Differences in impact of current and former shift work on cardiovascular risk factors, carotid atherosclerosis and white matter integrity

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Abstract

Study Objectives: The association of shift work and disrupted circadian rhythm with markers of large artery atherosclerosis and cerebral small vessel disease is uncertain. We aimed to study the separate association of current and former shift work (SW) with these markers.

Methods: We included participants from the population-based Hamburg City Health Study. SW was defined by monthly working hours between 6 p.m. and 7 a.m. containing night shifts for at least 12 months. Cross-sectional data were obtained from structured questionnaires, laboratory analyses, physical examinations, brain MRI, and carotid ultrasound. We performed multivariable regression analysis with carotid intima media thickness (CIMT), and peak-width skeletonized mean diffusivity (PSMD) as dependent variables.

Results: 344 current, 238 former and 7'162 never-shift workers were included. The median age was 60 years for both current and former shift workers, and total duration of SW was comparable for the two groups. Current shift workers were less frequently female (27.3% vs 44.5%; p<0.001), had more frequent hyperlipidemia (31.5% vs 22.3%; p=0.024), and diabetes (16.2% vs 3.2%; p<0.001). After adjustment for age and sex, reduced quality of sleep (β=1.61, p=0.001) and low education (β=2.63, p<0.001) were associated with current but not former SW. Adjusted for age and sex, current SW was associated with higher CIMT (β=0.02, p=0.001) and PSMD (β= 9.06e-06, p=0.006), whereas former SW was not. Adjusted for risk factors, current SW remained associated with PSMD (β=9.91e-06, p=0.006) but not with CIMT.
Conclusions Current SW was associated with CIMT and with PSMD, with the latter association remaining after adjustment for risk factors. Former SW showed no associations with CIMT or PSMD. This may indicate that current shift work is linked with increased neurovascular risk through disrupted circadian rhythms.

Trial Registration Information: The trial was submitted at http://www.clinicaltrials.gov, under NCT03934957 on January 4 2019. The first participant was enrolled in February 2016.

Keywords:

Night shift; Circadian rhythm; Carotid atherosclerosis; White matter integrity; Cerebral small vessel disease.
Introduction

In the EU and US, over 18% of employees are engaged in night shift or rotating shift work\textsuperscript{1,2}. Compared to regular day work, shift work including night shifts has been associated with cardiovascular risk factors, particularly diabetes, hypertension, smoking, and hyperlipidemia as well as with higher rates of myocardial infarction and stroke\textsuperscript{3–6}. Metabolic status and smoking were shown to be the main mediators between shift work and cardiovascular disease while social activity and habits had no influence\textsuperscript{7}. The increase of metabolic cardiovascular risk factors among shift workers is inferred to be due misaligned circadian rhythms given that disrupted circadian rhythms were shown in the same group of shift workers\textsuperscript{8}. The association of shift work with carotid atherosclerosis assessed by carotid intima media thickness (CIMT) as a measure for risk stratification was demonstrated in two studies without adjustment for cardiovascular risk factors\textsuperscript{9,10}.

Shift work’s clinical impact on impairments of mental health were also found to be associated with a disrupted circadian rhythm and did not persist after shift work cessation\textsuperscript{11–13}. They comprise mood disorders and cognitive impairments with a focus on speed and concentration\textsuperscript{11,12}. These kinds of behavioral and cognitive impairments related to circadian rhythm are characteristic for cerebral small vessel disease (CSVD). Of the available magnetic resonance imaging (MRI) markers of CSVD, peak-width skeletonized mean diffusivity (PSMD) is most constantly associated with cognitive impairments\textsuperscript{14}. PSMD is an advanced DTI metric for assessing white matter microstructure. It measures water diffusion variability along major white matter fibre bundles and is particularly sensitive to cerebrovascular abnormalities. The specificity of PSMD’s association with attention, speed and concentration could be shown in patients with CSVD pre-selected by white matter hyperintensities in FLAIR-sequences being the most generally established biomarker\textsuperscript{15}. As a DTI metric for cerebral microstructure, PSMD can capture changes at short intervals caused by alterations in circadian rhythm during shift work\textsuperscript{16,17}. In addition to the cognitive deficits, CSVD is
associated with similar metabolic cardiovascular risk factors as shift work and carotid atherosclerosis.

We hypothesized that current versus former shift work is associated with an increased neurovascular risk assessed by CIMT and PSMD.

Methods

Study design

The Hamburg City Health Study is a single-center, prospective, observational, population-based cohort study of randomly selected residents of the metropolitan region of Hamburg, Germany, between the age of 45 and 74 years. Enrollment started in February 2016. Assessments were comprised of laboratory, physical, carotid ultrasound, and patient-reported measures. Brain MRI was performed in a subgroup of patients. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Hamburg chamber of physicians. Its study design has been published\textsuperscript{18}, and the study is registered at clinicaltrials.gov, NCT03934957. The study was carried out following the Helsinki Declaration of the World Medical Association and according to the principles of good clinical and good scientific practice.

For the current analysis, we included all subjects of the first 10,000 participants with available carotid ultrasound data of common (CCA) and internal carotid arteries (ICA) as well as magnetic resonance imaging in a cross-sectional analysis. All clinical baseline data except for MRI were collected on one examination day. MRI examinations were performed a maximum of three months
after the baseline visit in a separate visit. Questionnaires were filled out in between invitation and baseline visit, during the baseline visit and immediately after the baseline visit.

Shift work and risk factor definitions

Shift work was defined by a reported history for at least 12 months of monthly working hours between 6 p.m. and 7 a.m. containing night shifts. The filter question for pre-selection was: ‘Have you worked in the frame of your employment monthly between 6 p.m. and 7 a.m.?’. This question had to be answered with yes in advance of the 2nd question: ‘When have you worked during your months of shift work: 1) Without night shifts. 2) Containing night shifts. 3) Only during night shifts. 4) I do not want to comment.’ This question had to be answered with 2) or 3) to be included in the analysis as shift worker.

Former shift work was distinguished from current shift work by the last instance of shift work being more than 12 months prior to participation in the study. All other participants were defined as never-shift workers and used as controls in the multivariable regression analyses.

Reduced quality of sleep was defined by a response of ‘On more than half of the days.’, or ‘On almost every day.’ to the question of difficulties falling asleep, staying asleep, or daytime sleepiness having occurred during the last two weeks. Hypertension was defined by intake of antihypertensive medication and/or participant’s statement and/or measured values of arterial blood pressure above 140/90 mmHg. Hyperlipidemia was defined by a LDL/HDL-ratio above 3.5 and/or statin medication. Stage one hypertension with a cut-off value at 130/70 mmHg according to the American Heart Association was not included because its evidence relies on populations younger than the one of this cohort\(^19\). The definition is therefore based on the one of the WHO and European Heart Association\(^20\).
Diabetes was defined by intake of antidiabetic medication and/or participant’s statement and/or fasting blood glucose above 126 mg/dl and/or non fasting blood glucose above 200 mg/dl. Smoking was defined by participant’s statement about current or previous smoking. Education was assessed and classified according to the international classification of education (ISCED) in low, mediocre, and high.

History, physical measures, and laboratory parameters

Demographics and medical history were assessed in interviews by structured questionnaires and blood pressure. Body weight and height were examined during visits of participants in our study center. Systolic and diastolic BP were measured twice on the right arm and the mean was taken for further analyses. Pulse pressure (PP) was calculated as systolic minus diastolic blood pressure.

Lipids (total cholesterol, HDL) were measured by immunoassays using Siemens Atellica®, and Roche Cobas e411®. Concentration of LDL-cholesterol were calculated by the Friedewald-formula.

Carotid ultrasound

Carotid ultrasound was performed using a Siemens SC2000® with a 7.5-MHz linear array transducer. Measurements of ultrasound parameters were made according to recommendations by the European Stroke Organisation. CIMT was measured in a longitudinal view of the left and right common carotid artery 1.0 cm proximal of the carotid bulbus for three times within a distance of 1.0 cm on the far wall and the mean calculated for further analyses.
MRI acquisition

Brain images were obtained on a 3-T Siemens Skyra MRI scanner (Siemens, Erlangen, Germany). The acquisition protocol has been reported previously\(^2^2\). In brief, for diffusion-weighted imaging, 75 axial slices were obtained covering the whole brain with gradients (\(b = 1000 \text{ s/mm}^2\)) applied along 64 noncollinear directions with a repetition time of 8500 ms, echo time of 75 ms, a slice thickness of 2 mm, in-plane resolution of \(2 \times 2 \text{ mm}\), and an anterior–posterior phase-encoding direction, 1 \(b_0\) volume. \(T_1\)-weighted images were obtained using a rapid acquisition gradient-echo (MPRAGE) sequence with repetition time (TR) = 2500 ms, echo time (TE) = 2.12 ms, 256 axial slices, slice thickness (ST) = 0.94 mm, and in-plane resolution (IPR) = 0.83 \(\times\) 0.83 mm.

Peak-width of skeletonized mean diffusivity (PSMD)

Preceding PSMD computation, diffusion-weighted MR images were preprocessed using QSIprep 0.14.2\(^2^3\), A detailed description of all preprocessing steps can be found in the supplementary materials. Next, PSMD was computed following on standard procedures (available at http://www.psmd-marker.com) with the exception of employing ANTs’ SyN registration for normalization of MD maps\(^1^4,2^4\). Put briefly, mean diffusivity (MD) maps were derived by applying a diffusion tensor fit and finally skeletonized maps were derived via the Tract Based Spatial Statistics Procedure (TBSS)\(^2^5\). PSMD was calculated as the difference between the 95\(^{th}\) and 5\(^{th}\) percentile of MD values on the white skeleton in standard (MNI) space.
Statistics

Categorical variables were tested using the chi-squared test and are presented as count and percentage. Continuous variables are presented as median and interquartile range, and a Mann-Whitney U test was performed to test for association. We used multivariable regression models to assess the association of cardiovascular risk factors, and shift work status with CIMT and PSMD. Current and former shift work were separately compared to never-shift work. We fitted two separate models to predict CIMT and PSMD. The first contained each separate factor adjusted for age and sex: CIMT/PSMD ~ Age (Years) + Sex (m/f) + risk factor (binary e.g. no vs. yes, low vs. medium/high education). In the second model, current and former shift work were included as separate independent factors adjusted for the cardiovascular risk factors significantly associated with the outcome in the first model: CIMT: CIMT (mm) ~ Age (Years) + Sex (m/f) + Shift work (never/former/current) + Diabetes mellitus (n/y) + Hypertension (n/y) + Hypercholesteremia (n/y) + Smoking (n/y) + BMI (num) + Education (medium to high/low); PSMD: PSMD ~ Age (Years) + Sex (m/f) + Shift work (never/former/current) + Diabetes mellitus (n/y) + Hypertension (n/y) + Smoking (n/y) + BMI (num).

In a separate multivariable regression model the association of a reduced quality of sleep with current and former shift work was assessed as a binary secondary outcome: Reduced quality of sleep (n/y) ~ Age (Years) + Sex (m/f) + Shift work (never/former/current).

Cardiovascular risk factors were chosen due to the potential association with CIMT and CSVD, based on the literature \(^{26-29}\). The models were built from participants with available data, and participants with missing values were excluded from analyses. Associations were considered significant for p-values <0.05. All statistical analyses were carried out using R-studio statistical package 1.1.453 (http://www.r-project.org/).
Data availability

Deidentified individual participant data will be made available upon reasonable request by the corresponding author. Where necessary, approval of the ethics committee will be obtained in advance.

Results

Characteristics of current and former shift workers

Of the first present cohort, we included 7744 participants with data from carotid ultrasound and data of shift work status (supplemental material Figure I). Of those, 2414 had MRI-sequences for calculation of PSMD\textsuperscript{30}, and 582 participants with of both imaging measures and met the criteria for shift work. The size of the analyzed groups including current, former, and never shift workers varied due to availability of data concerning different cardiovascular risk factors, ranging from 1,691 to 6,226 participants.

The 582 participants with both measures included shift workers with a median age of 62 years, a median CIMT of 0.76 mm [IQR: 0.67,0.85], and a median PSMD of 2.25e-04 mm\textsuperscript{2}/s x 10\textsuperscript{-4} [IQR:2.04e-04,2.50e.04]. A total of 344 were current workers and 238 were former ones with a median shift-work free interval of 26 years [IQR:16.00,34.00] at examination (for details see Table 1). Former and current shift workers differed in sex with 44.5% vs27.3% of women (p<0.001), respectively. Former workers were less likely to have diabetes (3.2%) compared to current workers (16.2%; p<0.001). Former workers were also less likely to have hyperlipidemia (22.3%) compared to current workers.
The median duration of shift work was 12 years [IQR: 5.00, 22.25] in the group of former shift-workers and 7.5 years [IQR: 0.00, 27.50] in the current shift workers.

Association of current and former shift work as independent outcomes with CIMT adjusted for risk factors

Current shift work was associated with higher CIMT (β=0.02, p=0.001) adjusted for age and sex. Former shift work was not associated with CIMT (β=-0.001, p=0.884) after adjustment for age and sex, and length of shift work by trend (p=0.071). After further adjustment for pre-selected cardiovascular risk factors additional to age and sex current shift work ceased to be significantly associated with CIMT (N = 6,226 participants). Of the analyzed cofactors age (β=0.01, p<0.001), female sex (β= -0.03, p<0.001), hypertension (β=0.02, p<0.001), hyperlipidemia (β=0.01, p=0.001), current or previous smoking (β=0.02, p<0.001), and BMI (β= 0.003, p<0.001), remained associated with CIMT, while diabetes and low education ceased to be (Figure 1, supplemental material Table II).

Association of current and former shift work as independent outcomes with PSMD adjusted for risk factors

Current shift work was significantly associated with PSMD (β= 9.06e-06, p=0.006) after adjustment for age and sex, whereas former shift work and length of shift work had no association with PSMD (all analyzed factors are shown in supplemental material Table I).

Current shift work remained associated with PSMD (β=9.91e-06, p=0.006) after the cardiovascular risk factors which had a significant association with PSMD in the prior analyses were included as cofactors in addition to age and sex in the analysis (N = 1,691 participants). The cofactors that contributed to the predictive value for PSMD were age (β=2.32e-06, p<0.001), female sex (β=-7.40e-06, p<0.001), diabetes (β=6.44e-06, p=0.034), and BMI (β=4.66e-07, p=0.024) (Figure 2, supplemental material Table III).
Associations of former and current shift work with cardiovascular risk factors are shown in Table IV in the supplemental material. Table IV comprises the risk factors which were associated with CIMT and PSMD after adjustment for age and sex. For further characterization of former and current shift work we additionally analyzed their association with reduced quality of sleep. After adjustment for age and sex reduced quality of sleep was associated with current (p<0.001) but not with former shift work (supplemental material Table V). Reduced quality of sleep was, however, not associated with CIMT and PSMD and consecutively not included in further multivariable regression models.

Discussion

This study demonstrates that current shift work is associated with CIMT and PSMD, the latter even when adjusted for traditional cardiovascular risk factors. In contrast, former shift work has no influence on these two markers of cerebral small and large vessel disease. Consistently, risk factors are present to a higher degree in current than former shift workers.

The study supports influence shown in literature of a disrupted circadian rhythm on cardiovascular risk factors through their association with current and only to a lesser degree with past shift work. This indicates the relevance of a misaligned circadian rhythm as a mediator of cardiovascular risk and warrants specific assessment in further studies. The mentioned difference between current and former shift work in risk factors and sleep quality suggests that certain factors may improve after cessation of working shifts. The higher prevalence of diabetes in the group of current shift workers indicates a relevant impact of endocrinologic factors among these. This estimation is in line with reported data, which have shown that diabetes is associated with misaligned circadian rhythms. Diabetes was not associated with duration of shift work but the current work at night shifts. Also, the prevalence of diabetes of shift workers has not been
connected to long lasting genetic changes and after cessation of shift work and treatment of overweight, the remission of diabetes could be shown.

In this study CIMT and PSMD were measured as markers of the neurovascular risk. The association of current shift work with CIMT confirms reported results. In the population-based cohort of this study the association relies on cardiovascular risk factors such as hypertension, hyperlipidemia, smoking, and BMI. These results revalue shift works effect on CIMT by indicating its dependence on risk factors. The lack of association of former shift work with CIMT before adjustment for risk factors as well as lower absolute values of former shift workers than of current ones may be explained by increased risk factors due to disrupted circadian rhythms (which was not directly tested here). Statin treatment has been shown to reduce carotid and coronary plaques. This stands in line with the higher percentage of hyperlipidemia among current shift-workers compared to former ones in our cohort.

PSMD was independently associated with current but not with former shift work. The difference measured is half of the values measured between manifestly depressive elderly patients and controls, and between controls and patients with mild cognitive impairment, which had a significantly lower score in Mini-Mental-Status-Examination. The association of current shift work with PSMD supports our hypothesis that impairment of white matter integrity is more pronounced in current shift work. This suggests that current shift work triggers and mediates the impairment of white matter integrity. Due to its association beyond cardiovascular risk factors, we judge shift works effects to be based on a present condition of misaligned circadian rhythms. This inference needs to be assessed by further studies, however.

Clinically, increased PSMD is related to impaired attention and executive cognitive function. A disrupted circadian rhythm or current shift work (but not past shift work) is associated with impairment of these cognitive domains, supporting our results given that these cognitive domains are associated with PSMD. Current shift work was associated with a reduced quality
of sleep, but we have found no direct association between a reduced quality of sleep and PSMD. The increase of PSMD may be preclinical, however, with PSMD being more sensitive than the questionnaires. Recent studies suggest this interpretation. Daytime sleepiness is associated with the integrity of periventricular white matter tracts to the thalamus, and sleep duration is associated with a u-shaped curve of DTI-measured white matter integrity in young healthy adults. The direction of causality, however, remains uncertain, with a bidirectional interaction possible or even likely. PSMDs association with current shift work beyond risk factors, suggests the relevance of other factors like endocrinologic ones. The mentioned difference between current and former shift work in the prevalence of diabetes indicates this assumption as well as PSMDs association with depressive disorders. Previous data have shown that in normal appearing white matter on FLAIR sequences, higher PSMD is associated with development of WMH, and that DTI measures change through cognitive and motor training. Thus changes measured by PSMD are more likely to show dynamics than parenchymal lesions which are part of WMH. Increased PSMD values may regress after normalization of circadian rhythms and recess upon treatment of underlying cardiovascular risk factors such as diabetes or hyperlipidemia.

Limitations of our study are the cross-sectional and monocentric design comprised of mainly citizens of an urban Middle-European area, and the different sex ratios between the compared groups. The underlying employment of women in shift work but similarity in risk associations is reported, however. Overall individual medical and lifestyle factors seem to be most relevant. We also had no information about the type of night shift work to specify the career area, which could include diverse careers such as seamen, medical staff, and filling station attendants. This may also be the cause of the differences in education. Lower education was to a higher percentage present in current shift workers. Taking the same age of former and current shift workers into account, two conclusions seem plausible. Former shift workers have performed their shift work at a younger age as a part of their education, i.e. as medical residents or during military or civil service. Their higher education gave them the ability to reach a position without having to work regularly at
night. Both conclusions suggest differences in the type of work and resources for compensation between former and current shift work and further explain the results.

The missing sub-specification and grouping of shift workers reveals shift work’s impact in general with a broader approach of relevance for occupational prevention. Therefore, our study provides a relevant size recruited from a population-based cohort without narrowly focusing on special characteristics, as previous studies did on steel workers or nurses. Additionally, we used carotid ultrasound as a well-established measure of atherosclerosis and PSMD as a novel marker for white matter integrity to characterize the risk profile both validly and innovative.

In conclusion, these data show that shift workers have a higher burden of cardiovascular risk factors such as BMI, smoking, diabetes, and hyperlipidemia with higher values for current vs former shift workers. Concerning the neurovascular risk profile, current shift work was associated with PSMD and CIMT, the latter of which was explained by increased cardiovascular risk factors. We speculate that a disrupted circadian rhythm in current shift workers impacts white matter integrity through further factors or pathways in a dynamic and partly transient way to increase neurovascular risk.
Disclosures

DLR, ELP, SA, MP, BC, FN, CM, VH, CT, SK, and TZ have nothing to report. CG reports personal fees from Amgen, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi Aventis, Abbott, and Prediction Biosciences outside the submitted work. GT reports receiving consulting fees from Acandis, grant support, and lecture fees from Bayer, lecture fees from Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and Daiichi Sankyo, and consulting fees and lecture fees from Stryker outside the submitted work.


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References


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Figure legends

**Figure 1**: Association of current and former shift work and cardiovascular risk factors with the carotid intima media thickness (CIMT) shown as beta estimates.

**Figure 2**: Association of current and former shift work and cardiovascular risk factors with the peak-width skeletonized mean diffusivity (PSMD) shown as beta estimates.
Table 1: Characteristics of daytime and shift workers

<table>
<thead>
<tr>
<th>Work type</th>
<th>Never shift work</th>
<th>Former shift work</th>
<th>Current shift work</th>
<th>p-value Current vs Former</th>
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<tbody>
<tr>
<td></td>
<td>&lt;1 year (n_max = 7162)</td>
<td>&gt;= 1 year ago (n = 238)</td>
<td>&lt;1 year ago (n = 344)</td>
<td></td>
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<tr>
<td>Duration of shift work y [IQR]</td>
<td>-</td>
<td>12.00 [5.00, 22.25]</td>
<td>7.50 [0.00, 27.50]</td>
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<tr>
<td>Time since shift work y [IQR]</td>
<td>-</td>
<td>26.00 [16.00, 34.00]</td>
<td>0.00 [0.00, 0.00]</td>
<td>&lt;0.001</td>
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<tr>
<td>Age y [IQR]</td>
<td>62.00 [55.00, 69.00]</td>
<td>60.00 [53.00, 68.00]</td>
<td>60.00 [53.00, 67.00]</td>
<td>0.943</td>
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<tr>
<td>Female sex (%)</td>
<td>3795 (53.0)</td>
<td>106 (44.5)</td>
<td>94 (27.3)</td>
<td>&lt;0.001</td>
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<td>CIMT mm [IQR]</td>
<td>0.74 [0.66, 0.84]</td>
<td>0.74 [0.66, 0.83]</td>
<td>0.76 [0.67, 0.87]</td>
<td>0.064</td>
</tr>
<tr>
<td>Diabetes yes (%)</td>
<td>499 (8)</td>
<td>7 (3.2)</td>
<td>51 (16.2)</td>
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<td>Hypertension yes (%)</td>
<td>4386 (64)</td>
<td>145 (64.7)</td>
<td>224 (67.9)</td>
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<td>Hyperlipidemia yes (%)</td>
<td>1520 (23)</td>
<td>50 (22.3)</td>
<td>100 (31.5)</td>
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<td>Current or previous smoking yes (%)</td>
<td>4455 (63)</td>
<td>168 (70.9)</td>
<td>253 (73.5)</td>
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<td>TSH µU/ml [IQR]</td>
<td>1.16 [0.81, 1.65]</td>
<td>1.19 [0.79, 1.69]</td>
<td>1.23 [0.86, 1.67]</td>
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<td>Reduced Quality of sleep yes (%)</td>
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<td>Low education yes (%)</td>
<td>242 (3.0)</td>
<td>6 (2.6)</td>
<td>20 (6.0)</td>
<td>0.088</td>
</tr>
</tbody>
</table>

Abbreviations: CIMT=carotid intima media thickness; PSMD=peak-width skeletonized mean diffusivity; BMI=body mass index; TSH=thyroid stimulating hormone.
Author Contributions

D. Leander Rimmle contributed to the planning of the study, acquisition, analysis and interpretation of the data and drafted the manuscript. Elina L. Petersen contributed to the acquisition and the analysis of data and revised the manuscript for intellectual content. Sarah Affolderbach contributed to the analysis of data and revised the manuscript for intellectual content. Marvin Petersen contributed to the analysis of MRI data and revised the manuscript for intellectual content. Bastian Cheng contributed to the acquisition and analysis of MRI data and revised the manuscript for intellectual content. Carola Mayer contributed to the analysis of MRI data. Felix Nägele contributed to the analysis of MRI data. Volker Harth contributed to the planning of the study. Claudia Terschüren contributed to the planning of the study. Simone Kühn revised the manuscript for intellectual content. Tanja Zeller contributed to the acquisition of biomarker data and revised the manuscript for intellectual content. Christian Gerloff contributed to the planning of the study and revised the manuscript for intellectual content. Götz Thomalla contributed to the planning of the study, interpretation of the data and revised the manuscript for intellectual content.

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Figure 1

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<th>p-value</th>
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<td>BMI</td>
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<td>Low Education</td>
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Figure 2

<table>
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<tr>
<td>Diabetes</td>
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<td>Hypertension</td>
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<td>Smoking</td>
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<tr>
<td>BMI</td>
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β = 0