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Research Paper

An adverse lipid profile is associated with disability and progression in disability, in people with MS

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Abstract

Background: There is accumulating data suggesting an association between serum lipids, apolipoproteins and disability in multiple sclerosis (MS).

Objectives: To investigate the associations between serum lipids, apolipoproteins and disability in MS.

Methods: A cohort of 178 participants with clinically-definite MS in southern Tasmania, Australia were prospectively followed from 2002 – 2005, and serum samples were obtained at study entry and at each biannual review, to measure lipid profile and apolipoprotein levels. Associations with disability and annual change in disability were evaluated using linear regression and multilevel mixed-effects linear regression.

Results: In the unadjusted analyses, nearly all lipid-related variables were positively associated with Expanded Disability Status Scale (EDSS). After adjustment for confounders, total cholesterol (TC) (p = 0.037), apolipoprotein B (ApoB) (p = 0.003), and the apolipoprotein B to apolipoprotein A-I ratio (ApoB/ApoA-I ratio) (p = 0.018) were independently associated with a higher EDSS. Higher body mass index (BMI) was also independently associated with higher EDSS (p = 0.013). With the progression analysis, the total cholesterol to high density lipoprotein (HDL) ratio (TC/HDL ratio) (p = 0.029) was prospectively associated with subsequent change in EDSS.

Conclusion: In this prospective population-based cohort study, an adverse lipid profile was associated with high levels of MS disability and disease progression. Improving serum lipids may be beneficial for MS patients, to potentially improve clinical outcomes and vascular comorbidities.

Keywords: Apolipoprotein, body mass index, cholesterol, disability, lipid profile, multiple sclerosis, progression

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Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating condition of the central nervous system (CNS). It has a highly variable inter- and intra-personal clinical course, suggesting multiple contributory factors,[1] but there is still little data on the factors that modify the disease course.

Lipids play important roles in the CNS and transport through the blood-brain barrier (BBB) is demonstrated.[2,3] Lipids are involved in the regulation of neural functions, cell signalling and in tissue structure and apolipoproteins are key players in the metabolism, transport and delivery of lipids.[4,5] Oxidative stress and consequent lipid peroxidation may play a role in the inflammatory processes and pathogenesis of MS.[6,7] Oxidative modifications of low density lipoprotein (LDL), the major carrier of plasma cholesterol, have been established in the parenchyma of MS plaques.[3] Lipid peroxidation and oxidised LDL uptake by activated microglia and infiltrating macrophages in the early stages of MS plaque development, are thought to play crucial roles in demyelination.[3] High density lipoprotein

(HDL), on the other hand, may have protective effects due to its antioxidant properties and role in reverse cholesterol transport.[2]

There is little epidemiological evidence on lipids and MS. High rates of obesity and overweight are reported in MS,[8,9] and vascular comorbidities seem to be more common in MS than the general population.[10] A high body mass index (BMI) during adolescence is associated with an increased MS risk.[11,12] Strong associations are found between total cholesterol (TC), LDL and the number of gadolinium-enhancing lesions on magnetic resonance imaging (MRI).[13] Lipoproteins and apolipoproteins are associated with new MRI lesions and grey matter atrophy in clinically-isolated syndrome (CIS)[14,15]; and a high cholesterol level is associated with low retinal nerve fibre layer thickness in MS patients with optic neuritis.[16] A prospective study found that higher baseline TC, LDL, triglycerides and lower HDL were associated with subsequent worsening in clinical disability,[17] but this study did not take confounding factors into account.

In this prospective clinical cohort of people with MS having repeated lipid measures, we examined the association between lipid-related measures (BMI, serum lipid and apolipoprotein levels), disability and progression in disability.

Methods

Study design

The Southern Tasmanian Multiple Sclerosis Longitudinal (MSL) Study is a prospective population-based study, which followed a cohort of 203 persons with clinically definite MS[18] living in Southern Tasmania, Australia from 2002 – 2005. An estimated 78% (203/259) of the eligible cases were included. The study retention rate was 90% (183/203), with 4% (8/203) withdrawing early and 6% (12/203) lost because they either moved interstate or died. Only one person participated in a pilot before Wave 1, and four participants were excluded, because they did not meet the criteria for definite MS after neurological review at the end of the study (with all available data). For this analysis, the sample was limited to those with BMI data (n = 178), excluding 20 people whose weight and height could not be assessed, because of their high disability.

The study methodology was previously described.[19] At each biannual review, participants were asked about their lifestyle, including physical activity, smoking, vitamin D supplement use and dosage, statin and other medication use. Height and weight was measured at baseline. The EDSS was assessed each winter by a single physician. The Multiple Sclerosis Severity Score (MSSS) was calculated from the EDSS and disease duration, by comparing it to the global MSSS reference dataset.[20] Ethics approval was obtained from the Southern Tasmania Human Research Ethics Committee and all participants provided informed consent.

Biological samples and measurements

Non-fasting serum samples were collected at study entry and at each biannual review, and stored in the − 80°C freezer until use. Traditionally, triglycerides were measured in a fasting state; however, there has been a shift to non-fasting samples, as post-prandial non-fasting values are more representative of the usual metabolic state.[21] Total cholesterol and triglycerides were measured using enzymatic colorimetry (Wako Chemicals, Richmond, VA, USA). HDL-cholesterol levels were measured using precipitation and enzymatic assay (Wako Chemicals, Richmond, VA, USA). LDL-cholesterol was estimated using the Friedewald equation,[22] except when triglyceride levels were above 5.1 mmol/L (n = 9), when it was measured by direct assay (Wako Chemicals, Richmond, VA, USA). Non-HDL-cholesterol levels were computed by subtracting HDL-cholesterol from total cholesterol.

The apolipoproteins, ApoA-I and ApoB, were measured as they are the main protein components of HDL and LDL/VLDL, respectively. Lipoprotein (a) (Lp (a)) is the complex of LDL-cholesterol and ApoA. ApoB, ApoE and ApoA-1 levels were measured by turbidimetric immunoassay, using goat anti-human ApoB or ApoA-I (Wako Chemicals, Richmond, VA, USA) and Lp(a) was measured by a sandwich Dissociation-enhanced lanthanide fluorescence immunoassay (DELFIA) (LKB-Pharmacia, Stockholm, Sweden). Serum levels of highly sensitive C-reactive protein (hs-CRP) were measured with an hs-CRP enzyme-linked immunosorbent assay (ELISA) Kit (Alpha Diagnostic, San Antonio, TX, USA), according to the manufacturer's instructions (detection limit 0.35 ng/ml). Samples were diluted 1:100 and studied in duplets and re-measurement with a dilution of 1:200 was performed for samples that were out of range.

Serum 25-OH-D levels were measured with a commercially available radioimmunoassay (DiaSorin, Stillwater, MN, USA). We found that inter-batch reproducibility was 4.6% at 32 nmol/L and 6.4% at 125 nmol/L.

Statistical analysis

The total cholesterol to HDL ratio (TC/HDL ratio), LDL to HDL ratio (LDL/HDL ratio) and ApoB to ApoA-I ratio (ApoB/ApoA-I ratio) were calculated, as they are validated predictors of cardiovascular disease risk.[23] We used the established cut-off points of the American Heart Association (AHA) for high and normal lipid levels.[24]

Associations with lipid-related variables and disability as outcome variables were assessed by linear regression (cross-sectional analyses). Associations with an annual change in disability were assessed by multilevel mixed-effects linear regression, to account for the intra-individual course over time (prospective analyses).

Associations with disability were adjusted for relevant confounders, including relapse at the time of disability assessment (no, yes), age at study entry, sex, smoking (no, yes), statin use (no, yes), BMI (kg/m^2), physical activity (Mets) and 25(OH)D (nmol/L). Associations with annual change in EDSS were also adjusted for a categorical term for baseline EDSS (0 – 3, 3.5 – 5.5, 6 – 7, ≥ 7.5), because the progression of disability depends on baseline disability, and for change in relapse at the time of disability assessment. Transformation was applied as required, to satisfy homoscedasticity; however, all coefficients are reported on the scale of the original disability measure. All analyses were done using STATA/IC for Windows (Version 12.1; StataCorp LP, College Station, TX, USA).

Our standard analysis evaluated the prospective associations of the lipid-related variables at a winter review, with the subsequent annual change in EDSS from that winter to the next winter as the outcome variable. In order to evaluate causality, we used a time-lag analysis, where we shifted the lipid-related variables 6 months and 12 months before or after the outcome variable. If the observed associations were due to reverse causality, one would expect the magnitude of effects to become stronger when associations are modelled 6 or 12 months after the outcome variable.

Results

Participant characteristics

Table 1 shows the characteristics of the cohort at study entry. The cohort was followed for an average of 2.2 (SD 0.5) years; 62.9% were overweight or obese (≥ 25 kg/m^2), and only 5.6% (n = 11) were treated with statins during the study. Using the established lipid cut-off points,[24] we found that 51% of the participants had TC above 5.2 mmol/L, 24% had HDL below 1 mmol/L, 67% had LDL above 2.6 mmol/L and 39% had triglyceride above 1.7 mmol/L.

Determinants of serum lipids and apolipoproteins

Supplementary Table 1 shows the correlation between the lipid-related variables and Supplementary Table 2 shows details on the determinants of serum lipids and apolipoproteins. In summary, strong correlations were observed between a number of lipid measures, for example between TC, LDL, nonHDL and ApoB (r > 0.87). A higher age was associated with many of the lipid and apolipoprotein measures. Importantly, BMI was a significant independent predictor of lipid and apolipoprotein levels, taking into account factors such as age, sex, smoking, physical activity and statin use; and some associations were also seen for physical activity and smoking.

Association between lipid-related variables and clinical disability

In the basic analyses, nearly all lipid-related variables, including BMI, were associated with clinical disability, as measured by EDSS (Table 2) and MSSS (data not shown), such that a higher TC, LDL, and triglycerides, as well as ApoE, ApoB, and Lp(a) were associated with higher disability. Age and sex explained part of the associations, as adjustment for age and sex attenuated the associations; additional adjustment for smoking and statin use did not affect the associations. Neither HDL nor its associated apolipoprotein Apo-A-I were associated with disability in any analysis.

In clinical terms, after adjusted for age and sex, those who had a 2 mmol/L higher TC, LDL and non-HDL, had on average a 0.61 (p = 0.006), 0.54 (p = 0.037) and 0.59 (p = 0.003) higher current EDSS level, respectively. From the regression lines (adjusted for age and sex), we estimated that those at the cut-off point of high TC, HDL and LDL had a mean EDSS of 3.9, 4.2 and 4.5, respectively. In relation to BMI, those who had a 5 kg/m^2 higher BMI score had on average a 0.38 higher EDSS level.

The cross-sectional associations above could reflect reverse causality, where increased disability acts via an increased BMI and reduced physical activity to yield an adverse lipid profile. To account for reverse

Table 1. Demographic and clinical characteristics of the MS cohort at study entry.

Characteristics	*n/N* (%)
Total	178/178 (100)
Female sex	128/178 (72)
MS course at study entry	
RRMS	149/178 (83)
SPMS	20/178 (11)
PPMS	9/178 (5)
Immunomodulatory therapy used during study	132/178 (74)
Smoker during study	48/178 (27)
BMI (Kg/m^2)	
Normal	66/178 (37.1)
Overweight	74/178 (41.6)
Obese	38/178 (21.3)
	Mean (SD; range)
Age	47.4 (11.4; 21 – 77)
	Median (IQR)
MS duration from diagnosis (years)	6.0 (2.0, 12.0)
EDSS at study entry	3.5 (2.0, 5.0)
MSSS at study entry	4.0 (2.3, 6.2)
Physical activity (Met)	17.6 (3.3, 40.0)
BMI (Kg/m^2)	26.31 (23.4, 28.8)
TC (mmol/L)	5.2 (4.5, 6.1)
LDL (mmol/L)	3.4 (2.3, 3.6)
ApoB (g/L)	0.97 (0.82, 1.2)
Non-HDL (mmol/L)	3.7 (3.0, 4.6)
Trig (mmol/L)	1.5 (1.1, 2.2)
HDL (mmol/L)	1.4 (1.1, 1.7)
ApoA-I (g/L)	1.6 (1.3, 1.8)
ApoE (mg/L)	52.0 (41.0, 64.0)
Lp(a) (µmol/L)	0.5 (0.2, 1.4)
hs-CRP (mg/L)	16.5 (8.0, 36.0)

ApoA-I: Apoprotein A-I; ApoB: apoprotein B; ApoE: apoprotein E; BMI: body mass index; EDSS: Expanded Disability Status Scale; IQR: Interquartile range; LDL: low density lipoprotein; Lp(a): lipoprotein a; HDL: high density lipoprotein; Hs-CRP: high sensitive C-reactive protein; MS: multiple sclerosis; MSSS: Multiple Sclerosis Severity Score; Non-HDL: non-high-density lipoprotein; PPMS: primary progressive MS; RRMS: relapsing–remitting MS; SPMS: secondary progressive MS; TC: total cholesterol; Trig: triglycerides.

causality, we further adjusted for BMI and self-reported physical activity in the period prior to lipid measurement. In general, adjustment for BMI and physical activity reduced the magnitude of the coefficients (Table 2), with most of it driven by BMI rather than physical activity, even though there was some association between physical activity and EDSS (basic model: – 0.012 (– 0.018, – 0.005), $p <$ 0.001; adjusted model 2: – 0.005 (– 0.010, 0.0003), $p = 0.06$). Importantly, the TC, ApoB, ApoB/ApoA-I ratios remained significantly associated, even after taking BMI, physical activity and other confounders into account. In addition, there was an independent effect of BMI on disability. Adjustment for comorbid hypertension status did not affect the magnitude of the associations.

Similar associations were observed with MSSS. In the unadjusted analyses, higher TC, LDL, non-HDL and LDL/HDL ratio were significantly associated with higher MSSS. Again, adjusting for variables such as age, sex, BMI and physical activity explained part of the association, but independent associations were observed for TC (0.51 (0.18, 0.85), $p = 0.003$), LDL (0.68 (0.29, 1.08), $p = 0.001$), non-HDL (0.48 (0.16, 0.79), $p = 0.003$), LDL/HDL ratio (0.43 (0.07, 0.79), $p = 0.019$), ApoB (2.40 (0.85, 3.95), $p = 0.003$) and ApoB/ApoA-I ratio (2.26 (0.40, 4.13), $p = 0.018$). Again, no

Table 2. Associations between lipid-related variables and EDSS.

	Basic model[a]		Adjusted model 1[b]		Adjusted model 2[c]	
	Coefficient	*p*-value	Coefficient	*p*-value	Coefficient	*p*-value
BMI (kg/m^2)	0.08 (0.03, 0.14)	**0.002**	0.07 (0.02, 0.11)	**0.004**	0.06 (0.01, 0.10)[d]	**0.013**
TC (mmol/L)	0.44 (0.20, 0.68)	**< 0.001**	0.30 (0.09, 0.52)	**0.006**	0.23 (0.01, 0.44)	**0.037**
LDL (mmol/L)	0.40 (0.11, 0.69)	**0.007**	0.27 (0.01, 0.53)	**0.039**	0.14 (–0.11, 0.40)	0.26
ApoB (g/L)	2.06 (0.98, 3.14)	**< 0.001**	1.53 (0.61, 2.45)	**0.001**	1.01 (0.09, 1.93)	**0.003**
Non-HDL (mmol/L)	0.40 (0.18, 0.62)	**0.001**	029 (0.10, 0.49)	**0.004**	0.18 (−0.02, 0.38)	0.08
Trig (mmol/L)	0.26 (0.07, 0.45)	**0.009**	0.17 (0.01, 0.34)	**0.038**	0.11 (−0.05, 0.27)	0.19
HDL (mmol/L)	− 0.10 (− 0.72, 0.51)	0.74	− 0.31 (− 0.86, 0.23)	0.26	0.01 (−0.56, 0.59)	0.96
ApoA-I (g/L)	0.18 (− 0.53, 0.89)	0.62	− 0.12 (− 0.77, 0.53)	0.73	0.28 (− 0.39, 0.95)	0.41
ApoE (mg/L)	0.02 (0.01, 0.03)	**0.005**	0.01 (− 0.0001, 0.02)	0.052	0.01 (− 0.001, 0.02)	0.26
Lp(a) (µmol/L)	0.20 (0.05, 0.35)	**0.011**	0.08 (− 0.05, 0.21)	0.22	0.08 (− 0.04, 0.21)	0.20
Hs-CRP (mg/L)	0.01 (0.001, 0.01)	**0.010**	0.005 (0.001, 0.01)	**0.014**	0.003 (− 0.001, 0.007)	0.54
TC/HDL ratio	0.18 (0.02, 0.34)	**0.024**	0.14 (−0.001, 0.28)	0.052	0.05 (−0.10, 0.19)	0.52
LDL/HDL ratio	0.28 (0.03, 0.48)	0.09	0.22 (− 0.01, 0.45)	0.058	0.06 (− 0.17, 0.29)	0.63
ApoB/ApoA-I ratio	1.42 (0.18, 2.66)	**0.004**	1.41 (.30, 2.51)	**0.013**	0.68 (− 0.41, 1.77)	**0.018**

[a]Basic Model: Adjusted for relapse at the time of review.
[b]Adjusted model 1: Further adjusted for age at study entry, sex, smoking and statin use.
[c]Adjusted model 2: Further adjusted for BMI and physical activity.
[d]Also adjusted for TC and triglycerides.
ApoB: Apoprotein B; ApoA-I: apoprotein A-I; ApoB: apoprotein B; ApoE: apoprotein E; BMI: body mass index; EDSS: Expanded Disability Status Scale; Lipo(a): lipoprotein a; HDL: high density lipoprotein; Hs-CRP: high sensitive C-reactive protein; LDL: low density lipoprotein; TC: total cholesterol; Trig: triglycerides.

associations were seen with HDL ($p = 0.12$) and ApoA-I ($p = 0.12$). For BMI, those who had a 5 kg/m^2 higher BMI score had on average a 0.63 higher MSSS level, independent of other confounding factors.

Associations between lipid-related variables and changes in clinical disability

We next sought to evaluate the relationship between lipid levels and the subsequent change in disability. The prospective model (Table 3) is the preferred model, where the lipid values are measured at the beginning of the interval of measuring change in disability. Only the TC/HDL ratio was significantly associated with an annual change in EDSS and this association remained in the fully-adjusted model. Examining different lags for this association (Supplementary Table 3) did not indicate that the effect was due to reverse causality, as the association was weaker when the TC/HDL ratio was measured in the middle, end or after the interval over which the change in EDSS was measured.

Stronger associations were observed in the basic model when lipids were measured in the middle of the outcome interval (defined as the cross-sectional model), but only HDL was significant in the fully adjusted model. From the findings on HDL using other lags for HDL, we could not determine whether or not this association was due to reverse causality.

BMI at baseline was not associated with a change in disability (basic model: coefficient 0.003 (– 0.011, 0.02), $p = 0.64$; adjusted model 1: coefficient 0.005 (– 0.01, 0.02) $p = 0.53$; adjusted model 2: coefficient – 0.002 (– 0.02, 0.01) $p = 0.82$). No associations were observed for any of the models for triglycerides, Lp(a), Hs-CRP and ApoE, nor for physical activity (data not shown).

Discussion

Using a prospective cohort design in people with MS, we found that higher TC, ApoB and ApoB/ApoA-I ratio were associated with higher disability; and that a higher TC/HDL ratio was associated with a faster accrual of disability, suggesting that lipid-lowering interventions may be of benefit for people with MS.

We observed that those with an adverse lipid profile (elevated TC, LDL, non-HDL, triglyceride, ApoB and ApoB/ApoA-I ratio) had higher levels of clinical disability. Part of the effect was explained by age and sex; however, as we examined these associations cross-sectionally, this raises the question of reverse causality, i.e. whether an increased BMI

Table 3. Prospective association between lipid-related variables and annual change in EDSS.

Model	TC	LDL	ApoB	Non-HDL	HDL	ApoA-I	TC/ HDL	LDL/ HDL	ApoB/ ApoA-I
Basic model	0.02	0.04	0.22	0.04	0.11	− 0.05	**0.05**	0.06	0.26
	(− 0.05, 0.09)	(− 0.04, 0.13)	(− 0.09, 0.52)	(− 0.02, 0.11)	− (− 0.28, 0.06)	(− 0.24, 0.14)	**(0.00, 0.09)**	(− 0.03, 0.15)	(− 0.12, 0.63)
	p = 0.50	*p* = 0.32	*p* = 0.16	*p* = 0.20	*p* = 0.19	*p* = 0.62	***p* = 0.045**	*p* = 0.17	*p* = 0.18
Adjusted model 1	0.03	0.05	0.21	0.04	− 0.10	− 0.01	**0.04**	0.05	0.24
	(− 0.05, 0.10)	(− 0.04, 0.13)	(− 0.10, 0.51)	(− 0.03, 0.11)	(− 0.27, 0.08)	(− 0.21, 0.19)	**(0.003, 0.09)**	(− 0.03, 0.14)	(− 0.13, 0.61)
	p = 0.47	*p* = 0.29	*p* = 0.18	*p* = 0.23	*p* = 0.28	*p* = 0.91	***p* = 0.07**	*p* = 0.23	*p* = 0.21
Adjusted model 2	0.04	0.05	0.26	0.05	− 0.10	− 0.005	**0.05**	0.06	0.28
	(− 0.04, 0.11)	(− 0.03, 0.14)	(− 0.05, 0.57)	(− 0.02, 0.11)	(− 0.28, 0.08)	(− 0.21, 0.20)	**(0.01, 0.10)**	(− 0.03, 0.16)	(− 0.11, 0.66)
	p = 0.33	*p* = 0.22	*p* = 0.10	*p* = 0.14	*p* = 0.29	*p* = 0.96	***p* = 0.029**	*p* = 0.16	*p* = 0.16

[a]Basic Model: Adjusted for change in relapse, EDSS at baseline.
[b]Adjusted model 1: Further adjusted for age at study entry, sex, MS duration, smoking and statin use.
[c]Adjusted model 2: Further adjusted for BMI and physical activity.
TC: Total cholesterol; ApoA-I: apoprotein A-I; ApoB: Apoprotein B; EDSS: Expanded Disability Status Scale; HDL: high density lipoprotein; LDL: low density lipoprotein; MS: multiple sclerosis.

and adverse lipid profile results in higher disability, or whether increased disability results in a higher BMI and more adverse lipid profile. We know that a higher BMI results in a more adverse lipid profile.[25–27] Indeed, adjustment for BMI and physical activity reduced the magnitude of the associations, but independent associations were still observed for TC, ApoB and the ApoB/ApoA-I ratio. In addition, we observed an effect of BMI on disability that was independent of the effect of lipids. Our findings agree with studies that have found associations between LDL,[10,28] TC,[10] TC/HDL ratio,[17] BMI[29] and disability.

We also examined whether lipid-related measures influenced the clinical course of MS by examining the association with the patients' annual change in disability. It was previously reported that higher baseline LDL, TC and triglycerides were associated with a worsening in EDSS and MSSS over 2.2 years, but that study did not adjust for potential confounders, apart from age and sex.[17] In our prospective analysis, we found that the TC/HDL ratio was associated with a higher annual change in EDSS. Examining different lags for this association did not indicate that the effect was due to reverse causality. Our findings are in line with a recent placebo-controlled trial in people with MS, which found that those using lipid-lowering statins had a lower change in EDSS after 2 years.[30] Baseline BMI was not associated with a change in disability.

Although comparable to that of the general population,[31] our MS population had, on average, high total cholesterol (5.36 mmol/L (SD1.14)) and LDL levels (3.12 mmol/L (SD 0.97)). The level of dyslipidaemia (TC > 5.5mmol/L) was also high, with 35% of participants classified as having dyslipidaemia. In analyses adjusted for age and sex, for each 2 mmol/L increase in TC, LDL and non-HDL, we found EDSS was 0.6 higher; and for each 5 kg/m^2 higher BMI, EDSS was 0.4 higher. Those with a lipid profile reaching the established cut-off points for high lipid levels[24] had, on average, an EDSS score of 3.6 to 4.8, depending on the lipid type measured. Considering that a 0.03 mmol/L increase in LDL cholesterol confers a > 1% increase in cardiovascular disease risk[32] and that vascular comorbidities are common in MS,[10] these levels will be associated with a significantly increased cardiovascular disease burden. Clinicians should therefore monitor lipid levels in people with MS and treat adverse levels as early as possible.

We found stronger associations for ApoB than for LDL, in relation to EDSS and change in EDSS, which

is in line with data demonstrating that ApoB is a better measure of the relative number of circulating LDL particles and a better indicator of heart disease risk than total cholesterol or LDL.[33]

It is known that 7-dehydrocholesterol is required as a substrate for the endogenous production of 25(OH)D in the skin, and previously, there were significant positive associations found between 25(OH)D and HDL[34] and negative associations with triglycerides.[34] We observed an independent association between higher 25(OH)D and higher HDL, ApoA-I, ApoE, a lower LDL/HDL ratio and a lower TC/HDL ratio.

Our study has significant strengths, including being a prospective population-based cohort study with the capability to adjust for relevant confounders and examine mediation pathways. The study had some limitations. The 2-year change in clinical disability measured is limited and a longer follow-up is preferable when measuring change in disability. We examined reverse causality, but this cannot be fully ruled out in observational studies. We used non-fasting serum samples, which may have influenced the levels of triglycerides,[35] and this could have contributed to observing non-significant associations with triglycerides. Some associations have been observed with MRI markers,[13–15] but we could not examine that in this study.

Clinicians should be aware of the associations between lipids, BMI and disability in MS; and monitor and treat adverse lipid profiles as early as possible, preferably in a clinical trial setting. Our findings that adverse lipid levels were associated with disability as well as disability progression suggested that reducing lipids, decreasing BMI into the healthy range and increasing physical activity may significantly reduce the accumulation of disability. Early interventions in the disease course are likely to be more successful, and our findings provide support for studies of lipid-reducing interventions in early MS, before sustained disability occurs.

Conflict of interest

The author declares that there is no conflict of interest.

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