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Inflammatory markers and imaging patterns of advanced brain aging in the general population

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Abstract

Inflammaging describes the complexity between low-grade chronic inflammation with the pathogenesis of brain aging and Alzheime's disease (AD). We aimed to find associations of inflammatory markers: i) white blood cell count (WBC), ii) high-sensitivity C-reactive protein (hs-CRP), and iii) fibrinogen with brain structures, sensitive neuroimaging markers of advanced brain aging and AD-like atrophy, and cognitive aging scores. We analyzed magnetic resonance

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Compliance with Ethical Standards

Ethical approval The Ethics Committee of the Medical Faculty of the University of Greifswald approved SHIP. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest All authors declare that they have no conflict of interest.

imaging (MRI) scans of 2204 participants from the Study of Health in Pomerania-2 (SHIP-2) and SHIP-Trend (55.6% women, mean age 52.4±13.7 years). Associations of the inflammatory markers with specific brain signatures of brain aging (SPARE-BA), AD-like brain atrophy (SPARE-AD) and white matter disease (white matter hyperintensities volume (WMHV)) were investigated. Furthermore we explored their association with general brain structures including total brain volume (TBV), gray matter volume (GMV), and white matter volume (WMV), as well as cognitive scores (Nurnberger Age Inventory (NAI); Verbal Learning and Memory Test (VLMT). We adjusted for multiple vascular risk factors (VRF; e.g. smoking and blood pressure) and corresponding medication use to take their brain aging effects into account and corrected for false-discovery rate (FDR). Results:WBC was inversely associated with SPARE-BA (FDR-adjusted p=0.003), TBV (FDR-adjusted p=0.019) and GMV (FDR-adjusted p= 0.017). GMV was also inversely associated with hs-CRP (FDR-adjusted p=0.039) and fibrinogen (FDR-adjusted p=0.039). None of the inflammatory markers was associated with WMHV. Regression analysis also revealed a trend-level interaction between intake of antiinflammatory medication and hs-CRP with brain aging (SPARE-BA; FDR-adjusted p=0.062). Inflammatatory markers are associated with neuroimaging markers, with elevated WBC leading to significant acceleration in brain aging patterns but not with AD-like imaging structural changes. Given the overlap between accelerated brain aging and AD-like atrophy, increased WBC might be associated with global dementia symptoms due to this overlap in atrophy patterns. Elevated WBC may be not causal to preclinical AD dementia, but an accessory symptom of inflammaging. At population level, our results support the relevant roles of inflammatory markers on brain aging related atrophy.

Keywords

Alzheimers; Epidemiology; Inflammation; Neuroimaging; hs-C-reactive protein

Introduction

Inflammaging describes the link between systemic low-grade chronic inflammation and (brain) aging processes (Franceschi et al. 2007). Several mechanisms have been suggested to explain how inflammation leads to accelerated brain aging and neurodegenerative disorders including Alzheimer's disease (AD): tissue damage, degeneration and gliosis (Franceschi and Campisi 2014) or impaired neural plasticity with immune response following Aβ deposition with dense accumulation of microglia (Wyss-Coray and Rogers 2012). In the absence of an effective drug for dementia and in the ongoing efforts for dementia drug development, it is of importance to account for the fact that low-grade chronic inflammation could be a contributor to the aging brain and AD.

Findings relating inflammatory markers and brain structures remain scarce or have been reported only in elderly subjects exploring limited neuroimaging markers such as total brain volume (TBV) (Jefferson et al. 2007). However, the associations of sensitive central neuroimaging markers, with inflammatory markers in the periphery such as white blood cell count (WBC), remain unexplored. In this study, we capitalized on a large sample from the general population (n=2204) including a wide age range (21–89 years, mean age 52.4±13.7 years) and considered three inflammatory markers. We first considered

WBC, a clinical routine, highly standardized analyte with low costs and high precision which predicts all-cause-mortality (Nilsson et al. 2014). WBC can be considered as a proxy marker for chronic inflammation and was reported to be elevated in subjects with AD (Shad et al. 2013) or change in cognitive performance (Warren et al. 2018). The second marker of our interest was high-sensitivity C-reactive protein (hs-CRP). This is an acute-phase protein which is elevated in any form of inflammatory condition and known to be associated with dementia, AD (Engelhart et al. 2004; Koyama et al. 2013; Ng et al. 2018) and impaired cognitive performance in longitudinal observations (Beydoun et al. 2018). The third marker we included in our study was fibrinogen, a second acute-phase protein which has been associated with cognitive decline (Xu et al. 2008), and dementia (Darweesh et al. 2018; van Oijen et al. 2005). Aβ interacts with fibrinogen and aggregates in brain parenchyma and cerebral blood vessels (Cortes-Canteli et al. 2012). Recent studies supposed that inflammatory markers in the plasma are increased years before the clinical syndrome of dementia appears (Darweesh et al. 2018; Engelhart et al. 2004; Schmidt et al. 2002). Results from epidemiological studies demonstrated that individuals treated with nonsteroidal antiinflammatory drugs for rheumatoid arthritis or heart disease had a reduced risk of developing AD, while clinical trials showed heterogeneous effects (for review see (Wyss-Coray and Rogers 2012)).

To our knowledge the relations of systemic inflammatory markers with neuroimaging measures, including advanced brain aging and AD-like degeneration patterns, have not been examined systematically in the general population. We hypothesized that elevated WBC, hs-CRP and fibrinogen are associated with advanced brain aging and AD imaging patterns in subjects without overt cognitive impairment. To investigate this hypothesis, we modelled structural magnetic resonance imaging (MRI) brain changes in a large population-based study using previously developed sensitive pattern-based indices of brain aging (Spatial Pattern of Atrophy for Recognition of brain aging (SPARE-BA) and Spatial Pattern of Atrophy for Recognition of Alzheime's disease summary indices (SPARE-AD) (Habes et al. 2018a; Habes et al. 2016a; Habes et al. 2016b). To investigate if inflammatory markers are also associated with cognitive functioning, we included cognitive scores as outcome measures (Beydoun et al. 2018; Warren et al. 2018). Moreover, we considered the intake of antiinflammatory medication in our analyses.

Methods

Participants from SHIP

The Study of Health in Pomerania (SHIP) is a prospective cohort from the general population living in West Pomerania in northeast Germany. The Institute for Community Medicine at the University Medicine Greifswald founded the SHIP study, which started with the baseline examination SHIP-0 between 1997 and 2001 (John et al. 2001). All participants were re-invited for a follow-up visit (SHIP-1) after five years. From 2008 to 2012 the second follow-up examination (SHIP-2) was carried out. A second population-based cohort (SHIP-Trend) from the same area was started in parallel with SHIP-2, with a similar examination protocol.

SHIP-2 and SHIP-Trend included whole-body MRI scans of 3066 subjects aged 21–89 years who underwent T1-weighted and Fluid-attenuated inversion recovery brain scans. Among these subjects, we excluded 862 individuals based upon: 1) presence of stroke, multiple sclerosis, epilepsy, cerebral tumor, intracranial cyst or hydrocephalus at baseline (n=150), 2) significant motion artifacts (n=98), 3) failed quality control of the automatically skull-stripped data (n=121) or the automated white matter hyperintensities segmentation (n=154), or 4) lack of clinical data (cognitive scores n=176, or covariates; n=163). The study follows the recommendations of the Declaration of Helsinki. The Ethics Committee of the Medical Faculty of the University of Greifswald has approved SHIP. All participants provided an informed consent in written form.

The SHIP personnel collected clinical data, including socio-demographic factors and medical history, in a standardized computer-assisted face-to-face interview. Smoking has been included as a categorical variable encoded as: none, previous smoker or current smoker. Clinical data for the current study has been described in more detail elsewhere (Habes et al. 2016a; Volzke et al. 2011). We included in our analysis the following vascular risk factors (VRF) for covariate adjustment: i) BMI (Body mass index; kg/m^2), ii) smoking, iii) blood pressure, iv) use of antihypertensive drugs, v) antidiabetic drug use, vi) hemoglobin A1c (HbA1c), vii) lipid lowering drug use, viii) total cholesterol, ix) low-density lipoprotein (LDL)-cholesterol, x) high-density lipoprotein (HDL) - cholesterol, xi) cholesterol ratio=HDL/LDL, xii) as well as educational background. Our sample from the general population consisted of two sub-cohorts SHIP-Trend and SHIP-2, with similar study protocols. However, as SHIP-Trend was observed at baseline and SHIP-2 at the second follow-up, mean age of SHIP-2 is higher. Differences in metabolic factors as hypertension, antihypertensive medication, lipid lowering drug use, and HbA1c between SHIP-2 and SHIP-Trend are primarily explained by the differences in mean age between the two cohorts.

Intake of medication was recorded and classified using the anatomical therapeutic chemical classification system (ATC (ATC-Index 2007)). All subjects that reported intake of the following substances (ATC: B01AC06*, B01AC08*, B01AC15*, B01AC34*, B01AC36*, B01AC56*, C01EB03*, C01EB16*, C10BX01*, C10BX02*, C10BX04*, C10BX05*, M01*, N02BA*, N02BB*, N02BG*) were indicated to be taking antiinflammatory drugs. Antidiabetics were defined as intake of ATC-code A10*, antihypertensives as intake of ATC-Code C02*, C03*, C07*, C08* and C09*and lipid lowering drugs as intake of C10*. Finally, we included the cognitive scores obtained in SHIP: the Verbal Learning and Memory Test (VLMT, the German version of the Rey auditory-verbal learning test (Bean 2011) for SHIP-2 conducted without list of interference (n=772) and the Nurnberg Age Inventory (NAI) for SHIP-Trend (n=1747). NAI is a German test developed to measure the cognitive abilities during brain aging (Fleischmann 1990). It consists of subtests including verbal learning and memory tests.

Laboratory Measurements

In SHIP-2 and SHIP-Trend, blood samples were taken from the cubital vein of participants in the supine position. WBC was determined in EDTA whole blood samples using the Sysmex XT 2000, XE 5000 or SE 9000 analyzers (Sysmex, Kobe, Japan) or the Advia

2120i (Siemens Healthcare Diagnostics, Eschborn, Germany). Hs-CRP concentrations were determined in serum by nephelometry on the Dimension VISTA (Siemens Healthcare Diagnostics, Eschborn, Germany). Fibrinogen concentrations were determined in citrate plasma according to Clauss using the BCS or the BCS XP system (Siemens Healthcare Diagnostics, Eschborn, Germany).

Image acquisition

In SHIP-2 and SHIP-Trend, a broad whole body MRI protocol has been included. The neurocranium unit of SHIP included a T1-weighted and Fluid-attenuated inversion recovery (FLAIR) sequence. MR scans were obtained using a 1.5 Tesla Siemens MRI machine (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany). For measuring regional patterns of aging and AD-related brain atrophy, we used the T1-weighted axial MPRAGE images. The T1-weighted images were acquired with the following parameters: 1×1 mm in-plane spatial resolution, slice thickness=1.0 mm (flip angle 15°), 3.4 ms echo-time and 1900 ms repetition-time. Axial T2-FLAIR sequence had following parameters: 0.9 × 0.9 mm in-plane spatial resolution; 3.0 mm slice thickness (flip-angle 15°); 325 ms echo-time; 5000 ms repetition-time.

Image processing

An automated skull stripping algorithm has been applied on the T1-weighted images. Each brain mask was visually inspected for quality, by M. H., and all masks rated with low quality brain mask (including an either under- or oversegmented brain) were excluded. A multi-atlas label fusion based segmentation method was applied for segmentation of the brain into a set of anatomical regions of interest in SHIP as described recently (Habes et al. 2016c). In our study, we included an estimate of total brain volume (TBV), total gray matter volume (GMV), total white matter volume (WMV) and total white matter hyperintensities volume (WMHV).

MRI Pattern Classification

We calculated two previously developed indices for SHIP participants: 1) (SPARE-AD), an index summarizing the high dimensional imaging data with a single value that quantifies the atrophy patterns in AD-related regions. SPARE-AD has been shown to discriminate between normal cognition and mild cognitive impairment and with conversion from mild cognitive impairment to AD (Da et al. 2014). More positive SPARE-AD implies the presence of more AD-like brain atrophy, while more negative values reflect more normal-like brain structure. 2) The SPARE-BA index was designed to summarize age related brain changes from the MR scan in a single score (Habes et al. 2016c). The SPARE-BA index for an individual implied less brain aging patterns for higher (positive) values and the presence of more aging related atrophy patterns for lower (negative) values. The SPARE-BA scores were derived using cross-validation (jack knifing), approaching preponderant independent generalization. While the SPARE-AD index captured more localized atrophy patterns in AD related regions, such as in the hippocampus and anterior temporal pole, the SPARE-BA index captured more aging specific patterns, including insular cortex, thalamus and cingulate cortex in addition to frontal, inferior parietal and lateral temporal cortex.

Statistical Analysis

WBC, hs-CRP, and fibrinogen were log transformed and WMHV was cube root transformed to achieve normal distribution. Analyses were performed using R software v3.3. First, we applied linear regression models, to analyse associations between SPARE-BA, SPARE-AD and WMHV (as outcomes) with WBC, hs-CRP, fibrinogen and antiinflammatory medication as predictors in separate models adjusting for age, age^2, sex, and study cohort effects. Second, we applied linear regression models to global measures of TBV, GMV and WMV as outcomes and WBC, hs-CRP, fibrinogen and antiinflammatory medication as predictors in separate models adjusting for age, age^2, sex, and study cohort effects.

In a following step we adjusted both analyses for additional demographic and VRF, including the following covariates: BMI, smoking, systolic blood pressure, use of antihypertensive drugs, use of antidiabetic drugs, HbA1c, cholesterol ratio, use of lipid lowering drugs and educational background. Finally, we investigated the significance of interaction terms between antiinflammatory medication and the inflammatory markers (WBC, hs-CRP and fibrinogen). This took place after separately including those interaction terms to the regression models as predictors for all structures with significant associations from the first analysis. Results were considered statistically significant if the false discovery rate (FDR) adjusted p-value was <0.05. Effect sizes were represented as R^2 (small effect sizes were considered as a rule of thumb 0.2; medium effect sizes as 0.13; strong effect sizes as 0.26).

We used Pearson's correlation coefficients to assess correlations between variables. We used Student's t-test to compare continuous variables and Pearson's chi squared test to compare categorical variables between SHIP-2 and SHIP-Trend.

Results

Table 1 summarizes characteristics of the study population. A total of 2204 participants (n=661 from SHIP-2 and n=1543 from SHIP-Trend), with a mean age of 52.4 years (SD=13.7 years), were included in the analyses. Cohorts differed in age ($p<0.0001$), education ($p=0.002$), smoking ($p=0.018$), systolic blood pressure ($p<0.0001$), antihypertensive drug use ($p=0.008$), lipid lowering drug use ($p<0.0001$), and HbA1c ($p=0.001$). These differences were taken into account in our further analyses. Cohorts differed as well in SPARE-BA ($p=0.001$). Pearson's correlation coefficients describing the relation between the various imaging markers and between the inflammatory markers are given in supplemantary tables 1 and 2 respectively.

Using linear regression models adjusted for VRF, we investigated the associations between inflammatory and imaging signatures of brain aging, AD and white matter disease (WMHV). We observed inverse associations between WBC with SPARE-BA (FDR-adjusted $p<0.001$) in the linear regression models (Table 2 with strong effect size (R^2:0.684–0.704). There was no association between WBC, hs-CRP, fibrinogen, and total WMHV or SPARE-AD. Antiinflammatory medication was not associated with any of the previous signatures.

Then we looked at the associations of the inflammatory markers with global measures of TBV, GMV and WMV. TBV was inversely associated with WBC (FDR-adjusted p=0.019). GMV was inversely associated with WBC (FDR-adjusted p=0.017), hsCRP (FDR-adjusted p=0.039) and fibrinogen (FDR-adjusted p=0.039). Antiinflammatory medication was not associated with any global MRI measure (Table 3).

In analyses without adjusting for VFR, we saw similar associations and additional associations between SPARE-BA and hs-CRP (fdr-adjusted p=0.016) (supplementary table 3). Furthermore, TBV was associated with fibrinogen (fdr-adjusted p=0.026) (supplementary table 4). There was no association between the inflammatory markers and the cognitive scores (supplementary table 5). Including interaction terms between antiinflammatory medication and the inflammatory markers in the linear regression models revealed only a trend-level interaction between intake of antiinflammatory medication and hs-CRP with brain aging (SPARE-BA; FDR-adjusted p=0.062) (supplementary tables 6 and 7).

Discussion

Capitalizing on a large epidemiological sample (n=2204) and highly sensitive neuroimaging markers, we demonstrated associations of inflammatory markers: i) WBC, ii) hs-CRP, and iii) fibrinogen with general brain structural changes and WBC were associated with advanced brain aging.

Association of WBC with brain imaging patterns

We have shown earlier that advanced brain aging is associated with vascular risk factors (Habes et al. 2016a, b, c). As VRF (in particular smoking) are prevalent in SHIP, and given the correlation between vascular disease and inflammatory markers, it could be assumed that VRF are on the causal pathway between inflammatory markers and brain aging. In comprehensive modeling to understand this relationship, we decided to investigate this association adjusting for VRF. After all adjustments made for age, sex and VRF we can see an association between higher WBC and advanced brain aging captured by SPARE-BA.

The pathomechanism that links elevated WBC to increased brain aging is not well understood. Elevated WBC could be involved directly in the pathogenesis of vascular diseases with inflammation or be an indicator of other factors causing vascular or neurodegenerative damage. WBC tends to cluster with VRF, such as smoking (Smith et al. 2003), diabetes (Gkrania-Klotsas et al. 2010), low HDL-cholesterol and high triglyceride concentrations (Nilsson et al. 2007; Nilsson et al. 2013). Interestingly, the association was not altered after adjustment for these risk factors, which is suggestive of additional independent mechanisms involved. Given the overlap between advanced brain aging and AD-like atrophy (Habes et al. 2016a, b, c), increased WBC might be associated with dementia symptoms due to this virtue overlap in atrophy patterns. Elevated WBC may be then not causal to preclinical AD dementia, but an accessory symptom.

However, we have to discuss this conjunction carefully, because WBC is not specific to monocytes. Furthermore, these associations do not give information on the innate or adaptive immune system. Room for discussion is left considering the associations we

discovered: if we would have observed effects between WMV or WMHV with WBC, it would be more likely for this measure of peripheral inflammation to inform on central inflammation.

Association of hs-CRP with brain imaging patterns

GMV was associated with increased hs-CRP. These results are in line with data from elderly participants showing associations between CRP with global markers of brain atrophy or all-cause dementia (Darweesh et al. 2018; Satizabal et al. 2012). Interestingly, Hsuchou et al. found that CRP itself increases the brain blood barrier permeability (Hsuchou et al. 2012).

Above this, there was no association between hs-CRP and SPARE-AD in our data, which confirms previous results obtained in AD patients (Swardfager et al. 2010). Ryu et al. only found a conjoint effect of CRP and serum alkaline phosphatase with WMHV as a marker for small vessel disease (Ryu et al. 2014).

Association of fibrinogen with brain imaging patterns

Fibrinogen was inversely associated with GMV. This change seems to be unspecific for aging or AD related brain changes, as there were no associations with the SPARE indices. Our results are thus in line with a recent meta-analysis from Darweesh et al. (Darweesh et al. 2018), who report associations between fibrinogen and increased risk of all-cause dementia, but not specific for AD (Darweesh et al. 2018).

Association of inflammatory markers with cognitive scores

Inflammatory markers were not associated with NAI or VLMT. The NAI was performed only in SHIP-Trend, the larger sample, while the VLMT was performed only in SHIP-2. The lower statistical power due to the different testing may explain the lack of associations observed with the two cognitive scores.

Effects of antiinflammatory medication

In previous studies, antiinflammatory medication was shown to have neuroprotective effects with antigliotic properties based e.g. on their COX-inhibition or inhibitory effects on nitrogen oxide synthesis (for review see (Asanuma et al. 2004; Marchetti and Abbracchio 2005; Zhang et al. 2018)). Our data does not support this hypothesis. There was no association between antiinflammatory medication and TBV, GMV, WM, SPARE-BA, SPARE-AD or cognitive scores. This may be due to low dosage or low frequency of antiinflammatory medication intake in our generally healthy population. Data on the duration of medication intake was not recorded. However, comparable to our results, Jefferson et al. also found no changes in TBV with antiinflammatory medication intake in a sample from the general population (Jefferson et al. 2007).

Interaction between intake of antiinflammatory medication and inflammatory markers on the association with brain aging

We found an interesting trend interaction term between antiinflammatory medication and hs-CRP with less brain aging. Antiinflammatory medication is often considered

to be neuroprotective as described above (Ajmone-Cat et al. 2010). Our data suggest that inflammatory processes underlying increased aging may be more complex, since antiinflammatory agents attenuate increased aging only when hs-CRP is elevated. Antiinflammatory medication may be only effective, if there is a response in hs-CRP during an inflammation activity. Little is known about interactions between antiinflammatory drugs, CRP, and brain aging. In rheumatoid arthritis, selective and nonselective antiinflammatory drugs had different associations with CRP (Tarp et al. 2012). Yet, we could not differentiate between antiinflammatory drugs in our study.

Our data did not show association between the inflammatory markers included in this study and WMHV. It has been documented in the literature that WMHV are heterogeneous (Habes et al. 2018b). Genome-wide association studies showed that WMHV were associated with genes related to vascular disease, neurodgeneterative disorders and inflammatory disease (Verhaaren et al. 2015). Habes et al. showed that age and VRF explained most of the variance of WMHV (Habes et al. 2016a, b, c), the current analysis however could not show an association with inflammatory markers. Possible explanation could be the relative low specificity of the included inflammatory markers. Cytokines may be more specific for further studies. Addtionally, serum peripheral markers might be limited in capturing effectes in the central nervous system. Discrepancy between inflammatory markers in periphery and central nervous system may be due to tissue reactions, vasodilatation, increased permeability, changes in blood flow and actions of various inflammatory mediators. We would recommend including cerebrospinal fluid or brain tissue in further studies.

Results without adustment for vascular risk factors (VRF)

In the supplementary analyses -without adjustment for VRF-two further associations emerged. First we saw an association between SPARE-BA with hs-CRP (p=0.016) and second we saw an association between TBV and fibrinogen (p=0.026) (supplementary table 4). The association of SPARE-BA and hc-CRP is in line with findings from Satizabal et al. (Satizabal et al. 2012). These differences may result from the high impact of the VRF on the neuroinflammaging on SPARE-BA and on global brain structures like TBV. Ebrahimi found that CRP was directly influenced by metabolic risk factors (Ebrahimi et al. 2016).

Relationship between the three inflammatory markers

Although these two cohorts showed significant differences in age and VRF we did not see differences in fibrinogen or WBC between SHIP-2 and SHIP-Trend. All inflammatory markers were correlated with each other, but neuroimaging markers demonstrated specific significant associations with inflammatory markers.

Strengths and limitations

The strengths of our study include the two large, population-based samples with MRIs, sensitive neuroimaging markers and blood collection, data for medication intake and comorbidities. Despite these strengths, there are some limitations to consider. First, we only included cross-sectional data with a single measurement of WBC, hs-CRP, and fibrinogen and had to rely on self-reported information on medication intake. Second, although the analyses included wide range of factors thought to influence WBC, hs-CRP or fibrinogen

and brain aging, it is likely that there are other, unmeasured confounding variables. Third, we used general peripheral whole blood (WBC), serum (hs-CRP) or plasma (fibrinogen) inflammatory markers, available in our sample from the general population. Future studies should consider more specific inflammatory markers such as cytokines that were not measured in SHIP-2 and Trend and and more brain-specific measures e.g. cerebrospinal fluid levels. Fourth, we trained the SPARE-BA model using SHIP and considering cross-validation to approach independent generalization. Further out of sample models would be ideal for additional confirmation. Finally, further research with consistent methods (e.g. in cognitive tests) needs to examine underlying mechanisms in inflammaging in longitudinal studies and whether interventions can reduce inflammation and the risk for neurodegeneration.

In conclusion, this study shows that increased peripheral inflammatory markers (notably WBC) are associated with acceleration in brain aging. Inflammaging is a complex interaction between low-grade chronic inflammation and the pathogenesis of brain aging patterns but not with AD-like imaging structural changes. Given the known overlap between imaging patterns of accelerated brain aging and AD-like atrophy, increased WBC might be associated with global dementia symptoms. Elevated WBC may be not causal to preclinical (AD) dementia, but an accessory symptom of inflammaging. At population level, our results support the relevant roles of inflammatory markers on brain aging related atrophy. Potential (protective) effects of antiinflammatory drugs need to be further explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Table 1

Characteristics of the study population

Characteristics	SHIP-2 (n=661)	SHIP-Trend (n=1543)	*P* value	SHIP-2 +SHIP-Trend (analysis sample) (n=2204)
Age, mean (sd), years	56.3 (12.3)	51.1 (14.1)	**<0.001** *	52.42 (13.7)
Education, n (%)			**0.002** *	
< 8 years	122 (18.4)	224 (14.5)		346 (15.7)
8–10 years	382 (57.8)	847 (54.9)		1229 (55.8)
> 10 years	157 (23.8)	472 (30.6)		629 (28.5)
Female, n (%)	359 (54.3)	867 (56.2)	0.444	1226 (55.6)
Body mas index, mean (sd), kg/m^2	27.5 (4.4)	27.5 (4.4)	0.914	27.5 (4.4)
Smoker, n (%)			**0.018** *	
None	263 (39.8)	628 (40.7)		891 (40.4)
Previous	272 (41.2)	551 (35.7)		823 (37.3)
Current	126 (19.1)	364 (23.6)		490 (22.2)
Systolic blood pressure, mean (sd), mmHg	131.3 (18.2)	125.5 (17.1)	**<0.001** *	127.3 (17.6)
Antihypertensive medication, n (%)	243 (36.7)	476 (30.8)	**0.008** *	719 (32.6)
HbA1c, %	5.4 (0.8)	5.3 (0.7)	**0.001** *	5.3 (0.7)
Antidiabetic medication, n (%)	31 (4.7)	56 (3.6)	0.292	87 (4.0)
Cholesterol, mean (sd), mmol/l	5.5 (1.1)	5.5 (1.1)	0.777	5.5 (1.1)
LDL-cholesterol, mean (sd), mmol/l	3.4 (1.0)	3.4 (0.9)	0.072	3.4 (0.9)
HDL-cholesterol, mean (sd), mmol/l	1.5 (0.4)	1.5 (0.4)	0.808	1.5 (0.4)
Lipid lowering medicaton, n (%)	101 (15.3)	129 (8.4)	**<0.001** *	230 (10.4)
WBC, mean (sd), Gpt/l	6.0 (1.8)	5.9 (2.1)	0.136	6.0 (2.0)
Antiinflammatory medication, n (%)	123 (18.6)	284 (18.4)	0.958	407 (18.5)
Fibrinogen[a], mean (sd), g/l	3.1(0.7)[a]	3.0 (0.7)[b]	0.05	3.0 (0.7)
Hs-CRP[c], mean (sd), mg/l		2.3 (3.7)		
Verbal Learning and Memory Test (sum immediate and delayed), mean (sd), arbitrary units	19.1 (5.1)			
Numberg Age Inventory (sum immediate and delayed), mean (sd), arbitrary units		11.2 (2.5)		
TBV, mean (sd), mm3	1246199 (129455)	1258055 (125436)	0.050	1254499 (126742)

Characteristics	SHIP-2 (n=661)	SHIP-Trend (n=1543)	*P* value	SHIP-2 +SHIP-Trend (analysis sample) (n=2204)
WMV, mean (sd), mm3	555096 (60744)	555161 (59344)	0.982	555142 (59753)
GMV, mean (sd), mm3	691103 (76346)	702894 (75581)	**0.001** *	699358 (75987)
WMHV, mean (sd), mm3	875 (2765)	702 (2536)	0.168	754 (2608)
SPARE-AD, arbitrary units	−3.0 (0.9)	−3.1 (0.9)	**0.023** *	−3.1 (0.9)
SPARE-BA, arbitrary units	−0.3 (1.8)	0.2 (1.9)	**0.001** *	0.1 (1.9)

Data consists of a number (proportion) or a mean (SD)

SD, Standard deviation; *HbA1c*, Glycated hemoglobin; *WBC*, white blood cell count; *LDL-cholesterol*, Low-density lipoprotein; *HDL-cholesterol*, High-density lipoprotein cholesterol; *hs-CRP*, high sensitive C-reactive protein; *TBV*, total brain volume; *WMV*, white matter volume; *GMV*, gray matter volume; *WBC*, white blood cell count; *SPARE-AD*, Spatial Pattern of Atrophy for Recognition of Alzheime's disease; *SPARE-BA*, Spatial Pattern of Atrophy for Recognition of brain aging; *SHIP*, Study of Health in Pomerania; *hs-CRP*, high sensitive C-reactive protein: *WMHV*, White matter hyperintensities volume

*significant at $p<0.05$; p-values are uncorrected in Table 1

[a]Measure available for n=659 subjects

[b]Measure available for n=1539 subjects

[c]Measure available for n=1446 subjects

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Table 2

Linear regression models in which imaging signatures of white matter disease (WMHV), Alzheimer's disease (SPARE-AD) and brain aging (SPARE-BA) are the outcomes and WBC, fibrinogen, hs-CRP and antiinflammatory medication are the predictors

Cohort	Predictors	Outcome											
		WMHV				SPARE-AD				SPARE-BA			
SHIP-2 and SHIP-Trend[§] (n= 2204)		**Coefficient**	**Standard error**	**FDR-adjusted *p* value**	**R^2**	**Coefficient**	**Standard error**	**FDR-adjusted *p* value**	**R^2**	**Coefficient**	**Standard error**	**FDR-adjusted *p* value**	**R^2**
	WBC	197	0.345	(0.757)	0.338	0.118	0.073	(0.420)	0.180	**−0.333**	**0.092**	**(0.003) ***	**0.686**
	hs-CRP[a]	−0.100	0.118	(0.757)	0.347	0.009	0.025	(0.796)	0.181	−0.064	0.031	(0.264)	0.704
	Fibrinogen[b]	−0.635	0.435	(0.435)	0.338	0.017	0.092	(0.850)	0.179	−0.048	0.116	(0.796)	0.684
	Antiinflammatory medication	−0.240	0.232	(0.602)	0.338	0.052	0.049	(0.602)	0.179	−0.037	0.062	(0.757)	0.684

[§]Models are adjusted for age, age^2, sex, body mass index, smoking, systolic blood pressure, antihypertension medication, antidiabetic drug use, HbA1c, cholesterol ratio, lipid lowering drug use, education and study cohort effects

SPARE-AD, Spatial Pattern of Atrophy for Recognition of Alzheime's disease; *SPARE-BA*, Spatial Pattern of Atrophy for Recognition of brain aging; *WMHV*, white matter hyperintensity volume; *SHIP*, Study of Health in Pomerania; *WBC*, white blood cell count; *hs-CRP*, high sensitive C-reactive protein

*significant at $p<0.05$

[a]Measure available for n=1446 subjects

[b]Measure available for n=2198 subjects

Table 3

Linear regression models in which total brain volume, white matter volume and gray matter volume are the outcomes and WBC, fibrinogen, hs-CRP and antiinflammatory medication are the predictors

Cohort	Predictors	Outcome											
		TBV				WMV				GMV			
SHIP-2 and SHIP-Trend[§] (n= 2204)		Coefficient	Standard error	FDR-adjusted *p* value	R^2	Coefficient	Standard error	FDR-adjusted *p* value	R^2	Coefficient	Standard error	FDR-adjusted *p* value	R^2
	WBC	**−23701**	**8065**	**(0.019)** *	**0.455**	−6500	4026	(0.159)	0.389	**−17201**	**4516**	**(0.017)** *	**0.525**
	hs-CRP[a]	−6231	2740	(0.055)	0.464	−2426	1363	(0.129)	0.409	**−3804**	**1541**	**(0.039)** *	**0.533**
	Fibrinogen[b]	−21942	10153	(0.062)	0.455	−7778	5064	(0.165)	0.390	**−14164**	**5693**	**(0.039)** *	**0.524**
	Antiinflammatory medication	−3959	5431	(0.508)	0.453	−1359	2708	(0.615)	0.388	−2599	3045	(0.393)	0.522

[§]Models are adjusted for age, age^2, sex, body mass index, smoking, systolic blood pressure, antihypertension medication, antidiabetic drug use, HbA1c, cholesterol ratio, lipid lowering drug use, education and study cohort effects

TBV, total brain volume; *WMV*, white matter volume; *GMV*, gray matter volume; *WBC*, white blood cell count; *hs-CRP*, high sensitive C-reactive protein

*significant at $p<0.05$

[a]Measure available for n=1446 subjects

[b]Measure available for n=2198 subjects