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Association of body mass index with longitudinal rates of retinal atrophy in multiple sclerosis

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Abstract

Background: Studies evaluating associations between body mass index (BMI) and optical coherence tomography (OCT) measures in multiple sclerosis (MS) are lacking.

Objective: To assess whether elevated BMI is associated with accelerated retinal atrophy.

Methods: In this observational study, 513 MS patients were followed with serial spectral-domain OCT for a median of 4.4 years. Participants were categorized as normal weight (BMI: 18.5–24.9kg/m²), overweight (BMI:25–29.9kg/m²), and obese (BMI: 30kg/m²). Participants with diabetes mellitus or uncontrolled hypertension, and eyes with optic neuritis (ON) 6 months prior

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to baseline OCT or during follow-up were excluded. Statistical analyses were performed with mixed-effects linear regression.

Results: Obese patients (n=146) exhibited accelerated rates of ganglion cell+inner plexiform layer (GCIPL) atrophy relative to normal weight patients (n=214) (−0.57%/year [95% CI: −0.65% to −0.48%] vs −0.42%/year [95% CI: −0.49% to −0.35%]; p=0.012). GCIPL atrophy rate did not differ between overweight (n=153) and normal weight patients (−0.47%/year vs. −0.42%/year; p=0.41). Each 1kg/m² higher BMI was associated with accelerated GCIPL (−0.011%/year; 95% CI: −0.019% to −0.004%; p=0.003) atrophy. Multivariable analyses accounting for age, sex, race, MS subtype, and ON history did not alter the above findings.

Conclusions: Elevated BMI, in the absence of overt metabolic co-morbidities, may be associated with accelerated GCIPL atrophy. Obesity, a modifiable risk factor, may be associated with accelerated neurodegeneration in MS.

Keywords

Multiple sclerosis; Retina; Body Mass Index; Optical Coherence Tomography

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disease of the central nervous system.¹ Several genetic and environmental factors have been implicated as MS risk factors, including elevated body mass index (BMI).^{1,2} MS is frequently characterized by transient episodes of neurologic dysfunction at onset, often followed by a progressive clinical course with gradual accumulation of disability, driven primarily by neuro-axonal degeneration.¹ In MS, elevated BMI has been associated with disability, cognitive dysfunction, and disease progression.³⁻⁷ However, the role of BMI in MS prognostication remains unclear. Recently, elevated BMI in MS has been shown to be associated with accelerated rates of brain atrophy, thought to primarily reflect neuro-axonal loss, the principal substrate underlying disability in MS.⁸ Confidence in these findings would be strengthened by confirmation in an independent cohort.

Optic neuropathy is virtually ubiquitous in MS.⁹ Optical coherence tomography (OCT) enables rapid, non-invasive, high-resolution, and reliable quantification of discrete retinal layers. OCT-determined reductions in peri-papillary retinal nerve fiber layer (pRNFL) and in particular ganglion cell+inner plexiform layer (GCIPL) thicknesses correlate not only with visual function, but global disability in MS.^{10,11} Furthermore, rates of GCIPL thinning are accelerated in MS patients exhibiting clinical or radiological disease activity and mirror brain atrophy.^{11,12} However, BMI association with rates of retinal atrophy in MS is unknown.

The aim of this longitudinal observational study was to assess whether elevated BMI is independently associated with accelerated rates of retinal layer atrophy in MS.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Review Board of Johns Hopkins University. All study participants provided written informed consent.

Study Design and Participants

Patients with MS were recruited by convenience sampling from the Johns Hopkins MS Center and were studied between 2008 and 2019. MS diagnosis was confirmed by the treating neurologist, according to the 2005 revised McDonald criteria.¹³ MS was classified as relapsing remitting (RRMS), secondary progressive (SPMS), or primary progressive MS (PPMS), according to the Lublin classification.¹⁴ Patients with progressive MS (SPMS and PPMS) were combined into a single cohort for analyses. MS patients with a baseline OCT assessment performed within 6 months of BMI measurement and 11 months of OCT follow-up were considered eligible for inclusion. Exclusion criteria included optic neuritis (ON) within 6 months of baseline OCT, prior ocular surgery or trauma, ocular refractive errors of greater than ± 6 diopters, glaucoma, or other significant neurological or ophthalmological disorders that may affect OCT measurements. We additionally excluded individuals with uncontrolled hypertension, or diabetes mellitus, in an effort to isolate the independent effects of BMI on retinal layer changes, as these comorbidities can affect the retina, and confound OCT measures, even in the absence of MS.¹⁵ All patients who attend the MS Center are encouraged to undergo routine annual physical assessments with their primary care provider, and annual ophthalmological assessments as part of routine standard of care. Fundus examination was performed at each visit as part of the standard neurological examination. Therefore, exclusion of patients secondary to the criteria above was based on a combination of history, physical examination, review of patients' electronic medical records (EMR), and assessments obtained through routine standard of care. Data from eyes that developed ON during the course of the study were censored at the time of the last available OCT prior to the ON event.

Participants underwent retinal imaging with serial OCT. Demographic and clinical data were recorded at baseline. Disease-modifying treatment (DMT) use was recorded at each OCT visit. We classified glatiramer acetate, interferon-beta and teriflunomide as low-potency DMTs, dimethyl fumarate and fingolimod as intermediate-potency DMTs, and natalizumab, ocrelizumab, rituximab, alemtuzumab, and daclizumab as high-potency DMTs.

BMI Measurements

Patient weight and height were measured and recorded in the EMR within 6 months of baseline OCT, with BMI calculated using the formula (weight [kg]/height [m²]). Patients were classified as underweight (<18.5kg/m²), normal weight (18.5-24.9kg/m²), overweight (25.0-29.9kg/m²), or obese (≥ 30 kg/m²) according to BMI criteria by the World Health Organization (WHO).

Procedures

Retinal imaging was performed using spectral-domain OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA), as previously described.¹⁶ Briefly, peri-papillary and macular scans were obtained with the Optic Disc Cube 200×200 protocol and Macular Cube 512×128 protocol, respectively. Scans with signal strength below 7/10, or with artifact, were excluded, in accordance with OSCAR-IB criteria.^{15,17}

Peri-papillary RNFL thickness values were generated by conventional Cirrus HD-OCT software, as described elsewhere.¹⁶ Segmentation of the GCIPL, inner nuclear layer (INL) and outer nuclear layer (ONL) was performed utilizing an open-source, validated segmentation algorithm, as previously described.^{18,19} Average thicknesses of the GCIPL, INL and ONL were calculated within an annulus centered on the fovea, with an internal diameter of 1mm and an external diameter of 5mm. Retinal layer segmentation was visually inspected and verified for all scans.

OCT methods and results are reported in accordance with consensus APOSTEL recommendations.²⁰

Statistical Analysis

Comparisons of baseline characteristics between groups were performed with one-way ANOVA and Student's t-test (age), Chi-squared test (sex, MS subtype, ON history), Fisher's exact test (race), Kruskal-Wallis test, and Wilcoxon rank-sum test (disease duration, follow-up time, expanded disability status scale [EDSS]). For the duration of follow-up, we calculated patient-years on low-potency, intermediate-potency and high-potency DMTs for each BMI cohort (normal weight, overweight, obese); comparisons between groups were performed utilizing the Chi-squared test.

Baseline OCT measures were compared between BMI groups with mixed-effects linear regression models, with subject-specific random intercepts, adjusted for age, sex, race, MS subtype and ON history, in order to account for within-subject inter-eye correlations.

To analyze rates of change of retinal layer thicknesses during follow-up, we applied mixed-effects linear regression models with subject-specific and eye-specific random intercepts and random slopes in time, using time from baseline OCT visit as a continuous variable, in order to account for within-subject inter-eye correlations. Log-linear models were utilized to estimate mean annualized percent change in retinal layer thickness, in order to facilitate interpretation of the obtained beta coefficients. We tested for differential rates of atrophy between BMI groups using a group*time interaction term.

In addition to the unadjusted model described above, additional multivariable analyses were performed, with inclusion of the following covariates: age (as a continuous variable), sex, race (as a dichotomous variable: African-American or non-African-American), MS subtype (as a dichotomous variable: relapsing-remitting or progressive subtype), ON history and interaction terms with follow-up time for sex (sex*time), race (race*time), and MS subtype (subtype*time). Additional analyses were performed, in which MS subtype was included as a categorical variable with three groups (RRMS, SPMS, PPMS), rather than two (RRMS,

progressive MS). These analyses did not significantly alter results of our primary outcome; therefore, results presented are only from models combining PPMS and SPMS into a single progressive MS subtype.

In order to further characterize the association of BMI with rates of retinal layer change, additional mixed-effects linear regression models were fitted, including BMI as a continuous independent variable and its interaction with follow-up time (BMI*time). Point estimates of GCIPL and pRNFL atrophy rates at specific BMIs (marginal effects) were estimated from this model. In sensitivity analyses, we allowed for potential nonlinear associations between BMI and rates of individual retinal layer atrophy using restricted cubic splines, or by inclusion of a quadratic term. This did not improve fit of our models (likelihood ratio test: $p > 0.05$ for all retinal layers examined), and therefore only results from models including linear BMI terms are presented.

Analyses were based on a priori established research hypotheses and consequently adjustment for multiple comparisons was not performed. Statistical analyses were performed using STATA version 13 (StataCorp, College Station, TX). Statistical significance was defined as $p < 0.05$. Figures were made using GraphPad Prism version 8.2 (GraphPad Software, La Jolla, CA, www.graphpad.com).

RESULTS

Study Population

522 MS patients (9 underweight, 214 normal weight, 153 overweight, and 146 obese) were eligible for inclusion in analyses (Figure 1). Median duration of follow-up was 4.4 years. The number of OCT assessments that were performed was 4710 eye-visits in total. The median number of visits for each patient was 4 (IQR: 3-6 visits), and the median interval between visits was 314 days (IQR: 192-510 days).

Baseline demographics and clinical characteristics are presented in Table 1. Data from nine MS patients who were underweight (BMI < 18.5 kg/m²) are provided for descriptive purposes but are not included in analyses utilizing the WHO BMI classification due to insufficient sample size.

There were no significant differences between BMI groups with respect to age, MS subtype, disease duration, ON history, and duration of follow-up. Sex differed between groups ($p < 0.001$), with females more likely to be classified as normal weight. Additionally, there were differences in racial demographics ($p = 0.001$), with the highest proportion of African-Americans in the obese cohort. Breakdown of patient-years on each category of DMT differed between BMI groups ($p = 0.007$). Among patients in the overweight cohort, we observed a greater proportion of follow-up on low-potency DMTs; this was relative to the obese cohort, who remained on no DMT for a greater proportion of follow-up (pairwise comparisons: normal weight vs overweight: $p = 0.09$, normal weight vs obese: $p = 0.10$, overweight vs obese: $p = 0.002$).

Baseline cross-sectional comparisons of OCT measures

Baseline retinal layer thicknesses and comparisons between BMI groups are presented in Table 2 and Supplementary Table 1. MS patients with normal weight had lower baseline GCIPL thickness compared to overweight ($p=0.018$) and obese patients ($p=0.021$). In multivariable analyses, these differences appeared to be primarily driven by more severe prior ON events in the normal weight cohort, resulting in lower GCIPL thickness in prior ON eyes in normal weight patients (normal weight vs. overweight: Difference: $-3.77\mu\text{m}$ [95% CI: -6.90 to -0.65], $p=0.018$; normal weight vs. obese: Difference: $-2.88\mu\text{m}$ [95% CI: -6.11 to 0.35], $p=0.08$, data not shown). However, lower baseline GCIPL thickness was observed in normal weight as compared to obese patients in analyses excluding eyes with prior ON (normal weight vs. overweight: Difference: $-1.45\mu\text{m}$ [95% CI: -3.12 to 0.22], $p=0.09$; normal weight vs. obese: Difference: $-1.72\mu\text{m}$ [95% CI: -3.42 to -0.01], $p=0.048$, data not shown). INL and ONL thicknesses did not differ between groups at baseline. Overall, retinal layer thicknesses did not differ between overweight and obese participants.

Longitudinal Retinal Atrophy Rates

Mean unadjusted annualized change in retinal layer thicknesses in normal weight, overweight, and obese participants are shown in Table 3 (% change/year), Supplementary Tables 2 and 3 (μm change/year) and Figure 2. Obese patients exhibited faster rates of GCIPL atrophy as compared to normal weight patients (-0.57% [95% CI: -0.65% to -0.48%] vs -0.42% [95% CI: -0.49% to -0.35%] per year, respectively; $p=0.012$). GCIPL atrophy rates did not differ significantly between overweight and normal weight patients nor between overweight and obese patients. No significant differences were observed between cohorts when analyzing atrophy rates of other retinal layers. Multivariable analyses (as described above) did not alter the above findings (Table 3, Supplementary Table 2 and 3). However, African-American race was independently associated with accelerated GCIPL atrophy (β_{race} : -0.16% [95% CI: -0.28% to -0.04%] per year, $p=0.009$).

Finally, consistent with already known negative prognostic factors in MS²¹, male sex and progressive MS subtype were independently associated with accelerated GCIPL atrophy (β_{sex} : -0.13% [95% CI: -0.23% to -0.02%] per year, $p=0.021$ for male sex; β_{subtype} : -0.18% [95% CI: -0.29% to -0.08%] per year, $p=0.001$ for progressive MS).

We furthermore aimed to characterize the association of BMI with longitudinal rates of retinal layer atrophy by fitting models, wherein BMI was included as a continuous independent variable with its interaction with follow-up time (BMI*time). In these analyses, each $1\text{kg}/\text{m}^2$ higher BMI was associated with accelerated GCIPL (-0.011% [95% CI: -0.019% to -0.004%] per year, $p=0.003$) atrophy. Utilizing this model, we calculated and present point estimates of annualized percent change in GCIPL thickness for BMIs of 20, 25, 30, 35, and 40 (Table 4). In multivariable analyses (as described above), these associations remained statistically significant for GCIPL thickness ($p=0.016$). BMI was not associated with rates of pRNFL, INL or ONL thinning (data not shown).

Given the higher proportion of African-Americans in the obese cohort, we performed sensitivity analyses restricted to Caucasian-Americans: each $1\text{kg}/\text{m}^2$ higher BMI was

associated with a trend towards accelerated GCIPL atrophy, although this association did not meet statistical significance in univariable ($-0.007\%/year$ [95% CI: -0.015% to 0.0001%], $p=0.054$), nor multivariable models ($p=0.11$), possibly due to a reduction in power.

DISCUSSION

In the current study, we demonstrate that higher baseline BMI is independently associated with an accelerated rate of GCIPL atrophy in MS. Highlighting the clinical relevance of our findings, rates of GCIPL thinning have been shown to be faster in MS patients with non-ocular clinical and/or radiological disease activity, as well as patients exhibiting disability progression.¹¹ Moreover, GCIPL atrophy has been shown to mirror rates of whole brain, and in particular cortical gray matter atrophy over time in MS.¹² While we did not observe similar associations with pRNFL atrophy, this is unsurprising given that previous studies have demonstrated the superiority of GCIPL as compared to pRNFL thickness in mirroring global neurodegeneration in MS. Specifically, GCIPL thickness has exhibited superior reliability, reproducibility, and structure-function relationships in MS relative to other retinal layers.^{10,12,22} Moreover, unlike the pRNFL, the GCIPL does not swell during acute optic neuritis, potentially making it a more stable measurement over time.²³ Our study findings indicate that MS patients with an elevated BMI may exhibit accelerated neuro-axonal loss and more profound neurodegeneration. Since neurodegeneration is the principal substrate of disability in MS, our findings therefore indicate that MS patients with higher BMI may be at increased risk for worse MS outcomes. Importantly, we demonstrate that accelerated retinal atrophy is most prominent in those patients on the extreme of the BMI spectrum (BMI ≥ 30 kg/m²), suggesting that they may represent a group at greater risk.

Our study findings are in accordance with prior work demonstrating that MS patients with an elevated BMI exhibit more rapid disease progression, including accelerated brain atrophy and worse outcomes in ambulation and global disability.⁶⁻⁸ Several previous studies have also reported associations between BMI and measures of disease severity, including cognitive performance and global disability; however, the cross-sectional design of these studies limits inferences about causality.^{3,5} Our study's cross-sectional findings at baseline demonstrated reduced mean GCIPL thickness and marginally reduced pRNFL thickness among the normal weight cohort with respect to the overweight and obese cohorts; however, these findings appear to have been primarily driven by disproportionate tissue injury resulting from prior ON events. Although analyses restricted to eyes without a history of ON also demonstrated thinner baseline GCIPL and pRNFL thickness, these differences of $\sim 2\mu m$ are likely of little clinical significance. Even though it is possible that these cross-sectional differences are mediated by obesity per se; the potential pathophysiological mechanism through which obesity would be postulated to mediate these changes is unclear, thus, this interpretation is probably less likely. Our cross-sectional results should therefore be interpreted with caution. In this regard, our longitudinal findings are far more informative, clearly illustrating the potential modification of retinal atrophy in MS by BMI. Since OCT is being increasingly incorporated in clinical trials aiming to demonstrate neuroprotective effects, these findings highlight BMI as a potential confounding factor that should be a consideration in the design of future studies.

Despite being identified as a risk factor for developing MS and, to some extent, for MS progression, the biological mechanisms by which obesity might affect the disease course of MS are poorly understood. Nevertheless, several factors have been proposed to play a potential role. Obesity modulates the immune response towards a proinflammatory profile, with reduced regulatory T-cell activity and increased Th1 cell response.^{24,25} Additionally, leptin specifically may be a contributor to neuroinflammation and neurodegeneration in MS.²⁶ The obese population may be more susceptible to neurodegeneration, since an elevated BMI appears to be associated with reduced whole brain and gray matter volumes in otherwise healthy adults, as well as an increased risk for Parkinson's, and Alzheimer's disease.²⁷⁻²⁹ Therefore, it is conceivable that these mechanisms are not specific to MS; they may in fact be at play in a variety of neurodegenerative conditions.

In the current study, we did not examine the effects of obesity-related comorbidities on rates of retinal atrophy, such as hyperlipidemia, diabetes mellitus, and hypertension, which occur with increased prevalence in individuals with an elevated BMI and have been associated with worse prognosis in MS, including more advanced brain atrophy, and disability progression.^{3,4,30,31} Thus, it is possible that the adverse effect of elevated BMI on MS outcomes is mediated, at least in part, by the complex interplay between obesity and metabolic comorbidities that have an increased prevalence in this population. While patients with overt metabolic abnormalities including diabetes mellitus or uncontrolled hypertension were excluded in the current study, we were unable to account for all clinical and, perhaps more importantly, subclinical cardiovascular comorbidities and lifestyle factors that may influence metabolic health. Considering the difficulty in isolating the effects of BMI on retinal layer atrophy, and the association of BMI with all-cause cardiovascular morbidity and mortality, we viewed BMI as an imperfect surrogate of global metabolic health, encapsulating potential cardiovascular comorbidities that may not overtly manifest at an individual level.^{32,33}

Similarly, clinical and demographic characteristics such as race, sex and MS subtype are thought to affect rates of retinal atrophy. Therefore, an important limitation of the current study is that, despite including these covariates and their respective interactions with follow-up time (sex*time, race*time, MS subtype*time) in our statistical models, the study likely does not accurately reflect the complex interplay between these characteristics and their modifying effect on retinal atrophy. While it is challenging to isolate these effects in an observational study, evaluation of these associations would be of interest in future studies. On this point, it is worth noting that there was a significantly higher proportion of African-American patients in the obese cohort compared to the normal and overweight cohorts. African-American patients with MS exhibit a more aggressive disease course, including accelerated brain and retinal atrophy.³⁴ However, accounting for race in our analyses, we found that both African-American race and elevated BMI were independently associated with faster rates of GCIPL atrophy, suggesting that the preponderance of African-American patients in the obese cohort did not influence our findings; rather, both race and BMI have significant associations with rates of retinal atrophy. Additionally, the study lacked data in healthy controls. This is an important consideration, since elevated BMI has been associated with ophthalmological abnormalities, including lower pRNFL and GCIPL thicknesses and elevated intraocular pressure (a risk factor for glaucoma), among otherwise healthy

individuals.³⁵ It is currently unclear if these associations are a direct effect of obesity or whether obesity per se confers an increased risk for glaucoma.³⁶ Nevertheless, given the previously reported association between obesity and reduced brain volumes, as well as between obesity and decreased inner retinal thickness among otherwise healthy adults, future studies are needed to evaluate the potential association between BMI and longitudinal retinal atrophy rates among healthy controls, and to compare whether the strength of this association differs from that observed among people with MS.^{27,35} Additionally, our models did not adjust for DMT use; this was primarily due to difficulties in accounting for individual variation in length of time on various DMTs, as the vast majority of study participants switched between several DMTs over the duration of follow-up. However, comparison between BMI cohorts demonstrated only minor differences in patient-years on different classes of DMT potency, and there were no significant differences in patient-years on high-potency DMTs. Exclusion criteria included individuals with diabetes mellitus, glaucoma, and comorbid ophthalmological disorders. As this was a retrospective study, screening for these conditions -through measurement of intraocular pressures and serum HbA1c, and baseline ophthalmological assessment- was not performed systematically; rather, we performed retrospective screening for documented evidence of these comorbidities using patients' EMR. Similarly, due to the retrospective nature of this study, BMI was not recorded in the EMR on the same day as OCT assessment in all cases - hence, we included BMI measurements within 6 months of OCT assessment, as significant change in BMI is unlikely to occur during such a short period of time. Furthermore, we utilized a single BMI measurement to predict changes in OCT measures. This approach did not account for potential changes in BMI over the duration of study follow-up. However, this would likely have had minimal impact on our findings, as we observed relatively minor changes in BMI among individuals over the duration of follow-up (average annualized change in BMI: +0.08 [SD: 0.98]), with only two patients transitioning from normal weight to obese, or vice versa. Finally, we utilized BMI as a surrogate marker for adiposity; however, BMI is only a crude measure of body fat, which does not account for differences in body composition and body fat percentage. Future studies could seek to investigate the potential associations between more precise measures of adiposity and MS imaging outcomes.

In summary, our study provides strong evidence that elevated BMI is associated with accelerated rates of retinal neuro-axonal loss in MS, and therefore may be a modifiable risk factor for MS severity. To our knowledge, this is the first large-scale longitudinal study to investigate the association of BMI with rates of retinal layer atrophy in MS. While it would be necessary to independently validate our findings, our observations are likely clinically relevant and may be suggestive of a relationship between metabolic health and disease progression in MS. These findings support the rationale for future studies to investigate whether the modification of obesity may improve outcomes in MS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Study profile

ERM: epiretinal membrane; HIV: human immunodeficiency virus; MS: multiple sclerosis;

OCT: optical coherence tomography; ON: optic neuritis

Figure 2.

Annualized percent change in GCIPL thickness by BMI category

The error bars represent 95% CI for the annualized % change in GCIPL thickness. P-values derived from mixed effects linear regression models, including follow-up time, BMI category and their interaction, accounting for within subject inter-eye correlations.

BMI: body mass index; GCIPL: ganglion cell + inner plexiform layer thickness

Table 1.

Demographics and Clinical Characteristics. Statistically significant results are in bold

	<i>Underweight</i> [BMI <18.5 kg/m ²]	Normal weight [BMI 18.5- 24.9 kg/m ²]	Overweight [BMI 25-29.9 kg/m ²]	Obese [BMI ≥30 kg/m ²]	p-value ^a
Participants, n (eyes, n)	9 (18 eyes)	214 (401 eyes)	153 (289 eyes)	146 (264 eyes)	
Age, years; mean (SD)	37.9 (10.0)	42.5 (12.2)	44.0 (12.3)	43.2 (11.5)	0.47 ^d
Female; n (%)	9 (100%)	171 (80%)	91 (60%)	105 (72%)	<0.001 ^e
Race^b					0.001^f
Caucasian-American; n, (%)	8 (89%)	167 (78%)	124 (81%)	99 (68%)	
African-American; n, (%)	1 (11%)	37 (17%)	22 (14%)	46 (32%)	
Other; n (%)	0 (0%)	10 (5%)	7 (5%)	1 (1%)	
MS subtype					0.93 ^g
PPMS; n (%)	0 (0%)	24 (11%)	14 (9%)	14 (10%)	
SPMS; n (%)	2 (22%)	40 (19%)	33 (22%)	28 (19%)	
RRMS; n (%)	7 (78%)	150 (70%)	106 (69%)	104 (71%)	
Eyes with a history of ON; n (%)	8 (56%)	99 (25%)	61 (22%)	56 (21%)	0.44 ^h
Patients with a history of ON; n (%)	7 (78%)	96 (45%)	65 (42%)	65 (45%)	0.9 ⁱ
EDSS; median (IQR)^c	n/a	3 (2-6) ^c	3.5 (2.5-5.5) ^c	3.75 (2.5-5.5) ^c	0.93 ^j
Disease duration, years; median (IQR)	11 (8-19)	8 (3-13)	7 (3-11)	6 (2-13)	0.26 ^k
Follow-up time, years; median (IQR)	3.87 (2.76-4.50)	4.83 (2.61-7.06)	3.94 (2.53-6.82)	4.37 (2.63-5.81)	0.16 ^l
Patient-years on disease-modifying treatments during follow-up^b					0.007^m
None; n (%)	2.2 (6%)	239.4 (24%)	137.2 (19%)	155.6 (24%)	
Low-potency; n (%)	10.7 (30%)	418.6 (41%)	321.9 (45%)	231.3 (36%)	
Intermediate-potency; n (%)	4.1 (11%)	156.2 (15%)	114.1 (16%)	116.9 (18%)	
High-potency; n (%)	19.1 (53%)	180.3 (18%)	127.6 (18%)	139.4 (21%)	
Other immunosuppressive medication; n (%)	0 (0%)	12.9 (1%)	17.2 (2%)	7.7 (1%)	

^aP-values for group comparisons between the normal weight, overweight and obese cohorts. Data from 9 MS patients who were underweight (BMI <18.5 kg/m²) are provided for descriptive reasons but are not included in analyses due to insufficient sample size.

^bThe sum of percentages is not 100% due to rounding.

^cBaseline EDSS data were available for 89 patients with normal weight, 64 overweight patients and 52 obese patients.

^dAge: one-way ANOVA; Pairwise comparisons by t-test: Normal weight vs Overweight (p=0.23), Normal weight vs Obese (p=0.54), Overweight vs Obese (p=0.58)

^eSex: chi-squared test; Pairwise comparisons: Normal weight vs Overweight (p<0.001), Normal weight vs Obese (p=0.08), Overweight vs Obese (p=0.024)

^fRace: Fisher's exact test; Pairwise comparisons: Normal weight vs Overweight (p=0.74), Normal weight vs Obese (p=0.001), Overweight vs Obese (p<0.001)

^gMS subtype: Chi-squared test; Pairwise comparisons: Normal weight vs Overweight (p=0.69), Normal weight vs Obese (p=0.89), Overweight vs Obese (p=0.88)

^hEyes with a history of ON: Chi-squared test; Pairwise comparisons: Normal weight vs Overweight (p=0.97), Normal weight vs Obese (p=0.43), Overweight vs Obese (p=0.44)

ⁱPatients with a history of ON: Chi-squared test; Pairwise comparisons: Normal weight vs Overweight (p=0.65), Normal weight vs Obese (p=0.95), Overweight vs Obese (p=0.72)

^jEDSS: Kruskal-Wallis test; Pairwise comparisons by Wilcoxon rank-sum test: Normal weight vs Overweight (p=0.85), Normal weight vs Obese (p=0.97), Overweight vs Obese (p=0.64)

^kDisease duration: Kruskal-Wallis test; Pairwise comparisons by Wilcoxon rank-sum test: Normal weight vs Overweight (p=0.35), Normal weight vs Obese (p=0.11), Overweight vs Obese (p=0.48)

^lFollow-up time: Kruskal-Wallis test; Pairwise comparisons by Wilcoxon rank-sum test: Normal weight vs Overweight (p=0.45), Normal weight vs Obese (p=0.27), Overweight vs Obese (p=0.94)

^mPatient-years on DMTs: Chi-squared test; Pairwise comparisons: Normal weight vs Overweight (p=0.09), Normal weight vs Obese (p=0.10), Overweight vs Obese (p=0.002)

BMI: body mass index; DMT: disease-modifying treatment; EDSS: expanded disability status scale; IQR: interquartile range; MS: multiple sclerosis; ON: optic neuritis; RRMS: relapsing remitting MS; PPMS: primary progressive MS; SPMS: secondary progressive MS

Table 2. Baseline retinal layer thicknesses and comparisons between groups. Statistically significant results are in bold

	Retinal layer thicknesses, μm ; mean (SD)				p-value ^a (unadjusted)			p-value ^a (adjusted ^b)	
	Underweight [BMI <18.5 kg/m ²] (n=18 eyes)	Normal weight [BMI 18.5- 24.9 kg/m ²] (n=401 eyes)	Overweight [BMI 25-29.9 kg/m ²] (n=289 eyes)	Obese [BMI ≥30 kg/m ²] (n=264 eyes)	Normal vs. overweight	Normal vs. obese	Overweight vs. obese	Normal vs. obese	Overweight vs. obese
GCIPL	65.3 (9.6)	68.6 (9.1)	70.6 (8.7)	70.2 (8.6)	0.023	0.046	0.82	0.018	0.99
INL	44.8 (2.6)	44.5 (2.8)	44.9 (3.0)	44.6 (3.2)	0.19	0.61	0.46	0.23	0.66
ONL	68.7 (7.0)	67.1 (5.6)	68.2 (5.7)	67.3 (5.6)	<i>0.051</i>	0.5	0.25	0.17	0.54
pRNFL	81.0 (15.2)	84.3 (12.7)	86.5 (12.4)	86.7 (13.5)	<i>0.08</i>	<i>0.06</i>	0.91	<i>0.05</i>	0.97

^aDerived from mixed effects linear regression models, accounting for within subject inter-eye correlations. P-values are for group comparisons between the normal weight, overweight and obese cohorts. Data from 9 MS patients who were underweight (BMI <18.5 kg/m²) are provided for descriptive reasons but are not included in analyses due to insufficient sample size.

^bMultivariable mixed-effects linear regression models including age, sex, race, MS subtype, ON history

BMI: body mass index; MS: multiple sclerosis; ON: optic neuritis; GCIPL: ganglion cell + inner plexiform layer; INL: inner nuclear layer; ONL: outer nuclear layer; pRNFL: peri-papillary retinal nerve fiber layer

Table 3.

Comparison of annualized percent change in retinal layer thickness by BMI category. Statistically significant results are in bold

	Annualized Percent Change, unadjusted β (95% CI)			p-value ^a (unadjusted)			p-value ^a (adjusted ^b)	
	Normal weight [BMI 18.5–24.9 kg/m ²] (n=401 eyes)	Overweight [BMI 25–29.9 kg/m ²] (n=289 eyes)	Obese [BMI ≥30 kg/m ²] (n=264 eyes)	Normal vs. overweight	Normal vs. obese	Overweight vs. obese	Normal vs. obese	Overweight vs. obese
GCIPL	−0.42% (−0.49% to −0.35%)	−0.47% (−0.55% to −0.38%)	−0.57% (−0.65% to −0.48%)	0.41	0.012	0.11	0.57	0.18
INL	−0.31% (−0.35% to −0.28%)	−0.30% (−0.34% to −0.25%)	−0.35% (−0.39% to −0.30%)	0.59	0.34	0.17	0.66	0.06
ONL	−0.21% (−0.26% to −0.17%)	−0.15% (−0.20% to −0.09%)	−0.19% (−0.25% to −0.13%)	0.09	0.53	0.35	0.09	0.4
pRNFL	−0.68% (−0.76% to −0.59%)	−0.68% (−0.79% to −0.58%)	−0.77% (−0.88% to −0.65%)	0.93	0.23	0.3	0.7	0.54

^aDerived from mixed effects linear regression models, including follow-up time, BMI category and their interaction, accounting for within subject inter-eye correlations

^bMultivariable mixed-effects linear regression models including sex, race, MS subtype and their respective interactions with follow-up time, age, ON history

BMI: body mass index; MS: multiple sclerosis; ON: optic neuritis; GCIPL: ganglion cell + inner plexiform layer; INL: inner nuclear layer; ONL: outer nuclear layer; pRNFL: peri-papillary retinal nerve fiber layer

Table 4.

Estimated annualized percent change in retinal layer thickness by BMI

BMI (kg/m ²)	Annualized percent change in GCIPL thickness, unadjusted β (95% CI)
20	−0.39% (−0.46% to −0.32%)
25	−0.45% (−0.49% to −0.40%)
30	−0.50% (−0.55% to −0.45%)
35	−0.56% (−0.63% to −0.49%)
40	−0.62% (−0.72% to −0.51%)

BMI: body mass index; GCIPL: ganglion cell + inner plexiform layer