Differences in white matter hyperintensities in socioeconomically deprived groups: results of the population-based LIFE Adult Study

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ABSTRACT

Objective: Previous studies have shown that socioeconomically deprived groups exhibit higher lesion load of the white matter (WM) in aging. The aim of this study was to (i) investigate to what extent education and income may contribute to differences in white matter hyperintensities (WMHs) and (ii) identify risk profiles related to a higher prevalence of age-associated WMH.

Design and Setting: Population-based adult study of the Leipzig Research Centre for Civilization Diseases (LIFE) in Leipzig, Germany.

Participants: Dementia-free sample aged 40–80 years ($n = 1,185$) derived from the population registry.

Measurements: Information was obtained in standardized interviews. WMH (including the derived Fazekas scores) were assessed using automated segmentation of high-resolution T1-weighted anatomical and fluid-attenuated inversion recovery (FLAIR) MRI acquired at 3T.

Results: Despite a significant association between income and WMH in univariate analyses, results from adjusted models (age, gender, arterial hypertension, heart disease, and APOE e4 allele) indicated no association between income and WMH. Education was associated with Fazekas scores, but not with WMH and not after Bonferroni correction. Prevalence of some health-related risk factors was significantly higher among low-income/education groups. After combining risk factors in a factor analysis, results from adjusted models indicated significant associations between higher distress and more WMH as well as between obesity and more deep WMH.

Conclusions: Previously observed differences in WMH between socioeconomically deprived groups might stem from differences in health-related risk factors. These risk factors should be targeted in prevention programs tailored to socioeconomically deprived individuals.

Key words: white matter hyperintensities, brain, aging, socioeconomic status, education, income, risk factors, lifestyle

Introduction

The advantages of an increasing life expectancy are confined by the fact that aging comes with higher risk for several health problems (World Health

Organization, 2015). One of the most challenging health problems is dementia because it impairs the person's thinking and their ability to manage life independently. In many forms of dementia, white matter hyperintensities (WMH) are observed on fluid-attenuated inversion recovery (FLAIR) MRI images. WMH are structural abnormalities of probable vascular origin. A great amount of the total pathology of the brain is WMH (Wardlaw *et al.*, 2019). White matter (WM) is formed in early childhood and reaches its peak volume after age 2 (Dai *et al.*, 2019). In a person's late 40s, WM volume starts to decrease (Moura *et al.*, 2019). Further, mainly age-related changes in WM occur later and are accompanied by increases in WMH, as observations from the Cardiovascular Health Study ($n = 3,658$) suggest (Longstreth *et al.*, 1996). WMH are clinically relevant because people with more WMH perform more poorly on cognitive tests (Au *et al.*, 2006). This is mainly due to small vessel disease (Lampe *et al.*, 2019) as well as WMH contributing to more aging and Alzheimer's disease-related pathology in the brain (Habes *et al.*, 2016).

People with a lower socioeconomic background show more WMH in old age (Murray *et al.*, 2014). As early as in childhood, lower family income is associated with poorer whole-brain WM structure (Dufford *et al.*, 2020) and WM organization (Dufford and Kim, 2017). In young adulthood, high-income volatility is associated with worse microstructural integrity of WM, as findings from the study Coronary Artery Risk Development in Young Adults ($n = 3,287$) demonstrate (Grasset *et al.*, 2019). Later in life, having had low family income during childhood is associated with less white and gray matter volume (Luby *et al.*, 2013) and decreased WM organization (Gianaros *et al.*, 2012). At an age of about 60–90 years, those who experienced disadvantageous socioeconomic conditions earlier in life have an accelerated decline of cognitive functioning (Chiao *et al.*, 2014). The effect is so pronounced that authors have argued that about half of dementia cases might be attributable to socioeconomic adversities (Scazufca *et al.*, 2010).

Given the impact, it is important to get a better insight into the nature of the association of socioeconomic status and WMH in aging. The construct of socioeconomic status encompasses education as well as income (Cutler *et al.*, 2008). To develop efficient societal prevention measures, it is necessary to first investigate the differential effects of these dimensions. Independent effects of education and income on dementia risk have been reported in a longitudinal analysis of 1,449 people (age 65 +) from the North Karelia Project and the FINMONICA study (Anttila *et al.*, 2002). Income might also have a different effect on WMH than education.

Changes in WMH are associated with medical risk constellations, such as higher systolic blood pressure and silent stroke (Longstreth *et al.*, 1996) as well as with stressful life events (in a dose-dependent manner) (Johnson *et al.*, 2017). Individuals with low income tend to live in resource-deprived situations, in which they experience more stress and are more prone to poor health. Low-income samples are therefore more likely to exhibit a higher WMH burden in old age. Education, on the other hand, does not seem to be significantly associated with WMH, as findings from the Personality and Total Health study of 40–48 year olds (Wen *et al.*, 2009) and the Helsinki Aging Brain Study of individuals aged 55 and older (Zhuang *et al.*, 2018) show. This observation is in line with the idea of cognitive reserve. In contrast to income, education is a resource compensating for brain pathology that has manifested while it does not necessarily prevent it from arising (Stern, 2002).

As education and income might differentially contribute to aging, it is necessary to investigate how each individual contribute to higher WM pathology in aging. The aim of this study was to systematically investigate the effects of education and income on WMH in a population-based sample aged 40 years and older. We hypothesized that lower income, but not lower education, would be associated with more WMH (Hypothesis 1) and that more WMH would be associated with poorer cognitive performance (Hypothesis 2), except in people with high education (Hypothesis 3). To increase anatomical specificity and for exploratory purposes, we also distinguished between deep and periventricular WMH in the analysis.

Further, it is plausible that neither education nor income themselves causes WMH differences. Rather, exposure to health-related risk factors might be causal. Previous studies have demonstrated that there is a tendency for a higher prevalence of diabetes, arterial hypertension, smoking (Alter *et al.*, 2004), higher body mass index, and sedentarism among low income groups (Diez-Roux *et al.*, 2000). People from low socioeconomic background might also be exposed to more psychosocial stress which might cause poor health outcomes (Baum *et al.*, 1999). Indeed, studies have shown associations between stressful life events (Johansson *et al.*, 2013; Tani *et al.*, 2020) and higher perceived stress (Aggarwal *et al.*, 2014; Munoz *et al.*, 2015) with faster cognitive decline and a higher risk for developing dementia. Hence, a further aim of the study was to identify risk profiles among people with high compared to low income that might be driving the prevalence of WMH. We selected any lifestyle and stress-related risk factors that were assessed in the study. We hypothesized that people with low income

are exposed to more health-related risk factors than people with high income (Hypothesis 4) and that those risk factors could explain the association between low income and WMH (Hypothesis 5).

Methods

Study design

Data were derived from the 'Adult Study' of the Leipzig Research Centre for Civilization Diseases (LIFE). The LIFE Adult Study is a large population-based study investigating prevalence, early onset markers, genetic predispositions, and the role of lifestyle factors in major civilization diseases. It was conducted between August 2011 and November 2014. The details of the study have been published elsewhere (Loeffler *et al.*, 2015). Briefly, a random age- and sex-stratified sample of residents of the city of Leipzig was obtained from the residents' registry office. A letter of invitation to participate in the study was sent to every individual on the list. The only exclusion criteria were being pregnant or being unable to follow assessment instructions. People who decided to participate gave written informed consent. The study was approved by the ethics review board of the Medical Faculty of the University of Leipzig and followed the principles outlined in the Declaration of Helsinki.

Data collection included physical and medical examinations as well as self-administered questionnaires and psychometric testing. Trained study assistants conducted the assessments following standardized study protocols. Experienced scientists from different fields monitored the quality of the assessments. A random subsample of participants completed magnetic resonance imaging (MRI) at a separate examination date (age 40–80 years: $n = 2,271$). Excluding participants with bad image quality (e.g., motion artifact) and major brain pathology, data from 2,140 participants were available for analysis. For the purpose of analysis, we further excluded participants with neurological disorders (total $n = 96$; $n = 51$ traumatic brain injury in the past, $n = 23$ epilepsy, $n = 7$ Parkinson's disease, $n = 7$ multiple sclerosis, $n = 4$ substance use disorder, $n = 2$ human immunodeficiency virus, $n = 1$ schizophrenia, $n = 1$ dementia). Dementia cases were identified via self-report in the medical examination as well as via performance in the cognitive testing and activities of daily living. Data available for analysis were further reduced due to missing items ($n = 430$ income, $n = 198$ arterial hypertension, $n = 130$ APOE e4 allele) and poor mapping of WMH imaging ($n = 101$). The final dataset used for analysis comprised $n = 1,185$.

Further, there were missing data on some of the health-related risk factors and the scores deep and periventricular WMH (due to poor mapping). Cases with missing data were excluded from the respective set of analyses. The n of these analyses are specified in the results.

Income and education

Self-reported household income was divided into quartiles ('very low', 'low', 'high', 'very high') to reflect the financial means available for living in comparison to the rest of the population. Education, as reported by the participant, was categorized as 'low' for having only completed high school or less, 'moderate' for having completed college or a professional training school, and 'high' for having completed a university degree.

White matter volume (WMV) and hyperintensities (WHM)

Three-dimensional Magnetization-Prepared Rapid Gradient Echo sequence (3D MP-RAGE) anatomical T1-weighted images of the brain were acquired at the same 3T Siemens Magnetom Verio Syngo MR B17. Generalized autocalibrating partially parallel acquisition parallel imaging technique (18) (according to the Alzheimer's Disease Neuroimaging Initiative standard protocol (19)) was applied using the following scanning variables: repetition time/echo time 2,300 ms/2.98 ms; flip angle 9°; slice/voxel size 1 mm/$1.0 \times 1.0 \times 1.0$ mm ($x \times y \times z$); slices 176; field of view 256 mm; bandwidth 240 Hz/Px; base resolution 256; scanning time 5 minutes 10 seconds. Clinical MRI ratings were performed by neuroradiologists blind to further assessment data. Intracranical volume (ICV) and total gray and WMV were derived from FreeSurfer analysis version 6, a free software package developed by the Athinoula A. Martinos Center for Biomedical Imaging of Harvard University (https://surfer.nmr.mgh.harvard.edu/). After deleting non-brain tissue, intracranial volume (ICV) was obtained by adding up gray matter, WM, and cerebrospinal fluid volume. We adjusted volumes for ICV according to (Kerti *et al.*, 2013; Raz *et al.*, 2005) using the following formula: adjusted volume (in mm³) = raw volume (in mm³) − ß * (ICV − ICVmean) with ß being the slope of regression of the respective volume on ICV.

Assessment of WMH has been described previously (Lampe *et al.*, 2019). Briefly, all images were checked by a radiologist for incidental findings and participants with hemorrhagic infarctions, ischemic infarctions, or other neuroradiological findings were excluded from the analysis. Using a validated

computer-based WMH segmentation algorithm (TOADS) and FLAIR images, WMH volume was determined and coregistered to a standardized Montreal Neurological Institute (MNI) template. Participants with erroneous warping were excluded. The previously used standard of 10 mm distance to the ventricular surface was applied to segregate periventricular WMH and deep WMH. Higher WMH scores reflect a higher burden. For the purpose of analysis, outliers with extraordinarily high values were assigned 600,000 mm³ for WMH (five changes) and 20,000 mm³ for deep and periventricular WMH (24 changes). Further, WMH were rated visually using the Fazekas score (0–3), a score commonly used in clinical practice. A score of 0 reflects no lesions, while a score of three reflects severe lesions.

Cognitive functioning

Cognitive performance was assessed by trained study assistants and was subject to regular quality control by experienced psychologists. Participants completed the Verbal Fluency Test (VFT), the Trail Making Test (TMT), and the Word List Test (WLT) – subtests of the German version of the neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer's disease (CERADplus (Morris *et al.*, 1988)). The German version of the CERADplus has been validated (Aebi *et al.*, 2002). On the VFT, participants are instructed to name as many animals as possible in 1 minute. The participant's score equals the number of correctly named animals and is thought to measure verbal abilities, semantic fluency, and semantic memory (Kraan *et al.*, 2013). For the TMT, participants are asked to, first, connect numbers in an ascending order as fast as they can (version A) and, second, to connect numbers and letters alternatingly (version B). When an error was made, the participants had to return to the number where the error originated. The participant's score corresponds to the number of seconds needed to complete the test and is thought to measure working memory, task-switching ability (Sanchez-Cubillo *et al.*, 2009), and executive control (Arbuthnott and Frank, 2010). For the WLT, participants are instructed to read out 10 words and later recall them. This is repeated three times. The participant's score is the number of words remembered correctly and is thought to measure memory and learning and is a good indicator for the severity of Alzheimer's disease (Welsh *et al.*, 1991).

Confounders and health-related risk factors

Age was calculated as the difference in years when subtracting the birth date from the interview date.

Gender was used as recorded (male/female) in the population registry. A nonbinary gender option was unfortunately not in use at the time.

APOE genotype was identified from peripheral blood leukocytes using an automated protocol on the Qiagen Autopure LS (Qiagen, Hilden, Germany) and by following the method of Aslanidis and Schmitz (1999) via Roche Lightcycler 480 (Aslanidis and Schmitz, 1999).

Social isolation was assessed via the short version of the Lubben Social Network Scale (Lubben *et al.*, 2006). People who scored less than 12 were considered to be socially isolated (according to (Lubben *et al.*, 2006)).

Smoking status was obtained by asking the participant standardized questions on whether they currently smoked or had smoked in the past. They were classified as nonsmokers (0), former smokers (1), and current smokers (2).

Physical activity was assessed via the International Physical Activity Questionnaire (IPAQ) – Short Form. Participants were categorized as either engaging in at least moderate activity (1; according to the IPAQ scoring schedule (Forde, 2018)) or not (0).

Information on heart disease, arterial hypertension, elevated blood lipids, type 2 diabetes, and depression was obtained by asking the participant "Have you ever been diagnosed with . . .?". The variable 'heart disease' was scored a 1 if the participants reported to have been diagnosed with either heart attack, coronary heart disease, heart insufficiency, tachycardia, arrhythmia, or having undergone heart bypass surgery.

Different types of stress were assessed via the Trier Inventory for Chronic Stress (Petrowski *et al.*, 2012) (TICS), a standardized instrument of nine types of chronic stress. Higher scores reflect more stress. Not all participants in the final sample completed all TICS questions (*n* in Table 2).

For the purpose of analysis, risk factors were clustered via factor analysis. We used a tetrachoric correlation matrix as many risk factors were binary. As the TICS scores were continuous, they were dichotomized (low/high) using median split. The screeplot suggested three factors (i.e., point when the eigenvalues level off). First, risk factors were assigned to the model factors in which they scored highest. In this version, *Factor 3* was loaded only with 'depression' and social isolation. Therefore, we created a second version in which all health-related risk factors with a factor loading of >0.3 on *Factor 3* were assigned to *Factor 3*. The second version had a slightly better fit (Akaike information criterion (AIC) 16015 vs. 15948). The factor model was validated using generalized equation modeling with Bernoulli distribution and unstructured

covariance matrix. As physical inactivity, social isolation, and obesity were not significant, these risk factors were excluded from the model factors, resulting in an improved model fit (AIC 12887). For details, see Supplementary file, Tables A.1 and A.2. In the final model, we identified *Factor 'Distress'*, comprising eight TICS scores and smoking, *Factor 'Health'*, comprising diabetes, arterial hypertension, and elevated blood lipids, and *Factor 'Feeling overloaded'*, comprising depression and the TICS scores 'work and social overload' and 'pressure to perform'. We used latent variable scores from this model to assign factor scores for each participant. To ease interpretation, we categorized the score into low (<25%), medium (25–75%), and high (>75%) groups.

Statistical analyzes

All statistical analyzes were performed using STATA 16. A significance level of $p < 0.05$ was used if not stated otherwise. Not normally distributed continuous data was log-transformed for analysis.

Hypothesis 1 was analyzed by, first, estimating differences in WMH by education and income via Kruskall–Wallis test. Then, a total of four (WMH, deep WMH, periventricular WMH, Fazekas score) linear regression maximum likelihood models with robust variance estimates were run. The Bonferroni corrected level of significance would be (0.05/4=) 0.0125. These models included education and income as well as age, gender, arterial hypertension, heart disease, and APOE e4 allele. Analyses were repeated with an interaction term for education*income.

Hypothesis 2 was tested by, first, estimating differences in cognitive performance (TMT A, TMT B, VFT, WLT) by education and income via Kruskall–Wallis test. These were then validated using linear regression maximum likelihood models with robust variance estimates including education, income, age, gender, arterial hypertension, heart disease, and APOE e4 allele. The Bonferroni corrected level of significance would be (0.05/4=) 0.0125. These regression models were then repeated to estimate the association between WMH measures (WMH, deep WMH, periventricular WMH, Fazekas score) and cognitive performance outcomes (TMT A, TMT B, VFT, WLT; total of 16 analyses). The Bonferroni corrected level of significance would be (0.05/16=) 0.003125. Hypothesis 3 was analyzed by repeating those analysis for each educational group separately.

Hypothesis 4 was investigated by estimating the distribution of health-related risk factors by income and education via chi-square test for categorical data

and Kruskall–Wallis test for continuous data. Hypothesis 5 was tested by estimating the associations of WMH measures (WMH, deep WMH, periventricular WMH, Fazekas score) with the three factors (*Distress, Health, Feeling overloaded*), obesity, social isolation, and physical inactivity via linear regression maximum likelihood models with robust variance estimates adjusted for confounders. The Bonferroni corrected level of significance would be (0.05/4=) 0.0125.

Results

The mean age was 63.5 (SD 10.2, range 40–80). A total of 58.9% were male, 25.2% had an APOE e4 allele, 14.7% had a heart disease, 34.4% had low, 26.2% middle, and 39.5% high education, and 28.2% had very low, 32.4% low, 23.2% high, and 16.2% very high income. People with high education had a significantly higher income (chi square 118.4, $p < 0.001$). Of the people with high education, 14.3% had a very low income, and of the people with low education, 9.6% had a very high income. Mean total WMH was 2,952.6 mm³ (SD 5,384.3 mm³, range 0–60,000.0 mm³). Deep WMH were on average 1,064.3 mm³ (SD 2,442.1 mm³, range 0–20,000.0 mm³) and periventricular WMH 2,266.1 mm³ (SD 2,948.2 mm³, range 115–20,000.0 mm³). 33.1% had a Fazekas score of 0, 53.8% of 1, 12.5% of 2, and 0.7% of 3.

## White matter lesions in association with education and income

Results from univariate analyses indicate that WMH were significantly associated with income, but not with education (see Figure 1, and Supplementary file, Table A.3). However, results from confounder-adjusted regression analyses revealed no significant association between WMH and income (see Table 1). Residuals of this regression were rather large (see Supplementary file, Figure A.1). Accordingly, we reject Hypothesis 1. In the same set of regression analyses, we observed an association of high education with a lower Fazekas score (see Table 1). However, this finding had not been present in the univariate analysis, the trend was not significant, and it did not hold up to Bonferroni correction.

We looked at possible interaction effects between education and income: There was only one significant interaction between high education and very high income on deep WMH (− 0.59, CI 95% − 1.11 to − 0.06, $p = 0.028$, $n = 1,126$). The interaction would not survive Bonferroni correction.
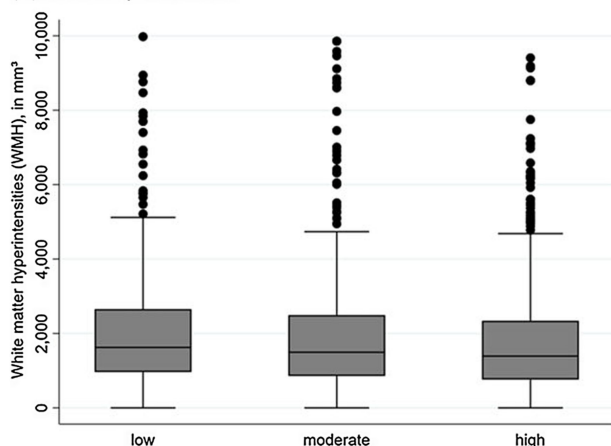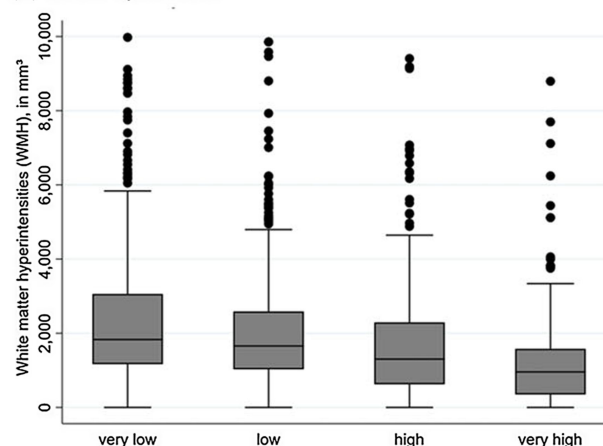
Figure 1. Means of white matter hyperintensities (WMH) by education (A) and income (B) ($n = 1,185$).

White matter lesions and cognitive abilities

In cognitive testing, the mean score in the TMT A was 38.3 seconds (SD 13.7 seconds), the TMT B 92.7 seconds (SD 44.5 seconds), the VFT 23.6 words (SD 6.2 words), and the WLT 22.2 words (SD 3.7 words). Higher education was significantly associated with better performance in the cognitive tests (see Table 1). Further, results suggest that a greater quantity of deep WMH and periventricular WMH were significantly associated with lower performance in the TMT B and WLT (see supplementary file, Table A.4). Only the association between periventricular WMH and WLT remained significant using Bonferroni correction. Thus, Hypothesis 2 is supported for this association only. Analyses by educational group revealed significant associations – considering Bonferroni correction – with WMH for people with high education (low education $b = -0.03$ (CI 95% -0.13 to 0.07), $p = 0.524$; moderate education $b = -0.08$ (CI 95% -0.13 to -0.02), $p = 0.006$; high education $b = -0.09$ (CI 95% -0.14 to -0.04), $p = 0.001$, $n = 1,174$; also shown in Figure A.2 in the Supplementary file). Accordingly, we cannot confirm Hypothesis 3.

White matter lesions and health-related risk factors

In our analysis sample, the distribution of health-related risk factors was the following: 13.8% were socially isolated ($n = 1,076$), 34.2% were former and 12.6% current smokers ($n = 1,143$), 13.8% reported having been diagnosed with diabetes ($n = 1,178$), 7.9% with depression ($n = 1,165$), 27.6% were obese ($n = 1,179$), 10.9% did not engage in at least moderate physical activity ($n = 1,162$), 50.9% had arterial hypertension ($n = 1,185$), and 37.4% higher blood lipids ($n = 1,150$). People from low-income and education groups were more likely to be socially isolated, physically inactive, and chronically worried, but also reported less overload and less pressure to perform (see Table 2). Those with low education were more likely to smoke, experience lacking social resources, excessive demands, and work discontent, while those with low-income groups were more likely to have chronic diseases such as diabetes, obesity, arterial hypertension, and elevated blood lipids (see Table 2). Accordingly, we confirm that people from low-income groups had a higher prevalence of risk factors than people from high income groups (Hypothesis 4).

To understand which health-related risk factors might be relevant for WMH, we used the risk factor scores (*Distress, Health, Feeling overloaded*) from the factor analysis in a confounder-adjusted regression analyses. Results are shown in Table 3 and indicate that people with moderate '*Distress*' had significantly more WMH than those with low '*Distress*' (see also Figure 2). Comparison to high '*Distress*' was not significant, ant the overall trend might not hold a Bonferroni correction. Obesity was significantly associated with a greater quantity of deep WMH (see also Figure 2). Further, higher education was associated with a higher Fazekas score. However, r^2 was only 0.095 compared to 0.247 in the model for WMH, the trend was not significant, and the significance did not survive Bonferroni correction. No other factor of interest was significant. Concerning Hypothesis 5, we have to conclude that only the risk factor obesity, which was more frequent in our low-income group, was associated with more WMH.

Discussion

The aim of our study was to investigate the differential effects of education and income on WMH and cognitive functioning and to identify risk profiles

Table 1. Estimates of regression analyses on the association of education and income on white matter hyperintensities in cm³ (WMH, Deep WMH, Periventricular WMH, Fazekas score) and cognitive functioning (TMT A, TMT B, VFT, WLT), adjusted for APOE e4 allele, arterial hypertension, and heart disease

	MODEL ON WMH$	MODEL ON DEEP WMH$	MODEL ON PERI. WMH$	MODEL ON FAZEKAS SCORE	MODEL ON TMT A	MODEL ON TMT B	MODEL ON VFT	MODEL ON WLT
	$N = 1,126$	$N = 863$	$N = 869$	$N = 1,179$	$N = 1,175$	$N = 1,166$	$N = 1,173$	$N = 1,174$
	B (CI 95%)	B (CI 95%)	B (CI 95%)	B (CI 95%)	B (CI 95%)	B (CI 95%)	B (CI 95%)	B (CI 95%)
Age	0.05 (0.04–0.06)***	0.05 (0.04–0.06)***	0.04 (0.04–0.05)***	0.08 (0.07–0.09)***	0.59 (0.52–0.67)***	1.56 (1.30–1.81)***	−0.10 (−0.14 to −0.06)***	−0.13 (−0.15 to −0.11)***
Gender (female)	0.30 (0.18–0.42)**	−0.19 (−0.35 to −0.03)*	−0.14 (−0.25 to −0.03)*	0.42 (0.18–0.66)**	−1.58 (−3.03 to −0.13)*	−5.66 (−10.40 to −0.92)**	0.73 (0.03–1.44)*	1.85 (1.45–2.24)***
Income								
Very low	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Low	−0.10 (−0.25 to 0.04)	−0.07 (−0.28 to 0.15)	−0.04 (−0.19 to 0.11)	−0.08 (−0.39 to 0.24)	−0.84 (−2.81 to 1.14)	−6.68 (−13.57 to 0.21)	0.33 (−0.57 to 1.22)	0.51 (−0.01 to 1.03)
High	−0.14 (−0.31 to 0.02)	−0.22 (−0.45 to 0.01)	−0.08 (−0.25 to 0.08)	−0.10 (−0.47 to 0.26)	−1.18 (−3.18 to 0.83)	−8.67 (−15.61 to −1.74)*	1.17 (0.13–2.20)*	0.55 (−0.03 to 1.14)
Very high	−0.19 (−0.41 to 0.02)	−0.02 (−0.27 to 0.23)	−0.09 (−0.27 to 0.08)	0.02 (−0.40 to 0.44)	−1.22 (−3.51 to 1.07)	−7.73 (−16.05 to 0.60)	−0.04 (−1.27 to 1.19)	0.89 (0.26–1.54)*
Education								
Low	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	−0.05 (−0.20 to 0.11)	0.04 (−0.16 to 0.25)	−0.04 (−0.18 to 0.09)	−0.19 (−0.49 to 0.11)	−2.43 (−4.25 to 0.59)**	−10.98 (−17.78 to −4.19)**	1.02 (0.15–1.89)*	0.34 (−0.15 to 0.83)
High	−0.08 (−0.22 to 0.06)	−0.04 (−0.24 to 0.15)	−0.07 (−0.20 to 0.06)	−0.34 (−0.65 to −0.04)*	−2.26 (−3.99 to 0.52)*	−19.47 (−25.75 to −13.19)***	2.83 (1.95–3.71)***	1.14 (0.67–1.61)***
	F (p)	F (p)	F (p)	F (p)	F (p)	F (p)	F (p)	F (p)
Trend for income	1.59 (0.191)	1.67 (0.171)	0.48 (0.669)	0.66 (0.883)	0.52 (0.667)	2.06 (0.103)	2.14 (0.093)	2.65 (0.048)
Trend for education	0.63 (0.532)	0.40 (0.669)	0.59 (0.552)	4.89 (0.087)	4.20 (0.015)	19.17 (<0.001)	20.02 (<0.001)	11.93 (<0.001)
	Change r^2	Change r^2	Change r^2	Change r^2	Change r^2	Change r^2	Change r^2	Change r^2
Comp. without education	0.008	0.001	0.0007	0.0022	0.0058	0.0294	0.0323	0.0051

Notes: $log-transformed; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; b, regression coefficient, CI 95%, confidence interval of 95%; Comp., compared to model; Peri., periventricular; REF, reference group; TMT, trail making test with lower scores reflecting better cognitive abilities; VFT, verbal fluency test; WLT, word list test; WM, white matter; WMH, white matter hyperintensities.

Table 2. Distribution of health-related risk factors over education and income groups

	INCOME							EDUCATION					
	VERY LOW	LOW	HIGH	VERY HIGH				LOW	MODERATE	HIGH			
	N (%)	N (%)	N (%)	N (%)	CHI^2	p	n	N (%)	N (%)	N (%)	CHI^2	p	n
Socially isolated	64 (21.1%)	47 (13.6%)	20 (8.0%)	17 (9.6%)	23.422	<0.001	1,076	69 (19.0%)	35 (12.5%)	44 (10.2%)	13.529	0.001	1,076
Smoking, former	96 (30.9%)	128 (34.6%)	101 (37.3%)	66 (34.6%)	5.461	0.486	1,143	117 (30.3%)	100 (34.0%)	174 (37.6%)	19.461	0.001	1,143
Current	42 (13.5%)	41 (11.1%)	31 (11.4%)	30 (15.7%)				70 (18.1%)	35 (11.9%)	39 (8.4%)			
Depression	36 (11.0%)	22 (5.7%)	21 (7.8%)	14 (7.5%)	6.761	0.080	1,165	36 (9.0%)	28 (9.2%)	29 (6.3%)	2.979	0.225	1,165
Diabetes	71 (21.3%)	58 (15.2%)	25 (9.1%)	8 (4.2%)	35.945	<0.001	1,178	62 (15.2%)	45 (14.6%)	55 (11.9%)	2.314	0.314	1,178
Physical activity§	52 (15.8%)	37 (9.8%)	23 (8.6%)	15 (8.0%)	11.660	0.009	1,162	56 (14.2%)	43 (14.1%)	28 (6.1%)	18.676	<0.001	1,162
Obesity	114 (34.3%)	113 (29.7%)	67 (24.4%)	31 (16.2%)	22.164	<0.001	1,179	123 (30.5%)	90 (29.1%)	112 (24.0%)	4.965	0.084	1,179
Elevated blood lipids	128 (40.4%)	158 (41.7%)	98 (36.6%)	46 (24.7%)	17.010	0.001	1,150	148 (37.9%)	111 (37.0%)	171 (37.3%)	0.059	0.971	1,150
Hypertension	205 (61.4%)	213 (55.5%)	120 (43.6%)	66 (34.4%)	44.662	<0.001	1,185	214 (52.4%)	160 (51.6%)	230 (49.2%)	1.097	0.578	1,185
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Chi^2	p		Mean (SD)	Mean (SD)	Mean (SD)	Chi^2	p	
TICS Work overload	7.8 (5.7)	7.9 (5.7)	9.9 (6.3)	10.9 (6.9)	28.681	<0.001	682	8.8 (6.1)	9.4 (6.3)	8.6 (6.2)	1.993	0.369	682
TICS Social overload	7.2 (4.4)	8.1 (4.4)	8.9 (4.7)	9.9 (4.6)	31.318	<0.001	689	7.6 (4.6)	8.9 (4.7)	8.7 (4.5)	10.138	0.006	689
TICS Pressure to perform	10.1 (5.8)	11.3 (6.0)	13.3 (6.8)	16.2 (7.3)	62.895	<0.001	678	11.3 (6.4)	12.0 (6.6)	13.3 (6.9)	10.932	0.004	678
TICS Work discontent	8.1 (4.4)	7.6 (3.7)	7.9 (4.5)	7.3 (4.0)	2.039	0.564	675	8.6 (4.5)	7.5 (3.8)	7.3 (3.9)	11.239	0.004	675
TICS Excessive demands	4.9 (3.1)	4.3 (2.9)	4.4 (3.2)	4.1 (3.1)	8.533	0.036	683	4.8 (2.9)	4.5 (3.0)	4.2 (3.2)	8.728	0.013	683
TICS Lack of social rec.	4.4 (2.9)	4.3 (2.8)	4.3 (3.1)	4.3 (2.8)	0.126	0.987	685	4.7 (3.0)	4.4 (2.6)	4.0 (2.9)	7.850	0.019	685
TICS Social tensions	5.1 (3.2)	4.9 (2.8)	5.1 (3.3)	4.9 (3.1)	0.514	0.916	687	5.0 (3.1)	4.9 (2.8)	5.1 (3.3)	0.044	0.978	687
TICS Feeling socially isol.	5.3 (3.9)	4.8 (3.1)	4.9 (3.6)	4.8 (3.8)	1.312	0.726	686	5.5 (3.8)	4.8 (3.4)	4.6 (3.4)	5.907	0.052	686
TICS Chronic worrying	4.9 (3.1)	4.3 (2.9)	4.4 (2.8)	4.1 (2.9)	8.025	0.046	692	4.7 (3.0)	4.6 (2.9)	4.2 (2.9)	5.696	0.058	692
TICS Chronic stress	12.4 (7.1)	11.1 (7.0)	12.0 (7.3)	11.5 (7.1)	4.399	0.222	677	12.6 (7.1)	11.9 (6.9)	10.9 (7.2)	9.860	0.007	677

Notes: §do not meet criteria for at least moderate physical activity; APOE, Apolipoprotein E; isol., isolated; n, number of participants; p, level of statistical significance; rec., recognition; TICS, German Trier Inventory for Chronic Stress.

Table 3. Estimates of the final models for the four white matter hyperintensities measures in cm³ (WMH, deep WMH, periventricular WMH, Fazekas score) separately, adjusted for age, APOE e4 allele, arterial hypertension, heart disease, gender, income, and education

		MODEL ON WMH$	MODEL ON DEEP WMH$	MODEL ON PERIVENTRICULAR WMH$	MODEL ON FAZEKAS SCORE
		$N = 995$	$N = 762$	$N = 767$	$N = 1,043$
		B (CI 95%)	B (CI 95%)	B (CI 95%)	B (CI 95%)
Income (ref = very low)	Low	−0.08 (−0.22 to 0.07)	−0.02 (−0.25 to 0.21)	−0.02 (−0.18 to 0.14)	−0.03 (−0.37 to 0.31)
	High	−0.09 (−0.27 to 0.07)	−0.12 (−0.35 to 0.12)	−0.07 (−0.24 to 0.11)	−0.08 (−0.48 to 0.32)
	Very high	−0.12 (−0.35 to 0.10)	0.09 (−0.19 to 0.37)	−0.01 (−0.21 to 0.18)	0.02 (−0.44 to 0.48)
Education (ref = low)	Moderate	0.07 (−0.09 to 0.23)	0.09 (−0.13 to 0.30)	−0.00 (−0.15 to 0.15)	−0.13 (−0.46 to 0.19)
	High	0.00 (−0.15 to 0.16)	−0.05 (−0.26 to 0.16)	−0.01 (−0.15 to 0.14)	−0.33 (−0.66 to −0.00)[*]
Physical activity[§]		−0.09 (−0.28 to 0.11)	−0.09 (−0.39 to 0.22)	−0.09 (−0.29 to 0.12)	0.02 (−0.47 to 0.50)
Obesity		0.09 (−0.05 to 0.22)	0.33[**] (0.12 to 0.53)	0.02 (−0.12 to 0.16)	0.05 (−0.25 to 0.36)
Social isolation		0.09 (−0.08 to 0.27)	0.16 (−0.12 to 0.43)	−0.01 (−0.22 to 0.19)	0.12 (−0.26 to 0.51)
Factor 'Distress'[#]	25%–75%	0.28[**] (0.08 to 0.49)	0.18 (−0.08 to 0.45)	0.23[*] (0.05 to 0.42)	0.04 (−0.38 to 0.45)
	>75%	0.25 (−0.00 to 0.49)	0.14 (−0.19 to 0.48)	0.19 (−0.04 to 0.43)	0.00 (−0.49 to 0.50)
Factor 'Health'[#]	25%–75%	0.02 (−0.16 to 0.20)	−0.15 (−0.39 to 0.08)	0.05 (−0.10 to 0.19)	−0.12 (−0.49 to 0.25)
	>75%	0.03 (−0.21 to 0.27)	−0.16 (−0.51 to 0.18)	0.03 (−0.20 to 0.26)	−0.17 (−0.68 to 0.35)
Factor 'Feeling overloaded'[#]	25%–75%	−0.15 (−0.36 to 0.05)	−0.11 (−0.39 to 0.17)	−0.07 (−0.28 to 0.14)	−0.12 (−0.56 to 0.32)
	>75%	−0.07 (−0.34 to 0.19)	0.09 (−0.45 to 0.28)	−0.05 (−0.30 to 0.20)	−0.14 (−0.68 to 0.41)
		F (p)	F (p)	F (p)	F (p)
Trend for education		0.46 (0.633)	0.89 (0.410)	0.00 (0.997)	4.01 (0.135)
Trend for obesity		1.43 (0.233)	10.04 (0.002)	0.08 (0.773)	0.11 (0.741)
Trend for distress		3.68 (0.026)	0.93 (0.393)	2.98 (0.052)	0.05 (0.976)
		Change r^2	Change r^2	Change r^2	Change r^2
Comp. without education		0.0007	0.0018	0.0000	0.0020
Comp. without obesity		0.0008	0.0131	0.0006	0.0002
Comp. without distress		0.0066	0.0022	0.0066	0.0000

Notes: [§]Meet criteria for at least moderate physical activity; [#]reference category is <25%; [$]log transformed; $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; b, regression coefficient, CI 95%, confidence interval of 95%; Comp., compared to model; WMH, white matter hyperintensities.
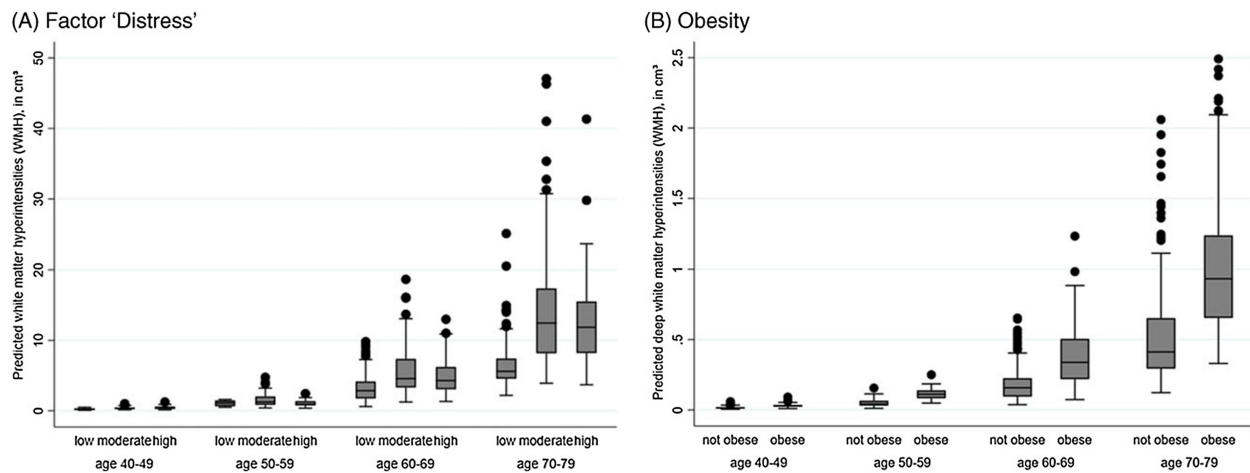
Figure 2. Predicted white matter hyperintensities (WMH) by the Factor 'Distress' (A, $n = 995$) and obesity (B, $n = 762$) as estimated in the confounder-adjusted final models.

among people with low income that might underlie the prevalence of WMH. Results from our population-based sample, aged 40–80 years, indicate a univariate association between income and WMH. However, we did not observe any statistically significant differences in WMH between education or income groups in confounder-adjusted analyses (Hypothesis 1).

Regarding cognition, higher education (to a small extend also higher income) and less periventricular WMH were associated with better performance in the WLT. Hence, we confirm Hypothesis 2 only for this association. As the WLT is a cognitive test sensitive for Alzheimer-related cognitive impairment (Albert, 1996), our findings emphasize the relevance of income, education, and WMH for cognitive health in old age. This is in line with previous research (Hu *et al.*, 2021; Valenzuela and Sachdev, 2006). Nonetheless, it is important to note that the effect of high education (more than one word more in the WLT) is much larger than the effect of WMH (for 5 cm^3, 0.3 words more in the WLT). Further, our findings do not support Hypothesis 3 (i.e., that people with higher education experience a weaker effect of WMH on cognition). Accordingly, we cannot provide evidence for a cognitive reserve effect of education on cognition (Stern, 2002) in the presence of WMH.

In many previous publications, authors have suggested that people from low socioeconomic groups are exposed to more health-related risk factors, which make them more vulnerable to developing dementia (Deckers *et al.*, 2019; Mortimer and Graves, 1993). Our results confirmed that more individuals from low-income and low-education groups had risk factors (e.g., social isolation, physical inactivity, chronic worrying, diabetes, obesity; Hypothesis 4). However, not all of these were

associated with more WMH in our analyses (hence, not confirming Hypothesis 5). Risk factors that were significantly associated with more WMH in our study were distress and obesity. Our estimates suggest an effect size of about 2 cm^3 of WMH, which is rather large considering that the average WMH in our sample was about 3 cm^3. Obesity is known to be a risk factor for WMH (Kim *et al.*, 2017). The finding on distress is novel. In the literature, we could identify one study that did not find an association between perceived stress and WMH (Aggarwal *et al.*, 2014) and second study that observed that an increase in stressor exposure came with an increase in WMH in old age (Johnson *et al.*, 2017). Our findings add to this by suggesting that subjective feelings of distress such as excessive demands, social tensions, work discontent, and chronic worrying might play a critical role in these observations. This would also match results showing associations between rumination and worrying with accelerated brain aging (Karim *et al.*, 2021). Given the accumulating evidence, further research is necessary to clarify the nature of these associations and underlying mechanisms. In our study, there was a tendency for individuals with low socioeconomic status to report more chronic worrying, excessive demands, and work discontent. It is possible that previously observed associations between socioeconomic status and WMH might be mediated by distress.

The lack of significant findings on education and income in our study might be based on constrained variability in the study's cultural setting. The social security system in Germany is highly developed, so that low-income groups might be experiencing less stress than in other countries. For instance, the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) SCAN study in Baltimore

found that people with low socioeconomic status had poorer WM integrity and greater diffusivity (Shaked *et al.*, 2019). Further, African Americans had, on average, more WMH than Whites (Waldstein *et al.*, 2017) indicating that either the race or the life circumstances of African Americans and/or people with low socioeconomic status might play a role in WM pathology. Since our study included only Europeans, we could observe only the variance of stressful life conditions in this group, which likely was not comparable.

In our study, we also explored differences in deep and periventricular WMH. While findings regarding WMH and periventricular WMH were similar, we found a unique association between deep WMH and obesity. This observation has been made before (Lampe *et al.*, 2019) and the association appears to be stronger in men (Alqarni *et al.*, 2021). Differentiating between the types of WMH may be important to understand the relevance of health-related risk factors for dementia pathology. For instance, more periventricular WMH (but not deep WMH) have been found to be associated with faster cognitive decline (De Groot *et al.*, 2002; van den Heuvel *et al.*, 2006), faster cortical thinning (Seo *et al.*, 2012), and a greater risk for dementia (Prins *et al.*, 2004). Accordingly, the risk factors that were significantly associated with periventricular WMH may be more critical for dementia prevention.

Our study has limitations. First, we used cross-sectional data. Longitudinal observations are necessary to validate hypothesized effects. In a similar vein, it should be noted that we took into account income at the time of the study rather than a history of family income across the lifespan. Second, we used a population-based sample from Germany. Findings in other cultural settings and economic conditions may diverge. Third, we cannot exclude the importance of risk factors other than those assessed in our study. Unknown factors, such as the availability of resources that enable a healthier lifestyle, might underlie observations. Fourth, in this paper, we have conducted a series of statistical analyses increasing the risk of chance findings. We did take measures to minimize this risk, such as working with predefined hypotheses, looking at univariate associations as well as confounder-adjusted models, checking whether a change in r^2 reflects the effect of the variable of interest on the model, and clustering variables in a factor analysis. Further, findings by chance can also be due to sample characteristics for which we cannot correct. Finally, excluding participants with missing data might have led to an unknown bias in our findings. However, we employed advanced neuroimaging methods to detect white matter lesions in the general population and our sample size can be considered large, leading to more robust findings.

In the present investigation, we wanted to gain more knowledge on socioeconomic differences in WMH in middle to late adulthood. Our results could not confirm differences by education or income. However, we observed significant associations of distress as well as obesity with these structural brain abnormalities. WMH are commonly seen in dementia. While the role of obesity in dementia risk is already established and targeted in prevention programs, further research is necessary to evaluate the role of distress in dementia pathology. Worldwide, socioeconomically deprived individuals are likely faced with stressful life circumstances. If this is a risk factor for dementia, then prevention programs should target these circumstances as well. Finally, we would like to emphasize that prevention measures must be implemented as early as in midlife. WMH that has already accumulated due to distress or other risk factors in the 50s or 60s of a person's life will not be reversible later.

Conflict of interest

Nothing to declare.

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Description of authors' roles

FSR: conception and design of the research question, analysis of data, interpretation of data and drafting the first draft of the manuscript.

LL: acquisition and analysis of data, interpretation of data and revised the manuscript.

MG: analysis of data, interpretation of data and revised the manuscript.

FB: interpretation of data and revised the manuscript.

RBa: acquisition of data and revised the manuscript.

RBu: acquisition of data and revised the manuscript.

MLS: acquisition of data and revised the manuscript.

CE: acquisition of data, funding acquisition, and revised the manuscript.

ML: conception and design of the study, funding acquisition, supervision, and revised the manuscript.

JT: conception and design of the study, funding acquisition, supervision, and revised the manuscript.

AV: conception and design of the study, supervision, and revised the manuscript.

SGRH: conception and design of the study, supervision, and revised the manuscript.

AVW: acquisition of data, checking data analysis and interpretation of results, supervision, and revised the manuscript.

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Supplementary material

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Data availability

Anonymized data are not published within this article but can be made available by request from any qualified investigator. Data requests can by made on this website https://www.uniklinikum-leipzig.de/einrichtungen/life/life-forschungszentrum/life-datenportal

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