Sleep Advances, 2024, **5**, zpae056
https://doi.org/10.1093/sleepadvances/zpae056
Advance access publication 31 July 2024
Original Article

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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 (SW) 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 SW with these markers.

Methods: We included participants from the population-based Hamburg City Health Study. SW was defined by monthly working hours between 06:00 pm and 07:00 am containing night shifts for at least 12 months. Cross-sectional data were obtained from structured questionnaires, laboratory analyses, physical examinations, brain magnetic resonance imaging, 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: Three hundred and forty-four current, 238 former, and 7162 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%; $p < .001$), had more frequent hyperlipidemia (31.5% vs. 22.3%; $p = .024$), and diabetes (16.2% vs. 3.2%; $p < .001$). After adjustment for age and sex, reduced quality of sleep (β = 1.61, $p = .001$) and low education (β = 2.63, $p < .001$) were associated with current but not former SW. Adjusted for age and sex, the current SW was associated with higher CIMT (β = 0.02, $p = .001$) and PSMD (β = 9.06e-06, $p = .006$), whereas former SW was not. Adjusted for risk factors, current SW remained associated with PSMD (β = 9.91e-06, $p = .006$) 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 SW 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.

Key words: night shift; circadian rhythm; carotid atherosclerosis; white matter integrity; cerebral small vessel disease

In the EU and United States, over 18% of employees are engaged in night shift or rotating shift work (SW) [1, 2]. Compared to regular day work, SW 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 [3–6]. Metabolic status and smoking were shown to be the main mediators between SW and cardiovascular disease while social activity and habits had no influence [7]. The increase in metabolic cardiovascular risk factors among shift workers is inferred to be due to misaligned circadian rhythms given that disrupted circadian rhythms were shown in the same group of shift workers [8]. The association of SW with carotid atherosclerosis assessed by carotid intima-media thickness (CIMT) as a measure for risk stratification was

Submitted for publication: October 8, 2023; **Revised:** July 11, 2024

demonstrated in two studies without adjustment for cardiovascular risk factors [9, 10].

SW´s clinical impact on impairments of mental health were also found to be associated with a disrupted circadian rhythm and did not persist after SW cessation [11–13]. They comprise mood disorders and cognitive impairments with a focus on speed and concentration [11, 12]. These kinds of behavioral and cognitive impairments related to circadian rhythm are characteristic of 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 [14]. PSMD is an advanced DTI metric for assessing white matter microstructure. It measures water diffusion variability along major white matter fiber 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 preselected by white matter hyperintensities in FLAIR-sequences being the most generally established biomarker [15]. As a DTI metric for cerebral microstructure, PSMD can capture changes at short intervals caused by alterations in circadian rhythm during shift work [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 SW 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 ages 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 [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 participants of the first 10 000 participants with available carotid ultrasound data of common (CCA) and internal carotid arteries as well as MRI 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 between invitation and baseline visit, during the baseline visit, and immediately after the baseline visit.

SW and risk factor definitions

SW was defined by a reported history for at least 12 months of monthly working hours between 06:00 pm and 07:00 am containing night shifts. The filter question for preselection was: `Have you worked in the frame of your employment monthly between 06:00 pm and 07:00 am?´ This question had to be answered with yes in advance of the second question: `When have you worked during your months of SW: (1) Without night shifts, (2) Containing night shifts, (3) Only during night shifts, and (4) I do not want to comment.´ This question had to be answered with (2) or (3) to be included in the analysis as a shift worker.

Former SW was distinguished from current SW by the last instance of SW 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 2 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 cutoff value of 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 nonfasting 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) as 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 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 Organization [21]. CIMT was measured in a longitudinal view of the left and right common carotid artery 1.0 cm proximal of the carotid bulbus three times within a distance of 1.0 cm on the far wall and the mean was 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 [22]. In brief, for diffusion-weighted imaging, 75 axial slices were obtained covering the whole brain with gradients ($b = 1000$ s/mm^2) applied along 64 non-collinear directions with a repetition time of 8500 ms, echo time of 75 ms, a slice thickness of 2 mm, in-plane resolution of 2 × 2 mm, and an anterior–posterior phase-encoding direction, 1 b0 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-plan resolution (IPR) = 0.83 × 0.83 mm.

Peak width of skeletonized mean diffusivity

Preceding peak-width of skeletonized mean diffusivity PSMD computation, diffusion-weighted MR images were preprocessed using QSIprep 0.14.2 [23], A detailed description of all preprocessing steps can be found in Supplementary Materials. Next, PSMD was computed following standard procedures (available at http://www.psmd-marker.com) with the exception of employing *ANTs*' SyN registration for the normalization of MD maps [14]. 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) [24].

PSMD was calculated as the difference between the 95th and 5th 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 SW status with CIMT and PSMD. Current and former SW were separately compared to never-SW. 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 SW 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) + SW (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) + SW (never/former/current) + diabetes mellitus (n/y) + hypertension (n/y) + smoking (n/y) + BMI (num).

In a separate multivariable regression model, the association of reduced quality of sleep with current and former SW was assessed as a binary secondary outcome: Reduced quality of sleep (n/y) ~ age (years) + sex (m/f) + SW (never/former/current). Cardiovascular risk factors were chosen due to the potential association with CIMT and CSVD, based on the literature [25–28]. 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 < .05. All statistical analyses were carried out using R-studio statistical package 1.1.453 (http://www.r-project.org/).

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 SW status (Supplementary Figure I). Of those, 2414 had MRI sequences for calculation of PSMD [29], and 582 participants with both imaging measures met the criteria for SW. The size of the analyzed groups including current, former, and never-shift workers varied due to the availability of data concerning different cardiovascular risk factors, ranging from 1691 to 6226 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^2 /s × 10^{-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% vs. 27.3% of women (p < .001), respectively. Former workers were less likely to have diabetes (3.2%) compared to current workers (16.2%; p < .001). Former workers were also less likely to have hyperlipidemia (22.3%) compared to current workers (31.5%; p = .024). The median duration of SW 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 SW as independent outcomes with CIMT adjusted for risk factors

Current SW was associated with higher CIMT (β = 0.02, p = .001) adjusted for age and sex. Former SW was not associated with CIMT (β = –0.001, p = .884) after adjustment for age and sex, and length of SW by trend (p = .071). After further adjustment for preselected cardiovascular risk factors additional to age and sex current SW ceased to be significantly associated with CIMT (N = 6226 participants). Of the analyzed cofactors age (β = 0.01, p < .001), female sex (β = –0.03, p < .001), hypertension (β = 0.02, p < .001), hyperlipidemia (β = 0.01, p = .001), current or previous smoking (β = 0.02, p < .001), and BMI (β = 0.003, p < .001), remained associated with CIMT, while diabetes and low education ceased to be (**Figure 1**, Supplementary Table II).

Association of current and former SW as independent outcomes with PSMD adjusted for risk factors.

Current SW was significantly associated with PSMD (β = 9.06e-06, p = .006) after adjustment for age and sex, whereas former SW and length of SW had no association with PSMD (all analyzed factors are shown in Supplementary Table I).

Current SW remained associated with PSMD (β = 9.91e-06, p = .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 = 1691 participants). The cofactors that contributed to the predictive value for PSMD were age (β = 2.32e-06, p < .001), female sex (β = –7.40e-06, p < .001), diabetes (β = 6.44e-06, p = .034), and BMI (β = 4.66e-07, p = .024; **Figure 2**, Supplementary Table III).

Associations of former and current SW with cardiovascular risk factors are shown in Supplementary Table IV. 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 SW 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 < .001) but not with former SW (Supplementary 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 SW is associated with CIMT and PSMD, the latter even when adjusted for traditional cardiovascular risk factors. In contrast, former SW has no influence on these two markers of cerebral small and large vessel disease.

Table 1. Characteristics of Daytime and Shift Workers

Work type	Never-shift work	Former shift work	Current shift work	*P*-value current vs former
	<1 year (nmax = 7162)	≥1 year ago (*n* = 238)	<1 year ago (*n* = 344)	
Duration of shift work y [IQR]	—	12.00 [5.00, 22.25]	7.50 [0.00, 27.50]	.061
Time since shift work y [IQR]	—	26.00 [16.00, 34.00]	0.00 [0.00, 0.00]	<.001
Age y [IQR]	62.00 [55.00, 69.00]	60.00 [53.00, 68.00]	60.00 [53.00, 67.00]	.943
Female sex (%)	3795 (53.0)	106 (44.5)	94 (27.3)	<.001
CIMT mm [IQR]	0.74 [0.66, 0.84]	0.74 [0.66, 0.83]	0.76 [0.67, 0.87]	.064
PSMD mm^2/s [IQR]	2.22e-04 [2.03e-04, 2.45e-04]	2.17e-04 [2.03e-04, 2.33e-04]	2.28e-04 [2.05e-04, 2.17e-04]	.160
Diabetes yes (%)	499 (8)	7 (3.2)	51 (16.2)	<.001
Hypertension yes (%)	4386 (64)	145 (64.7)	224 (67.9)	.497
Hyperlipidemia yes (%)	1520 (23)	50 (22.3)	100 (31.5)	.024
Current or previous smoking yes (%)	4455 (63)	168 (70.9)	253 (73.5)	.541
BMI kg/m^2 [IQR]	25.87 [23.40, 28.90]	26.95 [24.16, 29.66]	27.37 [24.57, 30.46]	.173
TSH µU/mL [IQR]	1.16 [0.81, 1.65]	1.19 [0.79, 1.69]	1.23 [0.86, 1.67]	.498
Reduced quality of sleep yes (%)	4087 (62)	143 (63.0)	224 (67.3)	.340
Low education yes (%)	242 (3.0)	6 (2.6)	20 (6.0)	.088

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

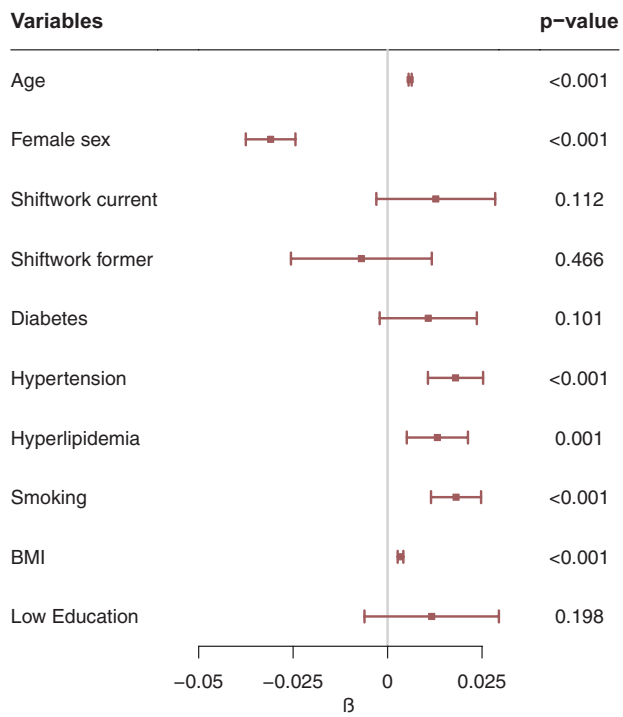

Figure 1. Association of current and former shift work and cardiovascular risk factors with the carotid intima-media thickness (CIMT) are shown as beta estimates.

Consistently, risk factors are present to a higher degree in current than former shift workers.

The study supports the influence shown in the literature of a disrupted circadian rhythm on cardiovascular risk factors through their association with current and only to a lesser degree with past SW. 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 SW 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 [3]. Diabetes was not associated with the duration of SW but with the current work at night shifts [30]. Also, the prevalence of diabetes among shift workers has not been connected to long-lasting genetic changes and after cessation of SW and treatment of over-weight, the remission of diabetes could be shown [31].

In this study, CIMT and PSMD were measured as markers of the neurovascular risk. The association of the current SW with CIMT confirms the reported results [9, 10]. 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 SWs effect on CIMT by indicating its dependence on risk factors. The lack of association of former SW 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 [32, 33]. 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 the current but not with the former SW. The difference measured is half of the values measured between manifestly depressive elderly patients and controls [34], and between controls and patients with mild cognitive impairment, which had a significantly lower score in Mini-Mental-Status-Examination [14]. The association of current

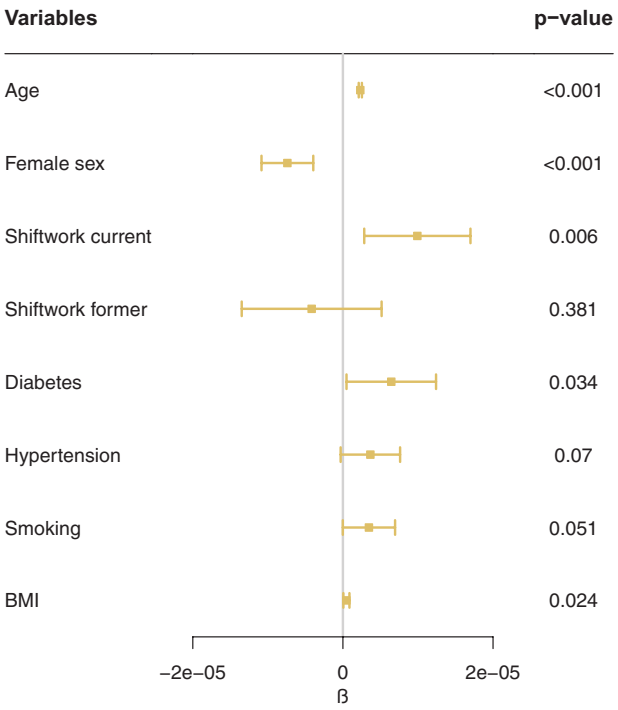

Figure 2. Association of current and former shift work and cardiovascular risk factors with the peak-width skeletonized mean diffusivity (PSMD) shown as beta estimates.

SW with PSMD supports our hypothesis that impairment of white matter integrity is more pronounced in current SW. This suggests that current SW triggers and mediates the impairment of white matter integrity. Due to its association with cardiovascular risk factors, we judge SWs 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 SW (but not past SW) is associated with impairment of these cognitive domains [11, 12], supporting our results given that these cognitive domains are associated with PSMD [14, 15, 35]. Current SW 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 in 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 [36], and sleep duration is associated with a u-shaped curve of DTI-measured white matter integrity in young healthy adults [37]. The direction of causality, however, remains uncertain, with a bidirectional interaction possible or even likely [38]. PSMDs association with current SW beyond risk factors, suggests the relevance of other factors like endocrinologic ones. The mentioned difference between current and former SW in the prevalence of diabetes indicates this assumption as well as PSMDs association with depressive disorders [34]. Previous data have shown that in normal-appearing white matter on FLAIR sequences, higher PSMD is associated with the development of WMH [39], and that DTI measures change through cognitive and motor training [16, 17]. 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 SW but similarity in risk associations is reported, however [40]. Overall individual medical and lifestyle factors seem to be most relevant [41, 42]. We also had no information about the type of night SW 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 SW 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 SW and further explain the results.

The missing sub-specification and grouping of shift workers reveal SW´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 impact 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 SW 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.

Supplementary Material

Supplementary material is available at *SLEEP Advances* online.

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.

Funding

This work was financially supported by the University Medical Center Hamburg-Eppendorf. No external funding has been received.

Acknowledgments

We thank Cina Joseph Nattenmüller for revising the language and style.

Disclosure Statement

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. The manuscript is published on a preprint server at https://ssrn.com/abstract=4362131 or https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4362131.

Author Contributions

David Rimmele (Conceptualization [lead], Formal analysis [equal], Methodology [equal], Resources [equal], Visualization [equal], Writing—original draft [lead]), Elina Petersen (Data curation [lead], Formal analysis [equal], Investigation [equal], Methodology [equal], Resources [lead], Software [lead]), Sarah Affolderbach (Investigation [equal], Writing—review & editing [equal]), Marvin Petersen (Data curation [supporting], Formal analysis [supporting], Methodology [supporting], Resources [supporting], Writing—review & editing [supporting]), Bastian Cheng (Data curation [supporting], Project administration [supporting], Resources [supporting], Software [supporting]), Carola Mayer (Data curation [supporting], Resources [supporting], Software [supporting]), Felix Nägele (Data curation [supporting], Formal analysis [supporting], Resources [supporting], Writing—review & editing [supporting]), Volker Harth (Project administration [supporting], Writing—review & editing [supporting]), Claudia Terschüren (Methodology [supporting], Project administration [supporting]), Simone Kühn (Project administration [supporting], Writing—review & editing [supporting]), Tanja Zeller (Project administration [supporting], Resources [supporting], Writing—review & editing [supporting]), Christian Gerloff (Supervision [supporting], Writing—review & editing [supporting]), and Götz Thomalla (Conceptualization [supporting], Data curation [supporting], Funding acquisition [lead], Methodology [supporting], Project administration [lead], Resources [supporting], Supervision [lead], Writing—review & editing [lead]).

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