenster. Participants gave written informed consent.

Clinical measures

Risk factors, medical histories and sociodemographic variables were asked in a face-to-face interview (Berger et al. 1996; Berger et al. 2000). Smoking was classified in current smoker, ex-smoker or never smoker. In addition, all participants received a standardized neurological examination (along with a neuropsychological test battery) as well as height, weight and blood pressure measurements. The evaluation of comorbidities was based on self-reports. Comorbidities were classified into two large groups. Bone related disorders included joint replacement, amputations of extremities and trauma of the backbone. “Cardiovascular disease” was defined as being diagnosed of a myocardial infarction or cardiac failure, diabetes or an apoplectic seizure, or of having had an operation of an arterial vessel in either legs, abdomen or carotids or an open heart surgery. Due to their frequency and functional consequences, it is important to consider these two groups in the elderly population.

Laboratory analyses

A non-fasting venous blood sample was taken from all participants between 08.00 and 11.00 A.M. For the following batch analysis, the serum was cooled down to a temperature of -80°C . Cytokine concentrations were quantified using cytometric bead array (CBA; BD Biosciences, San Diego, Calif; BD FACS Calibur) for the cytokines IL-1b, IL-6, IL-8, IL-10, IL-12p70 and TNF- α proteins following manufacturer’s instructions. Subsequent to the obtainment of sample data by usage of the flow cytometer, the findings were displayed in

tabular and graphical format utilizing the BD CBA Analysis Software. The intra-assay coefficients of variation were 4 to 7 % for IL-1b, 5 to 8 % for IL-6, 2 to 5 % for IL-8, 5 to 6 % for IL-10, 3 to 6 % for IL-12p70 and 6 to 10 % for TNF- α . The inter-assay coefficients of variation were 8 to 13 % for IL-1b, 8 to 10 % for IL-6, 4 to 7 % for IL-8, 8 to 11 % for IL-10, 6 to 9 % for IL-12p70 and 8 to 15 % for TNF- α . The IL-4sr enzyme-linked immunosorbent assay (ELISA) employs the quantitative sandwich enzyme immunoassay technique. The intra- and inter-assay coefficients of variation had a range from 2.6 to 4.4 % and 4.6 to 5.5 %, correspondingly.

MRI scans

All MRI scans were performed on a Philips 1.5 T scanner at the Department of Radiology, Central Hospital of Augsburg. Brain MRI's were carried out in all participants ($N = 268$, 69 %) without contraindications. MRI was not performed in 177 participants because of claustrophobia ($N = 16$), metal artefacts ($N = 69$), dissent ($N = 11$) or other reasons ($N = 21$). The MRI protocol consisted of T1- and T2-weighted images and proton density (PD) acquired with spin-echo sequences with 20 axial slices. The slice thickness was 5- or 6 mm with an interslice gap of 1 or 1.2 mm. The evaluation of the MRI images was performed by a single reader using an established rating scale (Scheltens et al. 1998; de Leeuw et al. 2001). The detailed account of the reading protocol is publicized elsewhere (Launer et al. 2000).

In this study, cortical atrophy was evaluated on a semi-quantitative score with categories (0–3) rated for each lobe and the sylvian fissure. A regional atrophy score of 0–1 was classified as low and a score of 2–3 as a high grade of atrophy. The calculated lobar ratings were subsequently added up to a comprehensive cortical score, ranging from 0 (no atrophy) to 15 (maximal atrophy). Ventricular enlargement was rated as the ratio of the biventricular width at the level of the occipital horns divided by the width of the brain at the same level.

The volume of subcortical WML was evaluated as a binary variable (one or more large (>10 mm) lesions) and as a continuous variable and subdivided into tertiles. The total volume of subcortical WML was assessed by multiplying each lesion by a size-dependent constant (0.0042 for small lesions, 0.114 for medium lesions and 0.95 for large lesions) and by subsequent summation of the results. Lacunar infarction on MRI was rated

as the presence of a hypointense (T1, PD) or hyperintense (T2) lesion of a cross-section dimension between 3 and 15 mm and categorized in a dichotomous variable (yes versus no). Of all participants with high global atrophy (upper quartile), 98 % also had a high atrophy in the frontal lobe (score 2–3); all (100 %) had regional high parietal atrophy, 94.9 % had high regional temporal fissure atrophy, 96.5 % had high regional occipital atrophy and all had high regional sylvian atrophy.

Follow-up of all-cause mortality

The vital status of all study participants and time of death were recorded prospectively until December 31, 2007. Death certificates were received from the local registration offices and encoded regarding the cause of death (ICD 9 Rev).

Statistical analysis

All inflammation and imaging markers were compared between survivors and non-survivors, using the Wilcoxon rank-sum test (non-normal distribution) and the Student t test for quantitative variables and the Pearson χ^2 test for categorical variables. Due to their skewed distributions, WML volume and inflammation markers were log-transformed for all analyses.

Cox proportional hazard models were used to estimate hazard rate ratios (HR) for all-cause mortality associated with the categorized imaging marker. We used two different modulations. Model 1 comprised of age, gender and smoking status. Model 2 comprised all variables of model 1 plus bone and vascular related disorders and global cortical atrophy as well as occipital ventricular enlargement, entered as continuous variables. Finally, we repeated the analyses in model 2 stratified by gender. The proportional hazard assumption was met for all corresponding analyses.

To test the hypothesis that the relation between imaging markers for SVD and atrophy and survival are mediated by inflammation processes, multiple linear regression analyses were applied according to Baron and Kenny (Baron and Kenny 1986). In particular, mediation was tested on the basis of three regression equations. In the first case, the dependent variable (DV) is regressed on the independent variable (IV); in the second case, the putative mediator (M) is regressed on IV and in the third case, the DV is regressed on both the IV and M. To establish mediation, the following criteria

Table 1 Baseline characteristics of MEMO study participants with brain MRI according to survival status

Characteristics (year 1998)	Death Yes (<i>N</i> = 77)	Survival No (<i>N</i> = 191)	<i>p</i> value
Age (mean, SD)	74.3 (4.6)	71.4 (4.1)	< 0.001 ^a
Gender (%)			0.008 ^b
Female	27 (35.1 %)	101 (52.9 %)	
Male	50 (64.9 %)	90 (47.1 %)	
Education (mean, SD)	8.9 (1.6)	9 (1.7)	0.622 ^a
Smoking status (%)			0.004 ^b
Smoker	14 (18.2 %)	12 (6.3 %)	
Ex-smoker	34 (44.2 %)	76 (39.8 %)	
Never smoker	29 (37.7 %)	103 (53.9 %)	
BMI (mean, SD)	27.7 (4)	27.9 (3.5)	0.682 ^a
Hypertension (%)			0.683 ^b
Yes	38 (49.4 %)	89 (46.6 %)	
No	39 (50.6 %)	102 (53.4 %)	
Stroke/TIA			0.022 ^b
Yes	11 (14.3 %)	11 (5.8 %)	
No	66 (85.7 %)	179 (94.2 %)	
Diabetes mellitus			0.249 ^b
Yes	9 (11.7 %)	14 (7.3 %)	
No	68 (88.3 %)	177 (92.7 %)	
Myocardial infarction			0.252 ^b
Yes	8 (10.4 %)	12 (6.3 %)	
No	69 (89.6 %)	178 (93.7 %)	
Any vascular morbidity			< 0.001 ^b
Yes	33 (42.9 %)	39 (20.2 %)	
No	44 (57.1 %)	152 (79.6 %)	
Any bone morbidity			0.192 ^b
Yes	12 (15.6 %)	19 (9.9 %)	
No	65 (84.4 %)	172 (90.1 %)	
Aggregation inhibitor use			0.647 ^b
Yes	26 (33.8 %)	59 (30.9 %)	
No	51 (66.2 %)	132 (69.1 %)	

^at-sample *t* test^bPearson χ^2

must be met: (1) in the first eq., IV must affect DV; (2) in the second eq., IV must effect M and (3) in the third eq., M must affect DV. If these conditions all hold in the predicted direction, then the effect of the independent variable on the dependent variable must be less in the third equation than in the second equation (Baron and Kenny 1986). Complete or perfect mediation was existent if the IV has not affected M, when M is controlled. Partial mediation emerges if the strength of the relation decreases between IV and DV when M is included in the model but is still greater than zero (Baron and Kenny 1986; Frazier et al. 2004). Separate analyses were carried out for the DV Death (yes/no) and for each putative mediator: CRP, TNF- α , IL-1b, IL-4 sr, IL-6, IL-8, IL-12

and TNF- α . The IV (global cortical atrophy) was inserted as a continuous variable in each analysis. To examine the significance of the mediation effects, in this case, the significance of the decrease of the strength of the IV-DV relation, a “z” score was calculated as follows:

$$ab/b^2 S_a^2 + a^2 S_b^2 + S_a^2 S_b^2$$

a and *b* are the non-standardized regression coefficient depicting the paths between IV and M and between M and DV, respectively, and *S_a* and *S_b* are their standard errors.

Table 2 Inflammation and imaging characteristics among participants stratified for survival status

MRI characteristics	Death Yes (N = 77)	Survival No (N = 191)	Crude <i>p</i> value ^b	Adjusted <i>p</i> value ^c
Ln_wmvol, mean	0.7	0.6	0.204	0.914
Large WM, yes	36 (46.8 %)	65 (34 %)	0.052	0.688
Frontal_WML, v (ln), median (IQR)	0.2 (1.04)	0.122 (0.36)	0.049	0.742
Parietal_WML, v (ln), median (IQR)	0.12 (1.09)	0.017 (1.06)	0.146	0.521
Temporal_WML, v (ln), median (IQR)	0 (0)	0 (0)	0.450	0.543
Occipital_WML, v (ln), median (IQR)	0.0042 (0.02)	0 (0.01)	0.389	0.954
WML (tertil)	Low 20 (39.2 %) High 13 (60.8 %)	69 (53.9 %) 59 (46.1 %)	0.076	0.882
Frontal_WML (tertil)	Low 20 (31.7 %) High 33 (62.3 %)	70 (55.1 %) 57 (44.9 %)	0.034	0.089
Parietal_WML (tertil)	Low 26 (47.3 %) High 29 (52.7 %)	74 (55.2 %) 60 (44.8 %)	0.320	0.554
Temporal_WML (tertil)	Low 51 (66.2 %) High 26 (33.8 %)	132 (69.1 %) 59 (30.9 %)	0.647	0.817
Occipital_WML (tertil)	Low 36 (46.8 %) High 22 (28.6 %)	103 (53.9 %) 50 (26.2 %)	0.473	0.852
Lacunar infarction (durch. 3–15 mm or more)	Yes 63 (81.8 %) No 14 (18.2 %)	164 (85.9 %) 27 (14.1 %)	0.405	0.891
Cortical atrophy, mean score ^a	9.7	8.2	< 0.001	0.010
Cortical atrophy (tertil)	Low 17 (22.1 %) High 29 (37.7 %)	73 (38.2 %) 29 (15.2 %)	< 0.001	0.026
Frontal atrophy (low = 0–1; high 2–3)	Low 17 (22.1 %) High 60 (77.9 %)	58 (30.4 %) 133 (69.6 %)	0.171	0.830
Parietal atrophy (low = 0–1; high 2–3)	Low 24 (31.2 %) High 53 (68.8 %)	78 (40.8 %) 113 (59.2 %)	0.140	0.693
Occipital atrophy (low = 0–1; high 2–3)	Low 23 (29.9 %) High 54 (70.1 %)	89 (46.6 %) 102 (53.4 %)	0.012	0.223
Sylvian fissure atrophy (low = 0–1; high 2–3)	Low 11 (14.3 %) High 66 (85.7 %)	61 (31.9 %) 130 (68.1 %)	0.03	0.058
Temporal fissure atrophy (low = 0–1; high 2–3)	Low 27 (35.1 %) High 50 (64.9 %)	99 (51.8 %) 92 (48.2 %)	0.03	0.068
Ventricular enlargement of the occipital horns, mean	0.48	0.46	< 0.001	0.018
Ln_CRP, mean	0.896	0.6035	0.062	0.123
Ln_TNF- α , mean	0.9456	0.7832	0.049	0.040
Ln_IL-1b, mean	1.65	1.2087	0.082	0.088
Ln_IL-4sr, mean	4.1868	1.1859	0.989	0.557
Ln_IL-6, mean	1.195	0.9989	0.021	0.166
Ln_IL-8, mean	2.3379	2.1796	0.001	0.022
Ln_IL-10, mean	0.7386	0.6257	0.214	0.309
Ln_IL-12, mean	1.1375	1.0037	0.150	0.148

^a Atrophy score with a scope from 15 (maximal atrophy) to 0 (no atrophy)^b Pearson χ^2 , t-test or Mann-Whitney test^c Separate logistic regression analyses for covariates age, gender, smoking

Table 3 Cox proportional hazard models for prediction of all-cause mortality among $N = 268$ subjects of the MEMO study

Atrophy parameters		Model 1	Model 2	Male ($N = 140$)	Female ($N = 128$)
		HR, p value	HR, p value	Model 2 HR, p value	Model 2 HR, p value
WML (tertil)	High/Low	0.988; 0.941	0.990; 0.951	1.336; 0.212	0.709; 0.163
Number of infarcts	No/Yes	1.171; 0.364	1.159; 0.413	1.276; 0.284	0.925; 0.797
Cortical atrophy (tertil)	High/Low	1.294; 0.158	1.306; 0.916	1.508; 0.094	0.993; 0.981
Cortical atrophy		1.057; 0.03	1.056; 0.03	1.086; 0.022	1.020; 0.571
Frontal atrophy (low = 0–1; high 2–3)	High/Low	1.124; 0.412	1.127; 0.404	1.116; 0.592	1.145; 0.500
Parietal atrophy (low = 0–1; high 2–3)	High/Low	1.180; 0.209	1.179; 0.212	1.250; 0.221	1.068; 0.738
Occipital atrophy (low = 0–1; high 2–3)	High/Low	1.06; 0.646	1.061; 0.642	1.356; 0.091	0.803; 0.238
Sylvian fissure atrophy (low = 0–1; high 2–3)	High/Low	1.211; 0.175	1.201; 0.200	1.471; 0.067	0.708; 0.117
Temporal fissure atrophy (low = 0–1 und high 2–3)	High/Low	1.379; 0.010	1.377; 0.011	1.325; 0.110	1.423; 0.054
Occipital ventricular enlargement		3.2; 0.452	3.041; 0.476	14.547; 0.234	0.495; 0.759

Model 1 age, gender and smoking

Model 2 Model 1 plus vascular and bone morbidity

¹ Numerator is the biventricular width in mm at the level of the occipital horns; denominator is the width of the brain at the level of the occipital horns

² Widening of the fissure indicating atrophy, scored as the average of the widening in the whole lobe (range 0–3)

Confidence intervals were calculated as $\pm 1.96S_{ab}$, where S_{ab} is the standard error of the mediated effect (Shrout and Bolger 2002). Inserted in all analyses were the following covariates: age, gender and smoking. Analyses were performed with SPSS version 22 software package (IBM Corporation, Armonk, NY).

Since we tested different atrophy and imaging markers, we additionally corrected for multiple testing. The Bonferroni correction sets the p value cut-off for significance to $p = 0.00625$ ($0.05:8 = 0.00625$).

Results

General sample characteristics stratified for survival status and gender

Table 1 summarizes the baseline characteristics of the study population. A total of $N = 268$ (70 %) participants had complete data on MRI. Nine years was the average follow-up time during this period. Among the participants, 77 (29 %) had died during the follow-up. Deaths were more frequent in men (64.9 %) as compared to women (35.1 %; $p = 0.008$). The age of the participants who are deceased during the follow-up period was of higher significance at baseline in comparison with the survivors (74.3 versus 71.4 years of age; $p < 0.0001$).

Participants with stroke and other vascular comorbidities as well as current smokers had a higher probability of dying than those without (Table 1). The proportion of current smokers was significant higher in male compared to females (11.4 versus 7.8 % ($p < 0.004$)). The remaining risk factors (myocardial infarction, stroke, diabetes mellitus, hypertension, vascular-and bone morbidity and aggregation inhibitor use) revealed no significant differences between men and women.

Imaging and inflammation characteristics stratified for survival status

We also stratified imaging and inflammation characteristics according for survival status (Table 2). In univariate analyses, we observed significantly worse brain imaging markers in subjects who had died at follow-up in comparison with survivors with higher global cortical- ($p < 0.001$) and regional atrophy (occipital-lobe ($p = 0.012$), sylvian- ($p = 0.03$) and temporal-fissure ($p = 0.03$), ventricular enlargement of the occipital horns ($p < 0.0001$) and frontal WML ($p = 0.034$). Also, the inflammation markers TNF- α ($p = 0.049$), IL-6 ($p = 0.021$) and IL-8 ($p = 0.001$) were significantly higher at baseline in participants who had died at follow-up. After adjustment for relevant confounders like age, gender and smoking, the atrophy markers global

cortical atrophy ($p = 0.010$) and ventricular enlargement of the occipital horns ($p = 0.018$) as well as the inflammation markers TNF- α ($p = 0.040$) and IL-8 ($p = 0.022$) were significantly lower in survivors compared to non-survivors (Table 2). The two imaging markers, WML volume and number of infarcts, indicators of small vessel disease did not differ between survivors and non-survivors ($p = 0.914$ and $p = 0.891$).

Cox proportional hazard models for prediction of all-cause mortality (stratified for gender)

We further investigated the effect of global and regional imaging markers on mortality (Table 3). Higher degrees of global cortical atrophy (HR 1.056; $p = 0.03$) and regional atrophy of the temporal lobe (HR 1.377; $p = 0.011$) were significantly associated with an increased risk of mortality across model 1 and 2. Additionally, we investigated effect modification of the imaging marker by gender. This analysis revealed that the significant effect of the global cortical atrophy originated in the male participants. No gender effects were noted for regional temporal atrophy.

Mediation analysis of imaging features on death by inflammation markers

The findings of the regression analyses are given in Table 4, and the findings of the corresponding tests of significance are resumed in Table 5. For the inflammation parameters IL-8 and IL-6, the conditions for partial mediation were met. For the dependent variable death, the strength of the association between the imaging marker global cortical atrophy and death decreased significantly, but still was larger than zero, in the case that IL-6 and IL-8 were included into the regression model. None of the putative mediators satisfied the conditions of complete mediation.

Discussion

In this population-based study of elderly people, we examined prospectively the association between MRI imaging markers and death rate and analysed the mediating role of inflammation over a follow-up period of 9 years. We found that global cortical brain atrophy is a powerful predictor of all-cause mortality and that it is partially mediated by the inflammation parameters IL-6

Table 4 Regression analyses testing mediation of the relation between imaging markers and death by inflammation markers

Equation	Dependent variable	Independent variable	Mediator	p value	Beta
1	Death (yes/no)	Atrophy		0.016	0.150
2	CRP	Atrophy		0.191	0.088
	TNF α	Atrophy		0.414	−0.055
	IL-1b	Atrophy		0.179	−0.091
	IL-4 sr	Atrophy		0.076	0.119
	IL-6	Atrophy		0.383	0.058
	IL-8	Atrophy		0.054	0.127
	IL-10	Atrophy		0.453	0.051
	IL-12	Atrophy		0.322	−0.67
3	Death (yes/no)	Atrophy	CRP	0.015	0.153
	Death (yes/no)	Atrophy	TNF- α	0.011	0.160
	Death (yes/no)	Atrophy	IL-1b	0.009	0.164
	Death (yes/no)	Atrophy	IL-4sr	0.012	0.159
	Death (yes/no)	Atrophy	IL-6	0.018	0.149
	Death (yes/no)	Atrophy	IL-8	0.030	0.137
	Death (yes/no)	Atrophy	IL-10	0.017	0.151
	Death (yes/no)	Atrophy	IL-12	0.011	0.159

Mediation is tested by means of three regression equations. (1) The dependent variable (DV) is regressed on the independent variable (IV), (2) the putative mediator (M) is regressed on IV and (3) the DV is regressed on both the IV and M. To establish mediation, 1) IV must affect DV in the first equation, 2) IV must effect M in the second equation and 3) M must affect DV in the third equation. Complete or perfect mediation is said to occur if the IV has no effect when M is controlled. Partial mediation occurs if the strength of the relation between IV and DV is reduced when M is included in the model but is nevertheless greater than zero.

and IL-8. However, these results would not withstand a stringent Bonferroni correction for multiple testing.

Among all MRI imaging markers examined, global cortical atrophy and temporal lobe atrophy as well as the inflammation markers TNF- α and IL-8 were significantly related to survival. These results are concordant to previous studies (Kuller et al. 2007; Baune et al. 2010; Olesen et al. 2011). Possible relationships between brain volume and survival have not been widely examined. However, there are a number of reasons why brain atrophy may have a negative impact on survival. First, brain atrophy is connected to various life style factors,

Table 5 Summary of the results of significance tests for the mediation of the relation between imaging markers and death by inflammation

Dependent variable	Independent variable	Mediator	a	S _a	b	S _b	a ²	Sa ²	b ²	sb ²	z ⁱ
Death (yes/no)	Atrophy	CRP	0.035	0.027	0.026	0.011	0.001225	0.000729	0.026	0.000121	47.41
Death (yes/no)	Atrophy	TNF- α	-0.013	0.015	0.027	0.011	-0.000169	0.000225	0.000729	0.000121	-2055.02
Death (yes/no)	Atrophy	IL-1b	-0.064	0.048	0.028	0.011	-0.004096	0.002304	0.000784	0.000121	-1127.39
Death (yes/no)	Atrophy	IL-4sr	0.021	0.012	0.027	0.011	0.000441	0.000144	0.000729	0.000121	143.23
Death (yes/no)	Atrophy	IL-6	0.014	0.016	0.025	0.011	0.000196	0.000256	0.000625	0.000121	1630.24
Death (yes/no)	Atrophy	IL-8	0.019	0.010	0.023	0.011	0.000361	0.0001	0.000529	0.000121	4020.94
Death (yes/no)	Atrophy	IL-10	0.011	0.015	0.026	0.011	0.000121	0.000225	0.000676	0.000121	1474.49
Death (yes/no)	Atrophy	IL-12	-0.017	0.017	0.027	0.011	-0.000289	0.000289	0.000729	0.000121	-2178.65

A and b are the unstandardized regression coefficients representing the paths between the independent variable (IV) and mediator (M), and between M and the dependent variable (DV), respectively; sa and sb are their standard errors, and $z = ab/b^2 Sa^2 + a^2 Sb^2 + Sa^2 Sb^2$. A “z” score of ≥ 2.54 is significant at the 0.01 level for a two-tail test. To establish mediation, 1) IV must affect DV in the first equation, 2) IV must effect M in the second equation and 3) M must affect DV in the third equation. Complete or perfect mediation is said to occur if the IV has no effect when M is controlled. Partial mediation occurs if the strength of the relation between IV and DV is reduced when M is included in the model but is nevertheless greater than zero

such as overweight and glucose disorders (Ward et al. 2005; Samaras et al. 2014), poor sleep quality (Sexton et al. 2014) and hypertension (Swan et al. 1998; Jochemsen et al. 2013). This might originate in the evolutionary role of the brain as a modulator of longevity, influencing body temperature, nutrient homeostasis, appetite and blood pressure (Cefalu and Wagner 1997; Tabarean et al. 2010; Blom et al. 2013). Consequently, brain atrophy may be a biomarker of poor health.

A major finding of the study is the mediating role of the cytokines IL-6 and IL-8 in the relation between global cortical atrophy and death. These associations were independent of age, gender and smoking. For this analysis, we assumed that the brain atrophy precedes the systemic inflammation. Our data are concordant with results from recent studies (Jefferson et al. 2007; Baune et al. 2009; Willette et al. 2013). Our approach suggests that an inflammatory state may be related to brain atrophy in the elderly, although its pathophysiology is largely unexplored. In general, the proposed pathogenesis of brain atrophy in combination with cytokines as mediators of inflammation is supported by shortly published studies in animals (Melton et al. 2003; Mraovitch 2003). Potential underlying mechanisms are behind the conjunction of chemokine-cytokine factors and atrophy include endothelial inflammation (Hassan et al. 2003). Markers of endothelial inflammation as IL-6 provoke vasoconstriction and interfere with endothelium-dependent vasodilatation predisposing to thrombosis, vessel spasm, and intensifying the link between

inflammation and vascular disease (Vila and Salaices 2005). In addition, inflammation of the brain may play an important role in many neurodegenerative disorders, for example, in Alzheimer’s disease (Hausse-Wegrzyniak et al. 2000) and cognitive performance in the elderly (Trollor et al. 2011). Further research is required to ensure the validity of our findings and to determine whether both inflammation markers serve as prognostic markers of therapeutic targets to combat cerebral small vessel disease.

The MEMO study has strengths and limitations. Strengths include the large range of assessed MRI parameters, the population basis of the study and the long-term follow-up period of 9 years. Limitations include the fact that MRI was performed only once and that only the vital status could be assessed at follow-up. There is need for longitudinal studies to investigate the impact of brain atrophy changes over time and the association with mortality. Second, we implemented only visual, semi-automated (Davidson et al. 2005) MRI scorings. However, the evaluation of the MRI scans was performed by a single reader using an established rating scale (Scheltens et al. 1998; de Leeuw et al. 2001). Finally, we examined a sample of the southern German population. Our results might therefore not be generalizable to other geographic areas. Furthermore, our results presented here point towards the larger context of biological ageing, loss of adaptive immunity and increase in innate immunity. Finally, the presented significant results would not withstand a stringent

Bonferroni correction for multiple testing; however, this may be a reflection of the relatively small sample size with insufficient statistical power used here. Hence, the presented interesting explorative results require replication in larger independent samples.

In summary, brain atrophy is a significant indicator of subsequent lower survival in the elderly. Our study supports a possible role for inflammation in the pathogenesis of brain atrophy. If validated in other samples IL-6 and IL-8 may improve risk prognostication and point to novel therapeutic targets to combat brain atrophy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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