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SHORT REPORT

Physical activity may protect myelin via modulation of high-density lipoprotein

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Abstract

INTRODUCTION: Physical activity is associated with greater myelin content in older individuals with cerebral small vessel disease (CSVD), a condition marked by demyelination. However, potential mechanisms underlying this relationship remain understudied.

METHODS: We assessed cross-sectionally whether serum high-density lipoprotein (HDL), low-density lipoprotein, and triglycerides moderated the association between physical activity and in vivo myelin in older individuals with CSVD and mild cognitive impairment.

RESULTS: We included 81 highly educated, community-dwelling older individuals (mean age 74.57 years), 64% of whom were female. Regression models revealed that HDL levels significantly moderated the relationship between physical activity and myelin in the sagittal stratum, wherein higher physical activity levels were linked to greater myelin levels for those with average or high HDL (standardized B [95% CI] = 0.289 [0.087 to 0.491], $p = 0.006$).

DISCUSSION: Physical activity may promote myelin health partly through HDL. Data from longitudinal studies are needed to confirm our findings.

KEYWORDS
aging, cerebrovascular health, exercise, fitness, lipids, neurodegeneration, white matter

Highlights

- Myelin loss is common in individuals with cerebral small vessel disease (CSVD).
- Physical activity was positively associated with myelin in older adults with CSVD.
- High-density lipoproteins (HDL) levels were also positively related to myelin.
- Physical activity effects on myelin were moderated by HDL levels.

1 | BACKGROUND

Myelination in the cerebral white matter is essential for effective and rapid transmission of neuronal activity.[1] Age-related and pathological disruption of the myelin sheath often results in cognitive and functional decline.[1] Recently, Faulkner and colleagues[2] reported that cardiorespiratory fitness, a measure highly associated with physical activity, is positively associated with myelin content in a cohort of individuals aged 22 to 94 years. We have also shown[3] that higher physical activity levels predicted higher myelin content in white matter tracts involved in higher-order cognitive function among individuals living with cerebral small vessel disease (CSVD) and mild cognitive impairment (MCI), a population presenting with high degree demyelination and white matter hyperintensity (WMH) burden.[4,5] These findings collectively suggest that being physically active is beneficial for myelin integrity across young and older individuals, including those at greater risk of dementia.[2,3]Although the mechanisms explaining these associations remain underexplored, it is plausible that the positive effects of physical activity on myelin are influenced by high-density lipoprotein (HDL) levels, a type of cholesterol involved in remyelination processes within the brain.[6] It is also plausible that physical activity affects myelin via regulation of low-density lipoprotein (LDL) and triglycerides, which are involved in the pathological mechanisms underlying the etiology of cerebrovascular diseases.[4,7] To address these hypotheses, we assessed whether serum levels of HDL, LDL, and triglycerides play a role in the association between physical activity and myelin in older individuals living with CSVD and MCI.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed existing literature using traditional sources (e.g., PubMed) on how physical activity, exercise, cardiometabolic health, and other lifestyle factors influence myelin in individuals with cerebral small vessel disease (CSVD). Despite myelin loss being a feature of CSVD, there is a dearth of research assessing the influence of lifestyle factors on myelin in this population.
2. **Interpretation**: In this cross-sectional analysis, physical activity and high-density lipoprotein (HDL) levels were positively related to myelin content in older individuals with CSVD. However, HDL levels moderated the associations between physical activity and myelin. The moderating effect suggests that HDL may play an important role in the how physical activity preserves or promotes myelination within the cerebral white matter.
3. **Future directions**: Further studies are needed to examine whether physical activity interventions impact myelin levels in individuals with CSVD and determine whether observed effects are influenced by changes in HDL levels.

2 | METHODS

2.1 | Study design

We conducted a cross-sectional analysis including data from 81 community-dwelling older individuals living with CSVD and MCI. Participants were recruited as a part of a randomized controlled trial, described previously.[8] This study reports on baseline data from the trial. Included participants had no significant functional impairment and no prior diagnosis of dementia. All demographic, neuroimaging, physical activity, and biomarker data included in the study were collected within 2 weeks of each other. Participants were recruited from The University of British Columbia Hospital Clinic for Alzheimer's Disease and Related Disorders, the Vancouver General Hospital (VGH) affiliated clinics, or from advertisements placed in the community (newspaper advertisements, flyers, and brochures). Individuals who were interested in participating were invited for a screening and consent session. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[9]

2.2 | Eligibility criteria

We included individuals aged 50 years or older who: (1) had evidence of CSVD defined as the presence of WMH on magnetic resonance imaging (MRI) or computer tomography scans, identified by expert assessors (W.A., E.D.) using the Fazekas Scale (score $\geq$1)[10]; (2) had MCI, without dementia, defined as a score $<$ 26 Montreal Cognitive Assessment (MoCA)[11] and a score $\geq$20 on the Mini-Mental State Examination (MMSE),[12] and (3) lived independently in the community (i.e., no significant functional limitations). The MoCA is a highly sensitive and specific screening tool for MCI in the overall population of older adults.[11] A MoCA score of $<$ 26 has 87% sensitivity and 63% specificity to detect MCI in older adults with cerebrovascular disease.[13] The MMSE score of $\geq$20 was used to reduce the possibility of including individuals with undiagnosed dementia.[12]

Participants were excluded based on the following criteria: (1) a history of dementia or any other neurodegenerative conditions (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis); (2) were taking medications that may negatively affect cognitive function such as anticholinergics, including agents with pronounced anticholinergic properties (e.g., amitriptyline), major tranquilizers (typical and atypical antipsychotics), and anticonvulsants (e.g., gabapentin, valproic acid); (3) were participating in a clinical drug trial; and (4) had contraindications to MRI scanning.

2.3 | Ethics approval

The study was approved by The University of British Columbia's Clinical Research Ethics Board (H15-00972) and the Vancouver Coastal Health Research Institute (V15-00972). All participants provided

written informed consent in accordance with the Declaration of Helsinki prior to study enrollment.

2.4 | Demographic and clinical characteristics

Global cognitive function and status were ascertained using the MMSE[12] and the MoCA.[11] Participant demographic baseline data included age, sex, weight, height, body mass index (BMI), and education. Clinical information was assessed via medical history using the functional comorbidity index, a measure used estimate the degree of comorbidity associated with physical functioning.[14]

2.5 | Physical activity levels

We used the Physical Activity Scale for the Elderly (PASE)[15] to assess current physical activity levels in our sample. The PASE is a brief paper-based questionnaire used to estimate physical activity from activities commonly performed by older individuals including household, leisure, and occupational activities. The questionnaire accounts for frequency, duration, and level of intensity of each activity and the total score ranges from 0 to 400 or higher. Scores ≤50 suggest limited physical activity, while 50.1-200 indicates low, and ≥200 indicates high physical activity levels.[16] Overall, the PASE is a brief, valid, and reliable scale to assess physical activity in community-dwelling older individuals with acceptable construct validity compared with other measures.[17]

2.6 | Imaging data collection

We collected MRI data at the UBC MRI Research Centre on either a 3T Philips Achieva (n = 46) or 3T Philips Elition (n = 35) MRI scanner using a sensitivity encoding head coil and parallel imaging. Whole brain myelin water imaging was performed using a 48-echo 3D gradient and spin echo (GRASE) sequence for T_2 measurement with the following parameters: repetition time (TR) = 1073 ms, echo time (TE) = 8, 16, 24…384 ms for a total of 48 echoes, flip angle $\theta = 90°$, field of view (FOV) = 230 × 190 × 100 mm^3, slice oversampling factor = 1.3, SENSE = 2, transverse orientation, acquired slices = 20, acquired voxel = 0.99 × 2.04 × 5 mm^3, reconstructed slices = 40, reconstructed voxel = 0.96 × 0.95 × 2.5 mm^3.

3D T_1-weighted anatomical scans were collected for registrations and computation of volumetric data (TR = 1800 ms, TE = 3.5 ms, TI = 800 ms, flip angle $\theta = 8°$, FOV = 256 × 200 × 170 mm^3, transverse orientation, 170 slices, acquired and reconstructed voxel = 1 × 1 × 1 mm^3). In addition, 3D T_2-weighted scans (TR = 2500 ms, TE = 363 ms, flip angle $\theta = 90°$, FOV = 256 × 160 × 256 mm^3, sagittal orientation, 200 slices, acquired voxel = 1 × 1 × 1.6mm^3, reconstructed voxel = 0.8 × 0.8 × 0.8 mm^3), and PD-weighted scans (TR = 3000 ms, TE = 30 ms, flip angle $\theta = 90°$, FOV = 250 × 170 × 250 mm^3, sagittal orientation, 170 slices, acquired voxel = 0.99 × 1 × 1 mm^3, reconstructed voxel = 0.98 × 0.98 × 1 mm^3) were collected for WMH lesion assessment and quantification.

2.7 | Imaging data preprocessing

Myelin content was indexed as myelin water fraction (MWF) in the current study. Voxel-wise T_2-weighted distributions were calculated from GRASE images using the DECAES software (version 0.5.0).[18] Myelin water fraction maps were derived from the fraction of T_2-weighted signal within 10 and < 40 ms over the entire T_2-weighted distribution. The T_2-weighted signal captured within this time window represent water molecules trapped within the lipid bilayers of the myelin membrane, and serves as a surrogate measure of myelin content.[19] Higher MWF is indicative of greater myelination within the white matter with MWF signal showing excellent correlation with histology markers of myelin.[19] We measured myelin in 16 regions of interest (ROIs) within the Johns Hopkins University white matter atlas. These ROIs were derived from a highly accurate standard template created at the UBC MRI Research Centre by Dvorak and colleagues.[20] Prior to data extraction, we performed a series of linear and non-linear registrations to bring the ROIs and myelin maps to participant's T_1-weighted space.[20] Preprocessing and registration steps included brain extraction via HD-BET (version 1.0.0),[21] inhomogeneity corrections and within-participant and participant-to-template registrations via ANTs (version 2.4.2).[22] Finally, mean MWF values were extracted from each ROI in the participants' T_1-weighted space using FSL (version 6.0.6).[23]

We quantified WMH volume from T_2- and PD-weighted scans following previous robust semi-automated segmentation methods.[24] A trained expert first identified and digitally marked the lesions with seed points on preprocessed, co-registered T_2- and PD-weighted scans. The seed points were then processed by a customized Parzen windows classifier to estimate the intensity distribution of each lesion.[24] From this method, binary lesion masks were generated and visually inspected to ensure segmentation accuracy. Edits were applied to fix any obvious segmentation errors during visual quality assurance by one of the investigators. The segmented lesions were quantified as WMH volumes in cubic centimeters (cm^3) and log-transformed due to skewness. Additionally, T_2- and PD-weighted scans were qualitatively assessed using the Fazekas Scale[10] by two trained experts (W.A., E.D.) to confirm study eligibility.

We estimated total intracranial volume (ICV) from T_1-weighted images processed in the *recon-all* pipeline implemented in FreeSurfer (version 7.1.1), developed at the Martinos Centre for Biomedical Imaging by the Laboratory for Computational Neuroimaging.[25] The ICV data were used account for differences in brain size in our analysis.

2.8 | Bloodwork

We conducted blood draws in the Vancouver Coastal Health Research Institute's Clinical Research Unit at VGH). Fasting blood samples were collected in the morning by standard venipuncture and were processed

and stored at -80°C as plasma, serum, and whole blood. Serum levels of total cholesterol, triglycerides, HDL, and LDL were processed using a standard blood analysis protocol at VGH.[8]

2.9 | Statistical analyses

We performed multiple regression assessing the relationship between physical activity, lipids, and myelin. The association between physical activity with HDL, LDL, and triglycerides were tested in individual models adjusting for age, sex, education, BMI, and total cholesterol. We assessed the relationship between physical activity and myelin content across three ROIs that we had previously shown a significant effect.[3] These models were adjusted for the influence age, sex, education, BMI, ICV, and WMH lesions. For models were HDL, LDL, and triglycerides were predictors of myelin, we explored the associations of these measures with myelin content across 16 ROIs.[20] These models were adjusted for age, sex, education, BMI, ICV, WMH lesions, total cholesterol, and were corrected for multiple comparisons using the false discovery rate (FDR) method.[26] Moderation was tested by including an interaction term between physical activity and the moderator variable of interest in the models (e.g., physical activity × HDL). We then performed simple slope analysis to assess the direction of the moderating effect in significant models by stratifying the moderating variable at the sample mean and 1 SD above and below the mean. We repeated all myelin content analyses after removing WMH voxels overlapping with the ROIs, referred to as "normal-appearing" white matter myelin analysis. For all models we further tested whether including use of medication for hyperlipidemia (yes or no), history of self-reported hypertension (yes or no), and diabetes (yes or no) as additional covariates would change the original findings.

Across all models, two-sided p values < 0.05 were considered statistically significant. Analyses were performed in R (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria) as implemented in RStudio (version 2024.4.2.764, RStudio Team, Posit Software, PBC, Boston, MA). We used the packages broom (version 1.0.6), emmeans (version 1.10.2), ggefects (version 1.7.0), knitr (version 1.47), performance (version 0.12.0), tableone (version 0.13.2), and tidyverse (version 2.0.0).

3 | RESULTS

We phone-screened 573 potentially eligible individuals, 179 passed initial screening and were invited to an in-person visit. Of these, 16 were not interested in participating in the study, 6 did not have visible WMH lesions (Fazekas score = 0), 64 were excluded as they did not meet other study eligibility criteria. Our recruited sample included 93 participants; however, 12 individuals were excluded prior to analysis because of data missingness. Thus, our final models included data from 81 individuals with complete physical activity, bloodwork, and MRI data. Demographic and clinical characteristics are presented on Table 1. Our sample consisted mostly of females, highly educated,

TABLE 1 Demographic and clinical characteristics of study participants.

Variables[a]	N = 81
Age, y	74.57 (5.80)
Females, *n* (%)	52 (64.2)
Education, *n* (%)	
High school or less	13 (16.0)
Some university	17 (21.0)
Trades or professional certificate	6 (7.4)
University degree	45 (55.6)
MMSE, score	27.30 (1.97)
MoCA, score	21.26 (3.36)
Height, cm	163.24 (10.30)
Weight, kg	73.91 (15.71)
BMI, kg/m^2	27.68 (5.26)
Functional comorbidity index, median (IQR), score[b]	3.50 (2.00, 5.00)
Diabetes, Yes, *n* (%)[b]	12 (15.0)
Hypertension, Yes, *n* (%)[b]	33 (41.2)
Hyperlipidemia medication, Yes, *n* (%)	35 (43.2)
Lipids, mmol/L	
Total cholesterol	4.90 (1.11)
Triglycerides	1.25 (0.59)
High-density lipoprotein cholesterol	1.67 (0.44)
Low-density lipoprotein cholesterol	2.66 (1.00)
Myelin water fraction, %	
All regions-of-interest	12.12 (1.67)
Cingulum	7.03 (1.74)
Corona radiata, anterior	8.27 (1.70)
Corona radiata, posterior	12.07 (1.72)
Corona radiata, superior	12.95 (2.08)
Corpus callosum, body	11.21 (1.65)
Corpus callosum, genu	9.53 (2.00)
Corpus callosum, splenium	14.27 (2.00)
External capsule	5.33 (1.26)
Fornix	14.46 (2.92)
Internal capsule, anterior	11.80 (2.38)
Internal capsule, posterior	18.07 (2.34)
Internal capsule, retrolenticular	12.99 (1.89)
Posterior thalamic radiation	12.88 (1.65)
Sagittal stratum	11.42 (2.09)
Estimated intracranial volume, cm^3	1536.73 (166.19)
White matter hyperintensities	
Volume, median (IQR), cm^3	6.16 (4.00, 12.43)
Volume, log-transformed	0.84 (0.41)
Fazekas Scale, median (IQR), score	1.00 (1.00, 2.00)

(Continues)

TABLE 1 (Continued)

Variables[a]	N = 81
PASE, score	109.79 (49.15)

Abbreviations: BMI, body mass index; FCI, Functional comorbidity index; IQR, interquartile range; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PASE, Physical Activity Scale for the Elderly.

[a]Data presented as mean (SD), unless otherwise stated.

[b]Data not collected for one participant ($n = 80$).

and living with several comorbidities. WMH lesion load was (median [interquartile range]) 6.16 cm^3 (4.00, 12.43) and Fazekas score ranged from 1 to 3. The PASE score was (mean [standard deviation]) 109.79 (49.15) indicating low physical activity levels.

Regression models showed that physical activity was positively associated with serum HDL (standardized B [95% confidence interval {CI}] = 0.253 [0.037 to 0.470], $p = 0.022$) but was not associated with LDL (standardized B [95% CI] = -0.075 [-0.154 to 0.003], $p = 0.061$) or triglycerides (standardized B [95% CI] = -0.097, [-0.320 to 0.127], $p = 0.204$). Additional adjustment for history of hypertension or diabetes, and use of medication for hyperlipidemia did not change these findings (see Table S1)

Physical activity was also positively associated with myelin content in regions in which we had previous reported this effect,[3] namely the anterior corona radiata (standardized B [95% CI] = 0.225 [0.004 to 0.445], $p = 0.046$), genu of the corpus callosum (standardized B [95% CI] = 0.261 [0.040 to 0.482], $p = 0.022$), and sagittal stratum (standardized B [95% CI] = 0.331 [0.114 to 0.549], $p = 0.003$). Additional adjustment for history of hypertension or diabetes, and use of medication for hyperlipidemia did not change these findings (see Table S2)

We report novel findings that higher levels of HDL were associated with higher myelin content after FDR correction in the body of the corpus callosum (standardized B [95% CI] = 0.344 [0.096 to 0.592], $p = 0.007$, q = 0.037), posterior corona radiata (standardized B [95% CI] = 0.317 [0.097 to 0.537], $p = 0.005$, q = 0.037), superior corona radiata (standardized B [95% CI] = 0.324 [0.095 to 0.552], $p = 0.006$, q = 0.037), and the superior longitudinal fasciculus (standardized B [95% CI] = 0.284 [0.072 to 0.495], $p = 0.009$, q = 0.037). These associations are illustrated on Figure 1. Additional adjustment for history of hypertension or diabetes, and use of medication for hyperlipidemia did not change these findings (see Table S3), No associations were observed between LDL or triglycerides with myelin after FDR correction.

To probe whether HDL moderated the relationship between physical activity levels and myelin, we conducted an exploratory analysis by entering physical activity × HDL as an interaction term in our regression models. We focused on the three ROIs showing an effect of physical activity of myelin. We found that HDL significantly moderated the effect of physical activity on myelin content in the sagittal stratum (standardized B [95% CI] = 0.289 [0.087 to 0.491], $p = 0.006$), wherein higher physical activity levels were associated with higher myelin levels for individuals with average or high HDL levels but not low HDL levels (see Figure 2). Additional adjustment for history of hypertension or diabetes, and use of medication for hyperlipidemia did not change these findings (see Table S4).

Our sensitivity analysis of normal-appearing white matter ROIs revealed similar findings across all models that included myelin as an outcome (see Tables S5-S7)

4 | DISCUSSION

Findings from pre-clinical, animal studies show that increasing physical activity via exercise improves myelin health.[27] Evidence is still scarce in humans; however, cross-sectional findings such as reported by Faulkner and colleagues[2] suggest that higher levels of cardiorespiratory fitness are associated with higher myelin content in otherwise healthy young and older individuals. Our previous results,[3] reproduced in this report, also indicated that higher physical activity levels are associated with higher myelin content in individuals living with CSVD, a disease hallmarked by white matter pathology culminating in myelin loss.[4]

Building on these findings, we report higher physical activity levels are associated with higher myelin content in individuals with average or high, but not low, HDL levels. This suggests that HDL is not only associated with higher myelin content but may also moderate the impact of physical activity on myelin. Considering our relatively small sample size, the moderating effect was primarily confined to the sagittal stratum, a region wherein physical activity was shown to have the strongest effect in our sample. The sagittal stratum is a complex and multilayered white matter bundle involved in visuospatial cognition, language, and semantic processing.[28,29] Whether these effects reflect improved cognition or physical function remains to be explored.

A potential mechanism to support the moderating role of peripheral HDL levels in the physical activity-myelin relationship could be via modulation of apolipoprotein A-1. As a main protein component of HDL,[30] apolipoprotein A-1 can enter the brain via the blood–cerebral spinal fluid barrier[30] wherein it has neuroprotective effects. For instance, apolipoprotein A-1 mimetics enhance cholesterol efflux and increase clearance of myelin-derived lipid debris by macrophages and microglia, which facilitate remyelination in the rodent brain.[6] Exercise is also implicated in remyelination via clearance of myelin-derived lipid debris,[27] suggesting overlapping biological pathways. Notably, physical activity interventions can increase peripheral levels of apolipoprotein A-1 in humans.[31]

We found that HDL was independently associated with myelin content in the body of the corpus callosum, posterior corona radiata, superior corona radiata, and superior longitudinal fasciculus. One possible explanation is that the corona radiata (superior and posterior) and the superior longitudinal fasciculus are located within regions commonly presenting with WMH,[32] wherein there may be a greater demand for myelin maintenance or repair via HDL/apolipoprotrein A-1. Thus, higher levels of HDL would facilitate myelin repair or maintenance, rendering positive associations between peripheral

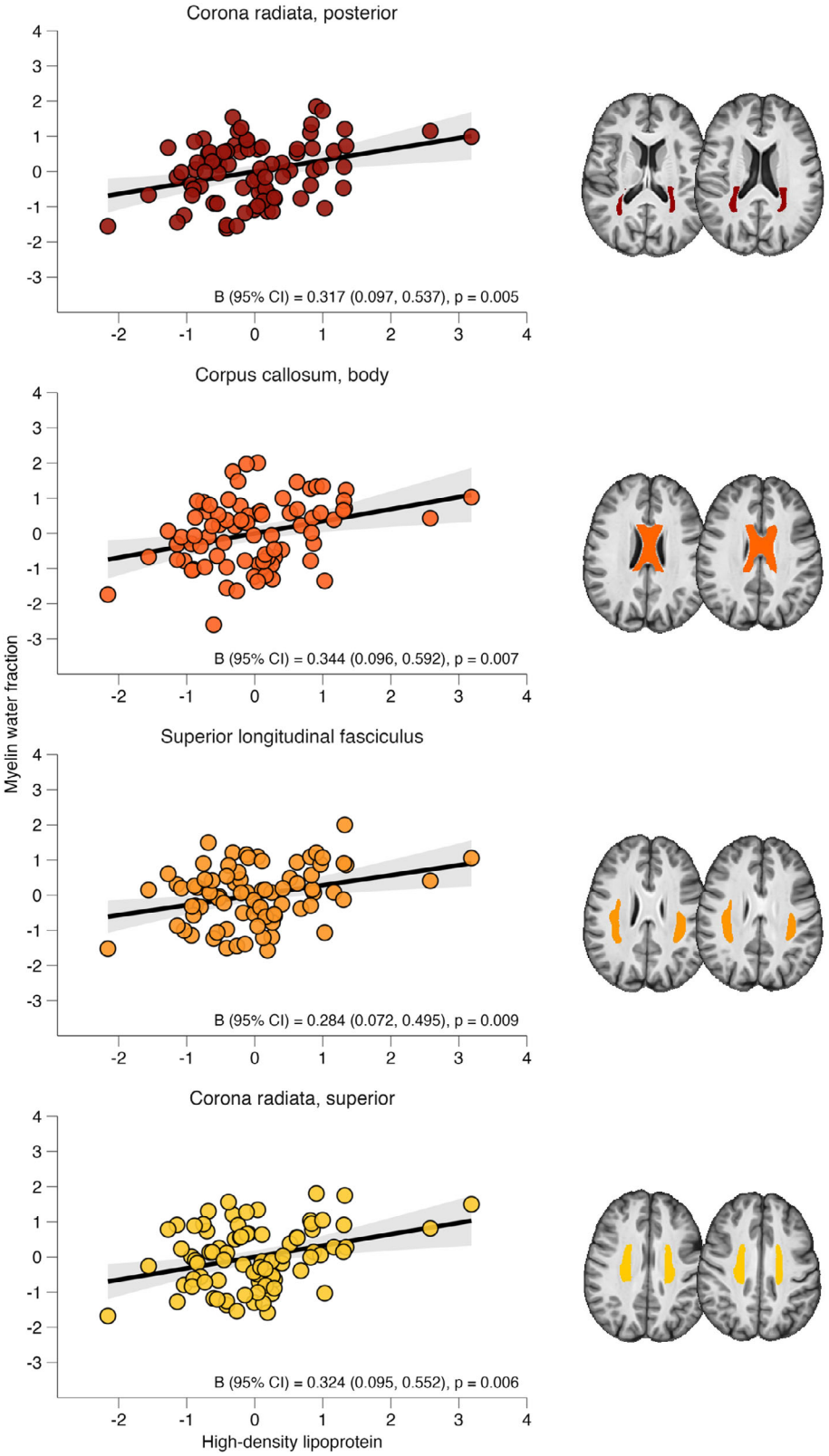

FIGURE 1 High-density lipoprotein levels are positively associated myelin content across several white matter regions. Data were converted to z-scores prior to analysis. Data displayed as model residuals accounting for the influence of age, sex, education, body mass index, total cholesterol, estimated total intracranial volume, and whole-brain white matter lesions. Relevant regions of interest are depicted within a standard magnetic rosonance imaging template used in the study.[20]

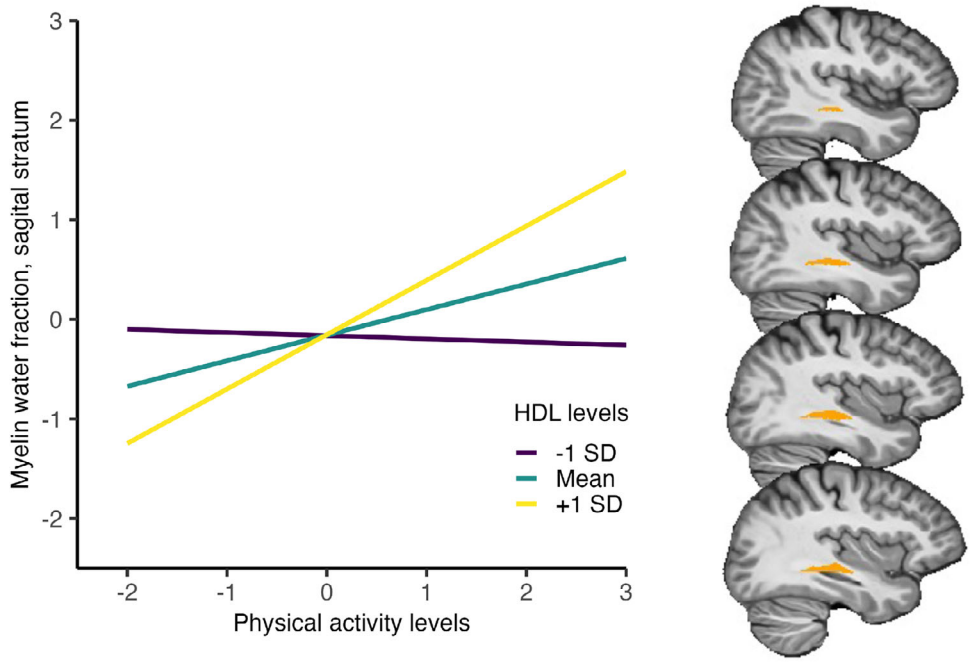

FIGURE 2 High-density lipoprotein (HDL) levels moderate the association between physical activity and myelin in the sagittal stratum such that higher physical activity levels are associated with higher myelin content in individuals with average or high HDL levels, but not in those with low HDL levels. Data were converted to z-scores prior to analysis. Associations are adjusted for age, sex, education, body mass index, total cholesterol, estimated total intracranial volume, and whole-brain white matter lesions. The sagittal stratum is depicted in orange within a standard magnetic resonance imaging template used in the study.[20]

levels of HDL with myelin content in these regions. Notably, although normal-appearing white matter surrounding WMH is affected by the underlying vascular pathologies,[33] myelin levels remain stable in perilesional regions.[34] This may explain why after removing WMH voxels from the white matter ROIs, significant associations between HDL and myelin content persisted. Regarding the body of the corpus callosum, previous evidence indicates that HDL is positively associated with white matter microstructural integrity in this region,[35] which aligns with our finding. However, other mechanisms must be at play to explain the associations considering that this region is less often impacted by WMH.[32] This remains be explored future research.

Our study presents some important limitations. Physical activity was measured subjectively via the PASE, which computes a total physical activity score considering household, leisure, and occupation activities; thus, we are not able to accurately determine which types of physical activity or which components (e.g., frequence, intensity, and duration) would be more strongly related to HDL and myelin content. Lastly, given the cross-sectional nature of our study, data from longitudinal studies and randomized controlled trials are needed to confirm our results.

Overall, our findings support the notion that the association between physical activity and myelin content could be explained, at least in part, by HDL levels. Future research could test whether physical activity interventions can causally increase myelin content and assess whether these effects are mediated by regulation of HDL and its subcomponent of apolipoprotein A-1.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All research participants provided informed consent to participate in the study.

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REFERENCES

1. Nave KA. Myelination and support of axonal integrity by glia. *Nature*. 2010;468:244-252. doi:10.1038/nature09614
2. Faulkner ME, Gong Z, Bilgel M, et al. Evidence of association between higher cardiorespiratory fitness and higher cerebral myelination in aging. *Proc Natl Acad Sci*. 2024;121:e2402813121. doi:10.1073/pnas.2402813121
3. Silva NCBS, Dao E, Hsu CL, et al. Myelin and physical activity in older adults with cerebral small vessel disease and mild cognitive impairment. *the journals of gerontology: series A*. 2022:glac149. doi:10.1093/gerona/glac149
4. Hainsworth AH, Markus HS, Schneider JA. Cerebral small vessel disease, hypertension, and vascular contributions to cognitive impairment and dementia. *Hypertension*. 2024;81:75-86. doi:10.1161/HYPERTENSIONAHA.123.19943
5. Ihara M, Polvikoski TM, Hall R, et al. Quantification of myelin loss in frontal lobe white matter in vascular dementia, Alzheimer's disease, and dementia with Lewy bodies. *Acta Neuropathol*. 2010;119:579-589. doi:10.1007/s00401-009-0635-8
6. Vanherle S, Jorissen W, Dierckx T, et al. The ApoA-I mimetic peptide 5A enhances remyelination by promoting clearance and degradation of myelin debris. *Cell Rep*. 2022;41:111591. doi:10.1016/j.celrep.2022.111591
7. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports Med*. 2014;44:211-221. doi:10.1007/s40279-013-0110-5
8. Liu-Ambrose T, Dao E, Crockett RA, et al. Reshaping the path of vascular cognitive impairment with resistance training: a study protocol for a randomized controlled trial. *Trials*. 2021;22:1-12. doi:10.1186/s13063-021-05156-1
9. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4:e296. doi:10.1371/journal.pmed.0040296
10. Fazekas F, Chawluk JB, Alavi A. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Neuroradiol*. 1987;8:421-426.
11. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695-699. doi:10.1111/j.1532-5415.2005.53221.x
12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198. doi:10.1016/0022-3956(75)90026-6
13. Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the national institute of neurological disorders and stroke-canadian stroke network vascular cognitive impairment harmonization standards neuropsychological battery after TIA and stroke. *Stroke*. 2012;43:464-469. doi:10.1161/STROKEAHA.111.633586
14. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. *J Clin Epidemiol*. 2005;58:595-602. doi:10.1016/j.jclinepi.2004.10.018
15. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol*. 1993;46:153-162. doi:10.1016/0895-4356(93)90053-4
16. Janney CA, Cauley JA, Cawthon PM, Kriska AM, Group OF in MS. Longitudinal physical activity changes in older men in the Osteoporotic Fractures in Men Study. *J Am Geriatr Soc*. 2010;58:1128-1133. doi:10.1111/j.1532-5415.2010.02861.x
17. Harada ND, Chiu V, King AC, Stewart AL. Activity Instruments for Older Adults. *Med Sci Sports Exerc*. 2001;33:962-970.
18. Doucette J, Kames C, Rauscher A. DECAES – DEcomposition and component analysis of exponential signals. *Zeitschrift Für Medizinische Physik*. 2020;30:271-278. doi:10.1016/J.ZEMEDI.2020.04.001
19. Laule C, Moore GRW. Myelin water imaging to detect demyelination and remyelination and its validation in pathology. *Brain Pathol*. 2018;28:750-764. doi:10.1111/bpa.12645
20. Dvorak AV, Swift-LaPointe T, Vavasour IM, et al. An atlas for human brain myelin content throughout the adult life span. *Sci Rep*. 2021;11:1-13. doi:10.1038/s41598-020-79540-3
21. Isensee F, Schell M, Pflueger I, et al. Automated brain extraction of multisequence MRI using artificial neural networks. *Hum Brain Mapp*. 2019;40:4952-4964. doi:10.1002/HBM.24750
22. Tustison NJ, Cook PA, Holbrook AJ, et al. The ANTsX ecosystem for quantitative biological and medical imaging. *Sci Rep*. 2021;11:9068. doi:10.1038/s41598-021-87564-6
23. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *Neuroimage*. 2012;62:782-790. doi:10.1016/J.NEUROIMAGE.2011.09.015
24. McAusland J, Tam RC, Wong E, Riddehough A, Li DKB. Optimizing the use of radiologist seed points for improved multiple sclerosis lesion segmentation. *IEEE Trans Biomed Eng*. 2010;57:2689-2698. doi:10.1109/TBME.2010.2055865
25. Fischl B. FreeSurfer. *Neuroimage*. 2012;62:774. doi:10.1016/J.NEUROIMAGE.2012.01.021
26. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a Practical and Powerful Approach to Multiple Testing. *J R Stat Soc Series B Stat Methodol*. 1995. doi:10.1111/j.2517-6161.1995.tb02031.x
27. Jensen SK, Michaels NJ, Ilyntskyy S, Keough MB, Kovalchuk O, Yong VW. Multimodal Enhancement of Remyelination by Exercise with a Pivotal Role for Oligodendroglial PGC1α. *Cell Rep*. 2018;24:3167-3179. doi:10.1016/j.celrep.2018.08.060
28. Berro DH, Herbet G, Duffau H. New insights into the anatomo-functional architecture of the right sagittal stratum and its surrounding pathways: an axonal electrostimulation mapping study. *Brain Structure and Function*. 2021;226:425-441. doi:10.1007/s00429-020-02186-4
29. Di Carlo DT, Benedetto N, Duffau H, et al. Microsurgical anatomy of the sagittal stratum. *Acta Neurochir (Wien)*. 2019;161:2319-2327. doi:10.1007/s00701-019-04019-8
30. Stukas S, Robert J, Lee M, et al. Intravenously injected human apolipoprotein A-I rapidly enters the central nervous system via the choroid plexus. *J Am Heart Assoc*. 2014;3:e001156. doi:10.1161/JAHA.114.001156
31. Muscella A, Stefàno E, Marsigliante S. The effects of exercise training on lipid metabolism and coronary heart disease. *Am J Physiol Heart Circ Physiol*. 2020;319:H76-88. doi:10.1152/ajpheart.00708.2019
32. Coenen M, Biessels GJ, DeCarli C, et al. Spatial distributions of white matter hyperintensities on brain MRI: a pooled analysis of individual participant data from 11 memory clinic cohorts. *NeuroImage: Clinical*. 2023;40:103547. doi:10.1016/j.nicl.2023.103547
33. Maillard P, Fletcher E, Harvey D, et al. White matter hyperintensity penumbra. *Stroke*. 2011;42:1917-1922. doi:10.1161/STROKEAHA.110.609768

34. Ferris JK, Greeley B, Vavasour IM, et al. In vivo myelin imaging and tissue microstructure in white matter hyperintensities and perilesional white matter. *Brain Commun*. 2022;4:fcac142. doi:10.1093/braincomms/fcac142
35. Johnson NF, Gold BT, Ross D, et al. Non-fasting high-density lipoprotein is associated with white matter microstructure in healthy older adults. *Front Aging Neurosci*. 2019;11:100. doi:10.3389/fnagi.2019.00100

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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