Multiple Sclerosis and Related Disorders 91 (2024) 105879

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Lipid measures are associated with cognitive functioning in multiple sclerosis patients

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ARTICLE INFO

Keywords:
LDL
HDL
Cognition
Multiple sclerosis

ABSTRACT

Background: An association between lipid measures and cognitive decline in patients with multiple sclerosis (MS) has been suggested.
Objectives: This study aimed to investigate relationships between lipid profile and cognitive performance in a large observational cohort of MS patients.
Materials and methods: We included 211 patients with 316 available pairs of lipid and cognitive measures performed over follow-up. The time between lipid and cognitive measures did not exceed 90 days. Baseline data were analyzed by non-parametric Spearman rank correlation test. Repeated measures were analyzed using linear mixed models adjusted for sex, age, education level, disease-modifying therapy status, and depression.
Results: Baseline analyses showed a correlation between higher low-density lipoprotein cholesterol (LDL-C) and lower Categorical Verbal Learning Test (CVLT) (rho=-0.15; $p = 0.04$), lower Symbol Digit Modalities Test (SDMT) (rho=-0.16; $p = 0.02$) and lower Brief Visuospatial Memory Test-Revised (BVMT-R) scores (rho=-0.12; $p = 0.04$). Higher high-density lipoprotein cholesterol (HDL-C) was negatively correlated with lower SDMT scores (rho=-0.16; $p = 0.02$) and lower Paced Auditory Serial Addition Test-3 (PASAT-3) scores (rho=-0.24; $p = 0.03$). Mixed model analyses of repeated measures showed a negative association between higher LDL-C and lower CVLT (B=-0.02; $p < 0.001$, Cohen's $d = 0.08$) and lower BVMT-R (B=-0.01; $p = 0.03$, Cohen's d=-0.12). Also, the negative association between HDL-C and PASAT-3 was confirmed in the mixed model analysis (B=-0.18; $p = 0.01$, Cohen's $d = 0.07$). Additional adjustments of the models for disability assessed by Expanded Disability Status Scale or Normalized Brain Volume did not change the results of the models substantially.
Conclusions: Our results suggest a mild negative impact of dyslipidemia on cognitive performance in patients with MS. We propose that dyslipidemia contributes, at least in part, to cognitive decline in MS patients, independent of brain atrophy.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system (CNS), characterized by demyelination followed by neuronal loss. MS is the leading cause of non-traumatic neurological disability in young adults (Browne et al., 2014). Motor and sensitive symptoms are usually the most prominent symptoms in MS patients (Williams and Brauer, 2022). In recent decades, cognitive impairment has been increasingly acknowledged as another crucial component of the complex disability profile experienced by patients with MS. Around 40 % to 60 % of patients in more advanced disease stages are affected by cognitive impairment (Staff et al., 2009). Information processing speed and episodic memory are the most affected cognitive domains closely followed by executive dysfunction, decreased verbal fluency, and

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https://doi.org/10.1016/j.msard.2024.105879
Received 30 April 2024; Received in revised form 20 August 2024; Accepted 5 September 2024
Available online 6 September 2024

visuospatial functions (Sumowski et al., 2018). The cognitive impairment in patients with MS poses a significant socioeconomic problem as the most affected cognitive domains are essential for everyday life functioning, quality of life, and employment (Jennum et al., 2013). Cognitive impairment is notably difficult to influence by medication and the efficacy of cognitive rehabilitation is a matter of ongoing debate (Tacchino et al., 2023) although studies are showing promising results (Andaloro et al., 2022), particularly in patients at early disease stages (Tulliani et al., 2022; Ziccardi et al., 2023). Therefore, it is important to identify other modifiable factors that are associated with a higher risk of developing or progressing of cognitive impairment. Modifiable risk factors of cognitive impairment such as improvement of cognitive reserve are of exceptional importance because their modification has the potential to positively influence cognitive performance in patients with MS (Sumowski et al., 2013).

While the impact of altered lipid metabolism on the cognitive performance of individuals with MS is not fully understood, a few recent studies have suggested that adverse lipid profiles in this population are linked to poorer cognitive outcomes (Table 1) (Andaloro et al., 2022; Noori et al., 2019; Hernandez-Ledesma et al., 2020; Siddiqui et al., 2023; Novakova et al., 2015; Silva et al., 2023; Reia et al., 2021). There is also an increasing amount of evidence of defective lipid metabolism affecting disease activity (Lorincz et al., 2022; Zhornitsky et al., 2016). In a recent study by Noori et al., patients with higher serum total cholesterol (TC) had lower Symbol Digit Modalities Test (SDMT) and lower scores in the Delis-Kaplan Executive Functions - Sorting Test (DKEFS-ST) and the Delis-Kaplan Executive Functions - Descriptive Test (DKEFS-DT). Lower DKEFS-ST and DKEFS-DT scores also correlated with higher low-density lipoprotein cholesterol (LDL-C) levels (Noori et al., 2019). Hernandez – Ledesma et al. showed that higher TC and LDL-C also correlates with worse scores in the Montreal Cognitive Assesement (MoCA) in MS patients. Memory recall and language were found to be the most affected domains (Hernandez-Ledesma et al., 2020). Andaloro et al. also showed on a cohort of 90 patients undergoing cognitive rehabilitation that higher levels of TC negatively impacted MoCA scores after completion of rehabilitation programme (Andaloro et al., 2022). In another larger cross-sectional study on 121 patients and 41 healthy controls, higher LDL-C to high-density lipoprotein (HDL-C) ratio was associated with worse SDMT and Nine-Hole Peg Test scores (Siddiqui et al., 2023). Adjustment for Brain Parenchymal Volume did not abrogate these findings. A recent meta-analysis showed only the correlation between TC and MoCA, but other correlations between lipid and cognitive measures were abrogated (Sarvin Sanaie et al., 2024). The association between altered lipid metabolism and cognitive impairment was also shown in other neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD) (Estes et al., 2021; Alecu and Bennett, 2019).

Although, there is a growing evidence suggesting a link between TC and LDL with cognitive outcomes of patients, this evidence is derived from a limited number of cross-sectional studies with high risk of bias and with using of different cognitive assessment scales and methods (Sarvin Sanaie et al., 2024). Therefore, the main aim of this study was to investigate the association between adverse lipid profiles and cognitive performance using standardized cognitive scales in a large sample of patients with MS.

Table 1
Summary of available studies elucidating on the association of lipid metabolism and cognitive impairment in MS.

Study	Sample size	Design	Cognitive measure	Result
Noori et al. (2019)	50 RRMS	Cross-sectional	MACFIMS	Higher TC was negatively correlated with SDMT, DKEFS-ST, and KEFS-DT. Higher LDL-C was negatively correlated with DKEFS-ST and DKEFS-DT.
Hernandez-Ledesma et al. (2020)	20 RRMS 10 HC	Cross-sectional	MoCa	Higher TC and LDL-C were negatively correlated with MoCa. Memory recall and language were the most affected domains.
Andaloro et al. (2022)	90 various MS phenotypes	Cross-sectional	MoCa; BRB-N; MSQoL-54	Higher TC negatively affected MocA score after cogitive rehabilitation.
Siddiqui et al. (2022)	122 various MS phenotypes 41 HC	Cross-sectional	NHPT; 25FW; SDMT; PASAT-3; BDI-FS	Higher LDL-C to HDL-C ratio was negatively associated with SDMT and 9-HPT. The result was not abbrogated by adjusting for brain atrophy.
Novakova et al. (2015)	31 RRMS	Longitudinal	SDMT	Serum 24-OHC was positively associated with SDMT pre- and post-natalizumab administration.
Silva et al. (2023)	33 RRMS 6 PMS	Cross-sectional	SDMT; CVLT-2; BVMT-R;	No lipid measure was associated with cognitive outcomes. Cognitive deficits were associated with TC and LDL-C.
Reia et al. (2021)	52 RRMS 17 PMS	Cross-sectional	SDMT; CVLT-2; BVMT-R	Higher TC was correlated with lower CVLT-2 scores.

Legend: 25FWT = 25-foot walk test; BDI-FS = Beck Depression Inventory Fast Screen; BRB-*N* = Brief Repeatable Battery of Neuropsychological Tests; BVMT-*R* = Brief Visuospatial Memory Test Revised; CVLT2 = California Verbal Learning Test-II; DKEFS-DT = Delis-Kaplan Executive Functions - Descriptive Test; DKEFS-ST = Delis-Kaplan Executive Functions - Sorting Test; HC = healthy controls; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; MoCa = Montreal Cognitive Assesment; Multiple Sclerosis Quality of Life-54 = MSQoL-54; NHPT = Nine Hole Peg Test; PASAT-3 = Paced Auditory Serial Addition Test 3; PMS = Progressive multiple sclerosis; RRMS = Relapsing-remitting multiple sclerosis; SDMT = Symbol Digit Modalities Test; TAG = Triacylglycerol; TC = Total Cholesterol.

2. Methods

2.1. Study cohort

We included 211 MS patients with 361 timepoints (repeated measures for a proportion of patients) from the MS Centre in the General University Hospital in Prague with available pairs of lipids and cognitive measures between 1/2000 and 12/2015. Inclusion criteria included a confirmed diagnosis of relapse-remitting, primary progressive or secondary progressive MS based on McDonald 2017 criteria (Thompson et al., 2018), availability of cognitive assessment and assessment of concentrations of lipid measures in serum. The time between the lipid and cognitive measures did not exceed 90 days.

Clinical and demographic data in this study from our MS center were collected via the Czech Republic nationwide registry (ReMuS). The guarantor of expertise of ReMuS is the Section for Neuroimmunology and Liquorology of the Czech Neurological Society. Data in ReMuS are collected using the standardised software iMed. Before the release of the

coded patient-level data to investigators, there is a multi-level quality control process (Stastna et al., 2023). The study protocol was approved by the Medical Ethics Committee of General University Hospital in Prague (113/22 S-IV). The study was carried out in accordance with the Declaration of Helsinki, and all patients provided written informed consent.

2.2. Cognitive performance data

Cognitive assessments were performed by two PhD neuropsychologists at the MS Center of General University Hospital in Prague. The most comprehensive and neuropsychologically validated group of tests is the Minimal Assessment of Cognitive Functions in MS (MACFIMS) battery (Benedict et al., 2002). A shorter and therefore more accessible version of this battery is the Brief International Cognitive Assessment in MS (BICAMS) (Benedict et al., 2012). In our study the previously described and validated Czech language adaptation of the BICAMS battery (Dusankova et al., 2012) was used for cognitive assessment which includes: SDMT, Categorical Verbal Learning Test (CVLT) with its structure resembling California Verbal Learning Test, Brief Visuospatial Memory Test Revised (BVMT-R). Additionally, the Paced Auditory Serial Addition Test 3 (PASAT-3) was performed. Depression was assessed by the Beck Depression Inventory-II (BDI-II) (Beck et al., 1961).

2.3. Biochemical analysis

Fasting or non-fasting blood draws were obtained in routine clinical practice (Langsted and Nordestgaard, 2019). Diagnostic reagent kits (Cholesterol Liquicolor and HDL Liquicolor; Human Gesellschaft für Biochemica und Diagnostica mbH, Germany) were used to measure serum TC, HDL-C and triglyceride (TG). LDL-C was obtained using the Friedewald equation (all patients had TAG <4.2) (Uher et al., 2017).

2.4. MRI data acquisition

MRI measures were obtained during regular follow-up of routine clinical practice at the Department of Radiology at the General University Hospital in Prague. A standardized protocol was performed using a single 3T scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The protocol included 3D magnetization-prepared 2 rapid acquisition gradient echoes (MP2RAGE) for T_1 mapping, along with 3D fluid-attenuated inversion recovery (FLAIR-SPACE) and magnetization-prepared acquisition gradient echo (MPRAGE). Brain volume was esimated from MPRAGE scan using the previously described research application MorphoBox (Schmitter et al., 2015). The Total Intracranial Volume (TIV)-normalized brain volume (NBV) was used for further analysis.

2.5. Statistical analysis

We used the R programming language (version 4.3.1) for data analysis. The R Studio (version 2023.06.2 Build 561) interface was used. Demographic statistical analysis was performed with the TableOne package (version 0.13.2). The LME4 (version 1.1–34) package was used for linear mixed model analysis. For distribution assessment the Shapiro-Wilk test was used. Non-normally distributed variables were logarithmically transformed.

We correlated lipid and cognitive measures at baseline using the non-parametric Spearman rank correlation test. Additionally, we calculated the rho-squared (coefficient of determination) to estimate the percentage of variance in cognitive performance explained by the covariance of lipid measures. Considering repeated measures over follow-up in some patients, we fitted a linear mixed effect model with a random intercept for patient and used cognitive data as the dependent variable. The model was adjusted for sex, age, DMT status (no DMT, DMTs with low and moderately-high efficacy, DMTs with high efficacy), and depression assessed by the BDI-II. We grouped interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, and fingolimod as DMTs with low or moderately-high efficacy, other DMTs (natalizumab, ocrelizumab, and alemtuzumab) were considered as high efficacy treatment. To address the concern of higher intelligence individuals performing better in cognitive testing we also adjusted the models for education level. We performed additional models adjusted also for Expanded Disability Status Scale (EDSS) scores or NBV. Given that only a negligible proportion of patients used hypolipidemic drugs, we did not adjust for hypolipidemic treatment in the analyses. The Benjamini-Hochberg procedure with $q = 0.05$ was used to control false discovery rate. A p-value of <0.05 was considered statistically significant.

We estimated effect size (Cohen f2) for the effect of lipid measures on the imaging metrics. Cohen f2 $\geq$ 0.02, f2 $\geq$ 0.15, and f2 $\geq$ 0.35 represent small, medium, and large effect sizes, respectively (Selya et al., 2012).

3. Results

The sample consisted of 69.7 % women, the mean age of patients was 41.55 (standard deviation [SD] = 10.29) years, and the mean disease duration was 10.89 (SD = 10.11) years at baseline. Of the patients 64 % were using moderate efficacy disease modifying therapy (DMT), 15 % were on high-efficacy DMT and 21 % were not treated with DMTs. The mean TC was 5.19 mmol/l (SD 1.13 mmol/l), mean LDL-C was 2.66 mmol/l (SD 1.22 mmol/l), and mean HDL-C was 1.35 mmol/l (SD 0.58 mmol/l). Median EDSS was 2.0 (interquartile range [IQR] 0.5–3.5). Only very small proportion of the patients (<0.5 %) used hypolipidemic drugs. Detailed descriptive data are shown in Table 2.

The results of Spearmaṅs correlation analysis between lipid and cognitive measures are shown in Table 3. We found a correlation between higher LDL-C and lower CVLT (rho = −0.15, $p = 0.04$), lower SDMT (rho = −0.16, $p = 0.02$) and lower BVMT-R scores (rho = −0.1, $p = 0.04$). Surprisingly higher HDL-C was also negatively correlated with lower SDMT scores (rho = −0.16, $p = 0.02$) and lower PASAT 3 scores (rho = −0.24, $p = 0.03$). The rho-squared values of these associations at baseline ranged from 0.014 to 0.058; however, these associations lost their statistical significance after correction for false discovery rate.

Table 2
Characteristics of the sample at baseline.

Number of patients	211
Age	41.55±10.29
Disease duration	10.89±10.11
Females	147 (69.7 %)*
TC (normal range)	5.19±1.13 mmol/l (2.9–5.2 mmol/l)
TAG (normal range)	1.60±1.04 mmol/l (0.45–1.7 mmol/l)
HDL-C (normal range)	1.35±0.58 mmol/l (1.0–2.0 mmol/l)
LDL-C (normal range)	2.66±1.22 mmol/l (1.2–3.0 mmol/l)
Education (years)	3.73±1.21
SMDT	56.74±10.98
CVLT2	55.85±10.45
BVMT-R	28.36±5.35
PASAT-3	46.83±1.09
EDSS	2.0 ± 0.5–3.5**
NBV	76.49±3.34
DMT status	
Low and Moderately-high efficacy	135 (64 %)*
High efficacy	32 (15 %)*
No DMT	44 (21 %)*

Legend: BVMT-*R* = Brief Visuospatial Memory Test Revised; CVLT2 = California Verbal Learning Test-II; DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; NBV = Normalized Brain Volume; PASAT-3 = Paced Auditory Serial Addition Test 3; SDMT = Symbol Digit Modalities Test; TAG = Triacylglycerol; TC = Total Cholesterol.
Unless threwise indicated reported mean ± standard deviation (SD).
* number (% proportion).
** mediand (interquartile range; IQR).

Table 3
Spearman's rank correlations between lipid and cognitive measures at baseline ($n = 211$).

	TC	LDL-C	HDL-C	TAG
SDMT	rho = −0.04 rho^2 = 0.002 p = 0.65	**rho = −0.16** **rho^2 = 0.026** ***p* = 0.020** ***adj.p[4]=0.080*** *	**rho = −0.16** **rho^2 = 0.026** ***p* = 0.020** ***adj.p[4]=0.080*** *	rho = −0.1 rho^2 = 0.010 p = 0.80
CVLT-2	rho = −0.12 rho^2 = 0.014 p < 0.09	**rho = −0.15** **rho^2 = 0.023** ***p* = 0.040** ***adj.p[4]=0.12****	rho = −0.14 rho^2 = 0.02 p = 0.061	rho = −0.07 rho^2 = 0.005 p = 0.35
BVMT-R	rho = −0.05 rho^2 = 0.003 p = 0.45	**rho = −0.12** **rho^2 = 0.014** ***p* = 0.040** ***adj.p[4]=0.080*** *	rho = −0.09 R^2 = 0.008 p = 0.20	rho = −0.08 rho^2 =0.006 p = 0.20
PASAT-3	rho = −0.15 rho^2 = 0.023 p = 0.20	rho = −0.20 rho^2 = 0.040 p = 0.092	**rho = −0.24** **rho^2 = 0.058** ***p* = 0.033** ***adj.p[4]=0.066*** *	rho = −0.03 rho^2 = 0.001 p = 0.74

Legend: adj.p = adjusted p value; BVMT-R = Brief Visuospatial Memory Test Revised; CVLT2 = California Verbal Learning Test-II; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; p = p-value; PASAT-3 = Paced Auditory Serial Addition Test 3; rho = Spearmańs correlation coefficient; SDMT = Symbol Digit Modalities Test; TAG = Triacylglycerol; TC = Total Cholesterol.

* The Benjamini-Hochberg procedure with $q = 0.05$ was used to control false discovery rate of dependent tests. The number in [brackets] following adjusted p refers to the number of comparisons.

Table 4
Association between repeated lipid and cognitive maeasures analyzed using the adjusted linear mixed effect models ($n = 316$).

	TC	LDL-C	HDL-C	TAG
SDMT	*B* = 0.30 CI = −0.33, 1.05 p = 0.30	*B* = −0.20 CI = −0.92, 0.37 p = 0.40	*B* = −0.80 CI = −2.12, 0.46 p = 0.20	*B* = 0.20 CI = −0.41, 0.93 p = 0.40
CVLT-2	***B* = −0.02 (−0.02*)** **CI = −0.04, 0.009** ***p* = 0.001 (0.005*)** ***adj.p[4]= 0.004***** **Cohenś *D* = 0.11**	***B* = −0.02 (−0.03*)** **CI = −0.04, −0.01** ***p* < 0.001 (< 0.001*)** ***adj.p[4] <0.001***** **Cohenś *D* = 0.08**	*B* = −0.02 CI = −0.05, 0.006 p = 0.12	*B* = −0.01 CI = −0.02,0.02 p = 0.90
BVMT-R	*B* = −0.01 CI = −0.03, 0.002 p = 0.10	***B* = −0.01 (−0.01*)** **CI = −0.03, -0.001** ***p* = 0.03 (0.04*)** ***adj.p[4]= 0.09***** **Cohenś *D* = −0.12**	*B* = −0.02 CI = −0.05, 0.007 p = 0.15	*B* = −0.01 CI = −0.02, 0.01 p = 0.60
PASAT-3	*B* = −0.04 CI = −0.13, 0.03 p = 0.20	*B* = −0.03 CI = −0.09,0.02 p = 0.22	***B* = −0.18 (−0.22*)** **CI = −0.35, −0.03** ***p* = 0.01 (0.02*)** ***adj.p[4]= 0.01***** **Cohenś *D* = 0.07**	*B* = 0.06 CI = −0.05, 0.18 p = 0.19

Legend: adj.p = adjusted p value; B = beta value; BVMT-R = Brief Visuospatial Memory Test Revised; CI = confidence interval; Cohenś D = measure of effect size; CVLT2 = California Verbal Learning Test-II; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; p = p-value; PASAT-3 = Paced Auditory Serial Addition Test 3; p = p-value; rho = Spearmańs correlation coefficient; SDMT = Symbol Digit Modalities Test; TAG = Triacylglycerol; TC = Total Cholesterol.

* The data presented in parentheses are after additional adjustment of the models for the Expanded Disability Status Scale (EDSS) and Normalized Brain Volume (NBV), both treated as independent variables.

** The Benjamini-Hochberg procedure with $q = 0.05$ was used to control false discovery rate of dependent tests. The number in [brackets] following adjusted p refers to the number of comparisons.

Effect sizes for significant results were calculated using Cohen's d.

The results of linear mixed model analysis between lipid profile and cognitive measures are shown in Table 4. We found a negative association between higher LDL-C and lower CVLT ($B = -0.02$, $p < 0.001$, Cohens $d = 0.08$) and lower BVMT-R ($B = -0.01$ $p = 0.03$, Cohens $d = -0.12$) (Figs. 1 and 2). However, the association between LDL-C and BVMT-R lost statistical significance after correction for false discovery rate (adjusted $p = 0.09$). Additional adjustment of the models for EDSS or NBV did not significantly change results of the models. The negative association between HDL-C and PASAT-3 was confirmed in the mixed model analysis ($B = -0.18$, $p = 0.01$, Cohens $d = 0.07$) (Fig. 3).

4. Discussion

In this study, we investigated the association between lipid profiles and cognitive measures in patients with MS. Elevated levels of LDL-C showed a weak but consistent correlation with lower cognitive performance, as assessed by the BICAMS battery and PASAT-3 test. The inverse associations observed between higher concentrations of LDL-C and poorer cognitive performance suggest a negative impact of altered lipid metabolism on cognitive functioning in patients with MS. However, the pathophysiological relevance was minimal, with lipid measures explaining only small amounth (between 1.4 and 5.8 %) of the variance in cognitive performance. The highest relevance was 5.8 % for PASAT-3 with HDL-C, while the other three associations were all below 3 %. Additionally, the associations between lipids and cognitive measures at baseline, but not when analyzing repeated measures, lost statistical significance after correction for false discovery rate. Otherwise, we found no association between other lipid measures such as TC or TAG and cognitive performance.

All these findings are in concordance with a few previous studies (Table 1) (Noori et al., 2019; Hernandez-Ledesma et al., 2020; Siddiqui et al., 2023). In this context, a discussion is emerging about the association between lipid metabolism and cognitive performance in different neurodegenerative diseases of the CNS associated with severe cognitive impairment, such as Alzheimer's disease (AD). The most common genetic risk factor of AD is the APOE ε4 genotype which is involved in lipid transport and metabolism in the CNS (Liu et al., 2013). In MS this association is not so well understood, although a recent meta-analysis reported minimal association between the APOE ε4 and cognitive performance (Naseri et al., 2022). In recent years, there has been a growing research emphasis on the role of complex lipidomic profiles in the pathogenesis of Alzheimer's disease (Kao et al., 2020). Dyslipidemia as a comorbidity has been shown to accelerate neurodegeneration in AD by worsening large—scale network integrity in the brain thus promoting neuropathological processes (Wang et al., 2022). Cholesterol has also been suggested as one of the main contributors to amyloid β-mediated neurotoxicity (Rudajev and Novotny, 2022). Furthermore, disturbances in the lipid profiles of lipid rafts in the frontal cortex are associated with development of different neurodegenerative disease such as PD, Lewy body dementia and AD (Marin et al., 2017). Adverse lipid profile is also a risk factor of atherosclerosis and brain ischemia which is one the leading causes of cognitive impairment and dementia (Yaghi and Elkind, 2015).

In addition to these observations, we found a trend for association between higher HDL-C and with lower PASAT-3 score. Although, this correlation was weak, had a small effect size, and was performed on

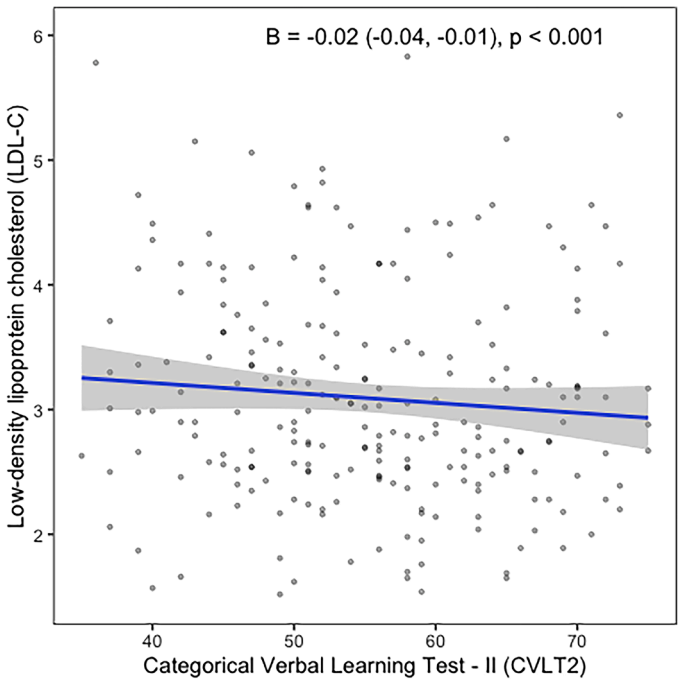

Fig. 1. The association between Low-density lipoprotein cholesterol (LDL-C) and Categorical Verbal Learning Test (CVLT2) score. ~~Statistiecaly significant~~ Results from the adjusted longitudinal mixed models analysis are reported.

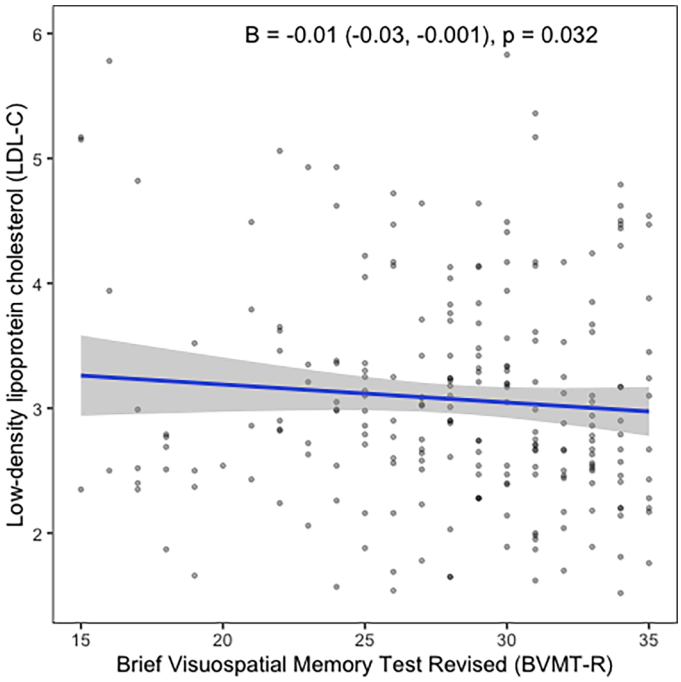

Fig. 2. The association between Low-density lipoprotein cholesterol (LDL-C) and Brief Visuospatial Memory Test Revised (BVMT-R). ~~Statistiecaly significant~~ Results from the adjusted longitudinal mixed models analysis are reported.

smaller number of patients, it may contradict the previously suggested exclusively neuroprotective effects of higher HDL-C. Few recent publications suggest a possible pro-inflammatory conversion of HDL-C subpopulations under systemic inflammatory conditions thus highlighting their possible lipotoxic effect (Charles-Schoeman et al., 2009; McMahon et al., 2009). In patients with MS higher levels of dysfunctional pro-inflammatory HDL-C molecules were shown (Jorissen et al., 2017).

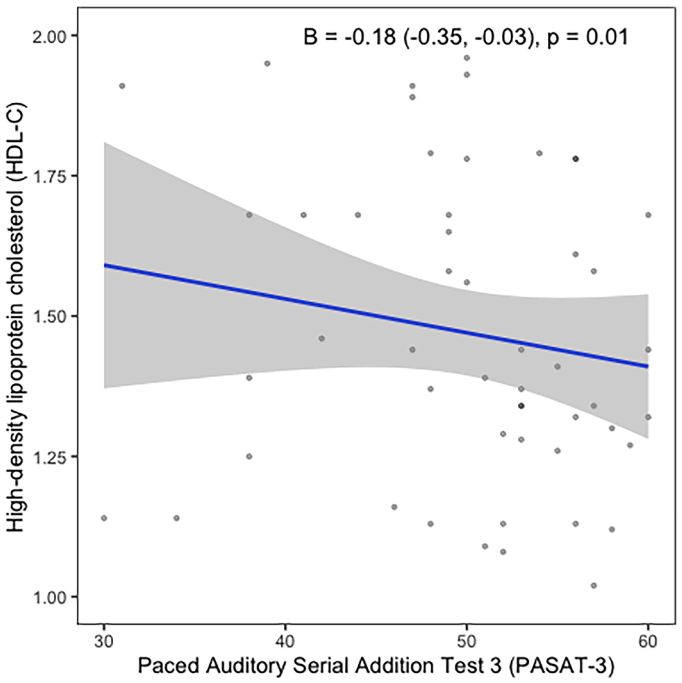

Fig. 3. The association between High-density lipoprotein cholesterol (HDL-C) and Paced Auditory Serial Addition Test 3 (PASAT-3). ~~Statistiecaly significant~~ Results from the adjusted longitudinal mixed models analysis are reported.

A recent large cohort study by Hussain et al. revealed that healthy individuals with very high levels of HDL-C were more susceptible to developing dementia compared to those with normal levels (Sultana Monira Hussain et al., 2023). In this context, we hypothesize that our findings may indicate a detrimental effect of HDL-C on brain health in certain individuals. These findings need to be confirmed in the future studies and require elaboration, including detailed analysis of HDL-C subtypes with diverse potentially functions on brain pathology as we found associaton only with PASAT-3 and the effect size of the result was weak.

In MS pathogenesis the possible effect of lipotoxicity on cognitive decline is less clear. Cognitive decline in MS has been attributed to global and regional brain atrophy (thalamic and hippocampal changes), fMRI abnormalities as well as glutamate toxicity (Jakimovski et al., 2020; Eijlers et al., 2018). We hypothesize that the dysregulated lipid metabolism observed in patients with MS may be linked to accelerated neurodegenerative processes, characterized by brain atrophy and cognitive impairment, akin to those observed in diseases such as AD or PD. Our hypothesis may be confirmed by the recent findings showing association between higher LDL-C levels and accelerated brain atrophy (Murali et al., 2020). This association may be driven not only by lipotoxicity, but also by altered cerebral blood flow caused by atherosclerosis of large vessels and disrupted endothelial and smooth muscle function on small cerebral vessels (Ayata et al., 2013) leading into ischemic brain tissue damage. In this context, chronic ischemic brain tissue damage is discussed as a one of the pathogenetic mechanisms of MS (Levin et al., 2014). This theory is also supported by findings of accelerated neurodegeneration in several disease including MS, AD and PD in obese patients (Neto et al., 2023).

There is evidence that disrupted lipid metabolism, mainly increased LDL-C levels, is associated with an increased disease activity in patients with MS. Higher LDL-C is associated with higher relapse rate, higher EDSS scores and their faster progression, larger number of contrast enhancing lesion on MRI after gadolinium administration and higher number and volume of T2 lesions (Murali et al., 2020; Weinstock-Guttman et al., 2011; Giubilei et al., 2002; Weinstock-Guttman et al., 2013). Increased levels of LDL-C also accelerate brain atrophy in

MS (Rojas et al., 2016). Considering a well-known association between brain atrophy and worse cognitive performance, it may be not surprising negative effect of dyslipidemia on worse cognitive performance (Lanz et al., 2007). Importantly, our study shows that an effect of dyslipidemia on the cognitive performance in MS is independent on brain atrophy. This important finding is consistent with a recent study of Siddiqui et al. showing independent effect of dyslipidemia and brain atrophy on cognitive performance in patients with MS (Siddiqui et al., 2023). Considering that both elevated LDL-C levels and brain atrophy were independently associated with cognitive performance, it may be suggested that the relationship between elevated LDL-C and poorer cognitive performance is not solely driven by brain atrophy, but also by other mechanisms potentially linked to lipid metabolism. Previously described alterations of lipid homeostasis in inflammatory conditions, lipid raft lipidomic changes, large-scale network integrity disruption, and dyslipidemia-associated brain ischemia might all play a role in this interaction. Therefore, dyslipidemia may represent an important disease-modifiable factor of cognitive performance in MS. Given that serum lipids levels may be influenced not only by lifestyle interventions, but also by medication further research in this area may have an important clinical relevance.

We acknowledge the limitations of our study, primarily its retrospective nature, lack of follow-up measures in all included patients, and absence of a comprehensive cognitive assessment covering all relevant cognitive domains. Another limiting factor is that individuals with higher intellectual performance often have lower lipid values and lead healthier lifestyles (Muldoon et al., 1997), which could potentially bias our results. In this context, repeated observations have shown a positive correlation between the number of years of formal education and cognitive function throughout adulthood, as well as a lower risk of dementia later in life (Lovden et al., 2020). Therefore, we adjusted our statistical models for years of formal education to partially mitigate the confounding effects of lifestyle on our results. We are aware of the possibility of Type 1 error with the large number of models run and small effect sizes. Therefore, we corrected our results for the false discovery rate, which led to the loss of statistical significance for some associations between lipid measures and cognitive performance at baseline. Finally, we investigated only basic lipid measures, therefore future studies should employ more detailed lipidomics data to improve our understanding of the association between dyslipidemia and cognitive decline in MS. Also, future longitudinal studies should incorporate longer follow-up periods.

In conclusion, our study confirms the association between adverse lipid profile and worse cognitive performance in pwMS, which is independent on brain atrophy. However, the degree of pathophysiological relevance was small, as the lipid measures explained only 1.4 % to 5.8 % of the variance in cognitive performance.

Funding

The project was supported by the National Institute for Neurological Research (Program EXCELES, ID project No LX22NPO5107) - funded by the European Union-Next Generation EU. The project was also supported by Czech Ministry of Health project NV22–04–00193 and the institutional support of a hospital research project (MH CZ-DRO-VFN64165), and by Czech Ministry of Education - Cooperation, 1.LF, Neuroscience.

CRediT authorship contribution statement

Balázs Lőrincz: Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jiří Motýl:** Validation, Methodology. **Lucie Friedová:** Validation, Methodology. **Daniel Hrych:** Data curation. **Eva Kubala Havrdová:** Supervision. **Jan Krásenský:** Supervision. **Tadeáš Urban:** Data curation. **Tobias Kober:** Methodology. **Bénédicte Maréchal:** Methodology. **Manuela Vaněčková:** Supervision. **Dana Horákova:** Supervision. **Michal Vrablik:** Supervision, Methodology, Investigation. **Tomáš Uher:** Writing – review & editing, Writing – original draft, Supervision.

Declaration of competing interest

Balazs Lorincz received financial support for conference travel from Merck, Medtronic, Bayer and speaker honoraria from Sandoz.

Jiri Motyl received compensation for traveling, conference fees and speaker honoraria from Sanofi Genzyme, Biogen, Novartis, and Merck.

Lucie Friedova has nothing to disclose

Daniel Hrych has received financial support for conference travel from Biogen.

Eva Kubala Havrdova received speaker honoraria and consultant fees from Biogen Idec, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen, and Merck Serono.

Dana Horakova received compensation for travel, speaker honoraria and consultant fees from Biogen, Novartis, Merck, Bayer, Sanofi Genzyme, Roche, and Teva, as well as support for research activities from Biogen.

Manuela Vaneckova received speaker honoraria, consultant fees, and travel expenses from Biogen Idec, Novartis, Roche, Genzyme, and Teva, as well as support for research activities from Biogen Idec.

Jan Krasensky received financial support for research activities from Biogen Idec.

Tobias Kober and Bénédicte Maréchal are Siemens Healthineers International AG employees.

Tadeas Urbas has nothing to disclose.

Michal Vrablik reports fees for clinical trials, consultancy and presentations from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Mylan, Novartis, Novo Nordisk, Sanofi and Zentiva.

Tomas Uher received financial support for conference travel and honoraria from Biogen Idec, Novartis, Roche, Genzyme, and Merck Serono, as well as support for research activities from Biogen Idec and Sanofi.

Acknowledgement

We thank Mrs. Filip Habarta for assistance with data management and statistical analysis.

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