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Associations of Alcohol Consumption and Smoking With Disease Risk and Neurodegeneration in Individuals With Multiple Sclerosis in the United Kingdom

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Abstract

IMPORTANCE Understanding the effects of modifiable risk factors on risk for multiple sclerosis (MS) and associated neurodegeneration is important to guide clinical counseling.

OBJECTIVE To investigate associations of alcohol use, smoking, and obesity with odds of MS diagnosis and macular ganglion cell layer and inner plexiform layer (mGCIPL) thickness.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study analyzed data from the community-based UK Biobank study on health behaviors and retinal thickness (measured by optical coherence tomography in both eyes) in individuals aged 40 to 69 years examined from December 1, 2009, to December 31, 2010. Risk factors were identified with multivariable logistic regression analyses. To adjust for intereye correlations, multivariable generalized estimating equations were used to explore associations of alcohol use and smoking with mGCIPL thickness. Finally, interaction models explored whether the correlations of alcohol and smoking with mGCIPL thickness differed for individuals with MS. Data were analyzed from February 1 to July 1, 2021.

EXPOSURES Smoking status (never, previous, or current), alcohol intake (never or special occasions only [low], once per month to ≤4 times per week [moderate], or daily/almost daily [high]), and body mass index.

MAIN OUTCOMES AND MEASURES Multiple sclerosis case status and mGCIPL thickness.

RESULTS A total of 71 981 individuals (38 685 women [53.7%] and 33 296 men [46.3%]; mean [SD] age, 56.7 [8.0] years) were included in the analysis (20 065 healthy control individuals, 51 737 control individuals with comorbidities, and 179 individuals with MS). Modifiable risk factors significantly associated with MS case status were current smoking (odds ratio [OR], 3.05 [95% CI, 1.95-4.64]), moderate alcohol intake (OR, 0.62 [95% CI, 0.43-0.91]), and obesity (OR, 1.72 [95% CI, 1.15-2.56]) compared with healthy control individuals. Compared with the control individuals with comorbidities, only smoking was associated with case status (OR, 2.30 [95% CI, 1.48-3.51]). High alcohol intake was associated with a thinner mGCIPL in individuals with MS (adjusted β = −3.09 [95% CI, −5.70 to −0.48] µm; $P = .02$). In the alcohol interaction model, high alcohol intake was associated with thinner mGCIPL in control individuals (β = −0.93 [95% CI, −1.07 to −0.79] µm; $P < .001$), but there was no statistically significant association in individuals with MS (β = −2.27 [95% CI, −4.76 to 0.22] µm; $P = .07$). Smoking was not associated with mGCIPL thickness in MS. However, smoking was associated with greater mGCIPL thickness in control individuals (β = 0.89 [95% CI, 0.74-1.05 µm]; $P < .001$).

(continued)

Key Points

Question How are modifiable risk factors such as alcohol consumption, smoking, and obesity associated with disease risk and neurodegeneration in individuals with multiple sclerosis (MS)?

Findings This cross-sectional study of 71 981 individuals in the United Kingdom found that high alcohol consumption was associated with retinal features indicative of more severe neurodegeneration, whereas smoking was associated with higher odds of being diagnosed with MS.

Meaning These findings suggest that current recommendations for the general population regarding smoking and moderating alcohol consumption may be particularly relevant for individuals who have been diagnosed with MS or who are at risk for the disease.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE These findings suggest that high alcohol intake was associated with retinal features indicative of more severe neurodegeneration, whereas smoking was associated with higher odds of being diagnosed with MS.

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Introduction

Multiple sclerosis (MS) is an immune-mediated, demyelinating disorder of the central nervous system, predominantly affecting women of child-bearing age.[1] Both genetic and environmental factors are known to play important roles in the pathophysiology of MS.[1-3] Understanding the role of modifiable risk factors, such as smoking, alcohol intake, and obesity, is important to guide clinical counseling.[4,5] Smoking is known to increase the risk of developing MS,[6] and advising patients to stop smoking to reduce the risk of conversion from clinically isolated syndrome (CIS) to MS is an important part of patient guidance.[7] Less is known about how health behaviors influence neurodegeneration in MS. Brain atrophy occurs in MS from disease diagnosis,[8] but its underlying mechanisms remain poorly understood. Reduced brain volumes are associated with more severe disability,[9] particularly in the cognitive domains.[10,11] Ameliorating neurodegeneration has therefore become an important treatment goal.[12]

Studies investigating brain atrophy are hampered by long magnetic resonance imaging scanning protocols. Retinal thickness measures have been identified as a surrogate for brain volume,[13,14] because the retina is developmentally and anatomically part of the central nervous system but is more easily assessable for imaging. Optical coherence tomography (OCT) provides fast, noninvasive retinal imaging.[15] Thickness of the macular ganglion cell and inner plexiform layer (mGCIPL) correlates with brain volume measures in the general population[16] and in patients with MS.[14] Retinal atrophy, independent of damage inflicted by optic neuritis, occurs from the early stages of disease[15,17] and correlates with MS disability scores.[18,19]

Because smoking and alcohol consumption are correlated behaviors,[20,21] it is difficult to disentangle their respective effects. In the general population, smoking and alcohol intake separately have been found to be related to brain atrophy,[22-30] and daily alcohol intake and maternal smoking during pregnancy have also been found to be associated with thinner retinal thickness.[31,32]

Smoking may also increase disease activity, disability progression,[6] and neurodegeneration[5] in MS. However, the findings of studies investigating associations between smoking and brain volume in MS have been inconclusive[5,33,34] and were not adjusted for the potential confounding effects of alcohol use. How alcohol affects MS is less clear, with both protective[35,36] and adverse effects[4,37] reported, and to our knowledge the association between alcohol consumption and brain atrophy in MS has not yet been investigated. Correlations of alcohol intake with health outcomes are complex, frequently following a J-shaped curve. Moderate alcohol consumption may be protective against developing cardiac infarction[38] and cataract,[39] for example. However, with regard to brain volume[27,30] and mortality,[38] most evidence points to a linear negative correlation with alcohol, without a protective effect of moderate consumption.

The purpose of this study was to investigate the associations of alcohol consumption and smoking with an MS diagnosis and mGCIPL thickness in a community-based cohort study comprising more than 70 000 adults in the United Kingdom. A better understanding of the roles of these modifiable risk factors may lead to better health outcomes and quality of life in MS.

Methods

Participants

The participants of this cross-sectional study were adults aged 40 to 69 years who were registered in the National Health Service (NHS) and who participated in an expanded ophthalmic protocol, including OCT, of the UK Biobank (UKBB) baseline visit between January 1, 2009, and December 31, 2010.[40] The North West Multi-Centre Research Ethics Committee approved the UKBB study protocol in accordance with the tenets of the Declaration of Helsinki. All participants gave written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Participants were categorized as having MS, no comorbidities, or comorbidities based on clinician-controlled *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), disease codes, available through record linking with the NHS.[41] The *ICD-10* code for MS, G35, is applicable to all forms of MS diagnosed by clinicians within the NHS, but does not specify which tests were used to reach a diagnosis. The cumulative disease burden was calculated by counting the number of *ICD-10* codes per participant. Individuals without MS were categorized as healthy if this cumulative disease burden was 0 and having comorbidities if it was 1 or greater.

Data Collection

In brief, undilated macular spectral domain OCT scans of both eyes were obtained in a dark room with a 3-dimensional scanner (3D OCT-1000 Mk-II; Topcon Corporation), in line with the Advised Protocol for OCT Study Terminology and Elements guidelines[42,43] as described in detail previously.[44] An extensive quality-control protocol, combining both automated and manual checks, was used to ensure sufficient image quality, complying with OSCAR-IB criteria (obvious problems; sufficient signal; correct centering of ring scan; algorithm failure; visible retinal pathology; well-illuminated fundus; and central measurement beam)[45] and accurate layer segmentation.[32,44]

Participants completed a self-administered touch-screen questionnaire on health-related behaviors, demographics, and socioeconomic data. Smoking and alcohol status were determined by asking the questions "Do you smoke tobacco?" (never, previously, or currently) and "How often do you drink alcohol?" (never, special occasions only, 1-3 times per month, 1-2 times per week, 3-4 times per week, daily, or almost daily). Responses to the alcohol-related question were consolidated into the categories low (never or special occasions only), moderate (drinking once per month to ≤4 times per week), and high (daily or almost daily). A sensitivity analysis was performed with the original alcohol intake levels and was reported if these results were materially different. Household passive smoking was determined by asking the question "Do any household members smoke tobacco?"

Race and ethnicity responses were collected given their know association with MS risk and were placed into 5 categories: (1) Asian (including Asian or Asian British, Bangladeshi, Chinese, Indian, Pakistani, or other Asian background), (2) Black (including African, Black or Black British, Caribbean, or other Black background), (3) White (including British, Irish, White, or other White background), (4) other and/or multiracial (White and Asian, White and Black African, White and Black Caribbean, other mixed background, mixed, or other ethnic group), and (5) missing (unknown and missing). Corneal compensated intraocular pressure (IOP) measurements were performed with an ocular response analyzer (Reichert Ophthalmic Instruments) from 1 eye. Weight and height were measured by trained trial personnel with a body composition analyzer (BV-418 MA; Tanita) and a medical measuring rod (Seca 202; Seca), respectively. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared and transformed into a categorical variable (<18.0 indicates underweight; 18.0-24.9, healthy weight; 25.0-30.0, overweight; and >30.0, obesity). Postal codes were used to determine Townsend Deprivation Score,[46] which was transformed into a categorical variable based on quartiles of equal group size.

Statistical Analysis

Data were analyzed from February 1 to July 1, 2021. Data distributions were tabulated using summary statistics for continuous variables (mean [SD]) and cross-tabulations (including percentages) for categorical variables. Data were inspected visually for normality and inconsistencies. Missing data were tabulated and were excluded from analysis.

MS Case Status

Univariable followed by multivariable logistic regression was used to identify factors associated with the odds of having an MS diagnosis. Results were reported with odds ratios (ORs) and 95% CIs. The healthy control group and the control group with comorbidities were used separately. Covariates considered were age, sex, Townsend deprivation score, race and ethnicity, and BMI. The assumed associations among the exposures, potential confounders, and outcomes are presented in a directed acyclic graph in the eFigure in Supplement 1.

mGCIPL Thickness in MS

Subsequently, we built a multivariable model investigating the associations of alcohol use and smoking with mGCIPL thickness in individuals with MS. To account for intereye correlations, generalized estimating equations were used.[42,43] A sensitivity analysis was performed with linear regression on the mean mGCIPL value of both eyes. Spearman correlations were performed between all covariates to identify evidence for multicollinearity ($\rho > 0.5$). Potential confounding factors were explored through univariable associations of covariates with exposures (smoking and alcohol intake) and outcome (mGCIPL thickness), separately. This was tested using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables. Age, sex, and IOP were included in the final model a priori. To explore potential multiplicative effects of combined smoking and alcohol use, we tested a model including interaction terms for the alcohol and smoking variables.

Effect Modification in MS

Finally, we explored whether associations of smoking and alcohol use with mGCIPL thickness differed between control individuals and individuals with MS. Two generalized estimating equations models were run on the complete cohort, including variables for MS case status, alcohol intake, and smoking status as well as an interaction term for MS and either smoking status or alcohol intake. These models were inspected for significant ($P < .05$) results for the Wald test of the interaction terms.

Analysis

A statistical significance threshold of 2-sided $P < .05$ was used. R software, version 4.1.1, and R Studio, version 1.4.1103 (R Project for Statistical Computing) were used for all statistical analyses.

Results

Participants

A total of 71 981 participants were included in the study (38 685 women [53.7%] and 33 296 men [46.3%]; mean [SD] age, 56.7 [8.0] years). In terms of diagnoses, 179 individuals with MS, 20 065 healthy control individuals and 51 737 control individuals with comorbidities were included (**Figure 1**). Among these participants, 130 individuals with MS (72.6%) and 38 555 control individuals (53.6%) were women; 49 individuals with MS (27.4%) and 33 247 control individuals (46.3%) were men (**Table 1**).[1] Individuals with MS had a mean (SD) age of 55.6 (7.7) years; control individuals, 56.6 (7.9) years. Three individuals with MS (1.7%) were classified as having underweight BMI, and this level was collapsed with healthy weight.

Odds of MS Case Status

Univariable logistic analysis and subsequent multivariable logistic regression (**Figure 2**A and eTable 1 in Supplement 1) were performed using the healthy control group and the control group with comorbidities separately. Ethnicity was not included because only 9 individuals with MS (5.0%) were of an ethnicity other than White. Household passive smoking was not associated with the odds of MS (OR for healthy control group, 1.46 [95% CI, 0.90-2.27]; OR for control group with comorbidities, 1.37 [95% CI, 0.84-2.13]) (eTable 1 in Supplement 1), and this variable was not included in multivariable analysis.

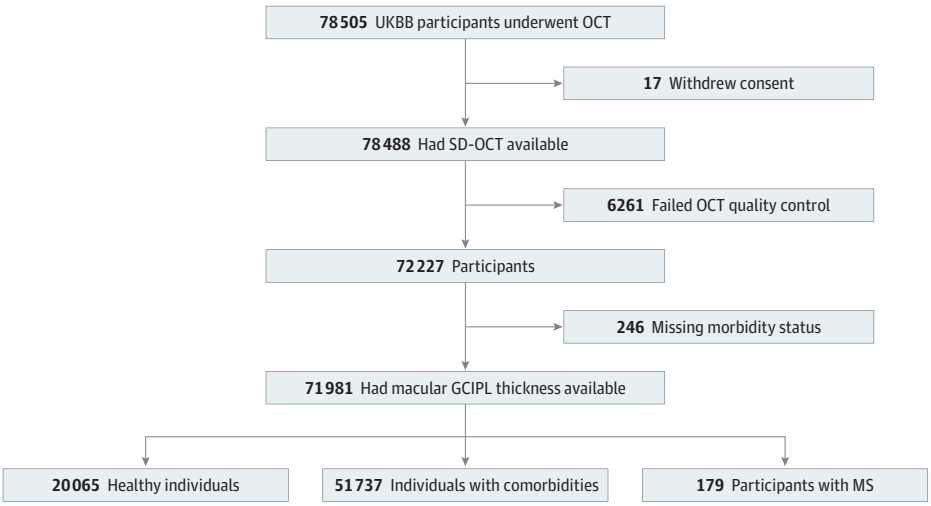
Compared with never having smoked, being a current or previous smoker was associated with ORs of 3.05 (95% CI, 1.95-4.64) and 1.59 (95% CI, 1.12-2.25), respectively, for having MS case status when using a healthy control group and ORs of 2.30 (95% CI, 1.48-3.51) and 1.25 (95% CI, 0.88-1.77), respectively, for having MS case status when using a control group with comorbidities. Moderate alcohol intake was associated with lower odds of MS case status using the healthy control group (adjusted OR [aOR], 0.62 [95% CI, 0.43-0.91]) but not the control group with comorbidities (aOR, 0.81 [95% CI, 0.56-1.18]). Having obesity was significantly associated with an increased odds of MS when comparing the healthy control group (aOR, 1.72 [95% CI, 1.15-2.56]) but not the control group with comorbidities (aOR, 1.02 [95% CI, 0.68-1.51]).

mGCIPL Thickness in MS

There was a significant univariable negative association of mGCIPL thickness with high alcohol consumption (β = −2.94 [95% CI, −5.49 to −0.68] µm; *P* = .02) (**Table 2**). Current smoking (β = −1.26 [95% CI, −4.14 to 0.93] µm; *P* = .30), previous smoking (β = −0.34 [95% CI, −2.36 to 2.02] µm; *P* = .75), and household passive smoking (β = −0.76 [95% CI, −2.43 to 2.01] µm; *P* = .61) were not significantly associated with mGCIPL thickness. Similarly, there were no associations of overweight BMI (β = −0.41 [95% CI, −3.34 to 2.63] µm; *P* = .72]) or obesity BMI (β = −0.41 [95% CI, −4.58 to 1.67] µm; *P* = .77]) with mGCIPL thickness.

Within the MS cohort, there was a significant association of smoking with sex (*P* = .01). There was no association with Townsend deprivation index (*P* = .07) and of alcohol intake with sex (*P* = .06) and with IOP (*P* = .05). Because BMI was not associated with mGCIPL or either explanatory variable, it was not taken forward for multivariable analysis. To explore potential multiplicative effects of combined alcohol intake and smoking, a model with interaction terms was created (eTable 2 in Supplement 1), which identified no evidence of interaction.

Figure 1. Study Flowchart



Individuals with multiple sclerosis (MS) were defined as those with an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), disease code of G35, indicating clinician-diagnosed MS. Healthy control individuals were those who had 0 *ICD-10* disease codes registered, whereas control individuals with comorbidities had 1 or more (non-MS) *ICD-10* disease codes registered. GCIPL indicates ganglion cell and inner plexiform layer; SD-OCT, spectral domain optical coherence tomography; and UKBB, UK Biobank study.

The final multivariable generalized estimating equation model, adjusted for smoking status, sex, age, Townsend deprivation score, and IOP, identified a significant association of high alcohol consumption with a thinner mGCIPL (adjusted β = −3.09 [95% CI, −5.70 to −0.48] μm; *P* = .02) (Table 2 and Figure 2B). There was a significant linear trend association across the alcohol intake parameters (adjusted β = −1.55 [95% CI, −3.20 to −0.35] μm; *P* = .02). No significant associations were identified for previous smokers or current smokers, compared with those who never smoked.

Table 1. Study Cohort Characteristics

Characteristic	Participant group[a]		
	Healthy control individuals (n = 20 065)	Control individuals with comorbidities (n = 51 737)	Individuals with MS (n = 179)
Sex			
Women	10 064 (50.2)	28 491 (55.1)	130 (72.6)
Men	10 001 (49.8)	23 246 (44.9)	49 (27.4)
Age, mean (SD), y	55.2 (7.9)	57.2 (8.0)	55.6 (7.7)
Smoking status			
Never	12 071 (60.2)	27 896 (53.9)	81 (45.3)
Previous	6210 (30.9)	18 666 (36.1)	63 (35.2)
Current	1702 (8.5)	4858 (9.4)	33 (18.4)
Missing/no answer	82 (0.4)	317 (0.6)	2 (1.1)
Alcohol consumption[b]			
Low	3267 (16.3)	10 832 (20.9)	47 (26.3)
Moderate	12 228 (60.9)	30 251 (58.5)	89 (49.7)
High	4515 (22.5)	10 489 (20.3)	41 (22.9)
Missing or no answer	55 (0.3)	165 (0.3)	2 (1.1)
Race and ethnicity			
Asian	705 (3.5)	1594 (3.1)	4 (2.2)
Black	537 (26.8)	1394 (26.9)	3 (1.7)
White	18 232 (90.9)	47 333 (91.5)	168 (93.9)
Other or mixed[c]	529 (2.6)	1205 (2.3)	2 (1.1)
Missing or no answer	62 (0.3)	211 (0.4)	2 (1.1)
Townsend deprivation index, quartile			
Lowest	5234 (26.1)	12 720 (24.6)	33 (18.4)
Low-middle	4975 (24.8)	12 958 (25.0)	46 (25.7)
High-middle	5063 (25.2)	12 865 (24.9)	43 (24.0)
Highest	4770 (23.8)	13 135 (25.4)	57 (31.8)
Missing or no answer	23 (0.1)	59 (0.1)	0
BMI group			
Low or normal weight (<18.0-24.9)	7841 (39.1)	16 731 (32.3)	60 (33.5)
Overweight (25.0-30.0)	8549 (42.6)	21 767 (42.1)	67 (37.4)
Obese (>30.0)	3603 (18.0)	13 026 (25.2)	43 (24.0)
Missing	72 (0.4)	213 (0.4)	9 (5.0)
Intraocular pressure			
Mean (SD), mm Hg	16.0 (4.3)	15.9 (4.3)	15.1 (3.7)
Missing	657 (3.3)	1618 (3.1)	12 (6.7)
Household passive smoking			
Yes	1820 (9.1)	4896 (9.5)	21 (11.7)
No	16 979 (84.6)	42 926 (83.0)	134 (74.9)
Missing	1266 (6.3)	3915 (7.6)	24 (13.4)
mGCIPL, mean (SD), μm			
Thickness	72.8 (6.0)	72.2 (6.0)	67.8 (6.3)
IEPD	2.6 (3.4)	2.8 (3.6)	6.4 (6.3)
IEAD	2.0 (2.5)	2.1 (2.7)	4.5 (4.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IEAD, intereye absolute difference in mGCIPL; IEPD, intereye percent difference in mGCIPL; mGCIPL, macular ganglion cell layer and inner plexiform layer; MS, multiple sclerosis.

[a] Unless otherwise indicated, data are expressed as number (%) of participants. Percentages have been rounded and may not total 100.

[b] Defined as never or special occasions only (low), once per month to no more than 4 times per week (moderate), or daily or almost daily (high).

[c] Includes White and Asian, White and Black African, White and Black Caribbean, other mixed background, mixed, or other ethnic group.

A sensitivity analysis using multivariable linear regression found similar results for high alcohol intake (adjusted β = −3.12 [95% CI, −5.55 to −0.46] µm; *P* = .04). Finally, after excluding the 9 individuals with MS who were not of White ethnicity, high alcohol intake remained significantly associated with mGCIPL (adjusted β = −3.01 [95% CI, −5.41 to −0.44] µm; *P* = .03).

Differences in Associations Based on MS Case Status

The smoking interaction model suggested that the association of smoking with mGCIPL thickness differed by MS case status, because current smoking was associated with thicker mGCIPL in the control group (β = 0.89 [95% CI, 0.74-1.05] µm; *P* < .001), but was not associated with mGCIPL in individuals with MS (β = −2.14 [95% CI, −4.52 to 0.23] µm; *P* = .08) (eTable 3 in Supplement 1). In the alcohol interaction model, high alcohol intake was associated with thinner mGCIPL in control individuals (β = −0.93 [95% CI, −1.07 to −0.79] µm; *P* < .001), but there was no statistically significant association in MS (β = −2.27 [95% CI, −4.76 to 0.22] µm; *P* = .07) (**Figure 3**).

Discussion

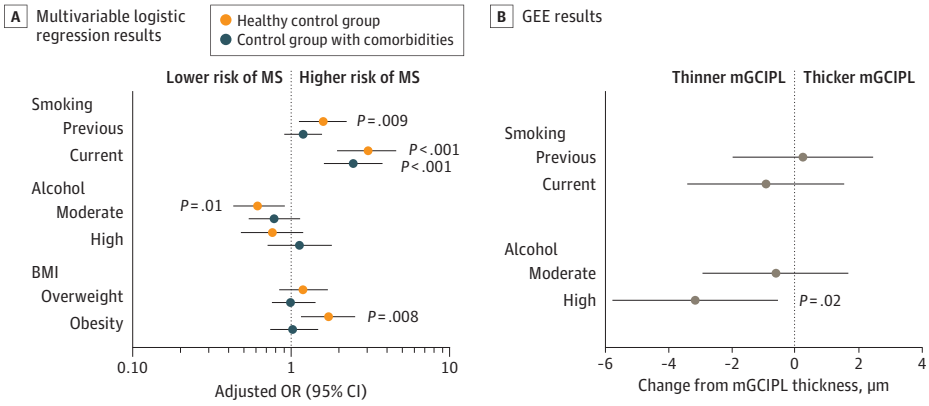
In this cross-sectional study, smoking was associated with an increased odds of having an MS diagnosis and high alcohol consumption was associated with a thinner mGCIPL in individuals with MS. Paradoxically, moderate alcohol intake was associated with a lower odds of having been diagnosed with MS. The associations of smoking and alcohol use with mGCIPL thickness may be different in individuals with MS compared with control individuals.

Our findings replicate associations of smoking and obesity with increased odds of MS diagnosis status.[1,6,47] Only smoking remained significantly associated with odds of having an MS diagnosis when using the control group with comorbidities. This finding illustrates the importance of choice of control group, because risk factors and protective factors are likely similar across various diseases, which can obscure associations.

Moderate alcohol consumption was associated with a lower odds of having an MS diagnosis. A protective effect of moderate alcohol consumption on MS risk has been reported before,[35,36] although an increased risk has been reported as well.[4,37] Owing to the cross-sectional nature of the present study, the "sick quitters effect"—that is, the tendency to quit or profoundly limit alcohol intake when ill could have influenced our findings.[48]

This study identified a novel association of high alcohol consumption with a thinner mGCIPL in MS, whereas there was no association with smoking. Participants with self-reported high alcohol intake had almost 5% thinner mGCIPLs, a substantial difference in retinal thickness. This seems to be in line with reported associations of alcohol use with lower brain volumes[27,30] and a large recent

Figure 2. Line Plots Visualizing Associations of Modifiable Risk Factors With Multiple Sclerosis (MS) Risk and Macular Ganglion Cell and Inner Plexiform Layer (mGCIPL) Thickness



A, Multivariable logistic regression results visualizing factors associated with risk of being diagnosed with MS. Circles represent odds ratios; whiskers represent 95% CIs. Analysis is adjusted for age, sex, and Townsend deprivation score. The x-axis is log-transformed. B, Multivariable generalized estimating equations (GEEs) results visualizing the associations with smoking status and alcohol intake (adjusted for age, sex, Townsend deprivation score, and intraocular pressure [IOP]) with mGCIPL thickness in individuals with MS. Reference groups include individuals who never smoked, had low alcohol use, and had a healthy body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Alcohol consumption was classified as never or special occasions only (low), once per month to no more than 4 times per week (moderate), or daily or almost daily (high); BMI was classified as underweight or healthy weight (<18.0 to 24.9), overweight (25.0-30.0), and obesity (>30.0). OR indicates odds ratio.

population-based study,[30] which found that alcohol consumption explained 7.7% of variance in gray matter volume, compared with 1.7% by smoking status. A previous study[34] found that smoking was not associated with retinal thickness in MS. Other studies[5] identified significant correlations of smoking with brain atrophy in MS, but these studies were not adjusted for alcohol consumption. We observed a linear negative association of alcohol with mGCIPL thickness in MS, without protective effects of moderate alcohol consumption. This resembles previous findings in the general population.[27,30]

The observed association of high alcohol consumption with lower mGCIPL thickness in MS remains an imperfect surrogate for clinically relevant metrics such as disability load. Smoking has been shown to be associated with increased disease severity.[6] In contrast, alcohol has been reported to ameliorate MS disease severity and progression,[36,49] particularly in smokers,[50] while at the same time being associated with increased cerebral lesion load.[51] However, as in the present study, these studies were cross-sectional, and the sick quitters effect could have influenced the results. The association of alcohol consumption with MS severity is complex, and future prospective studies using measures of physical and cognitive disability are needed to elucidate these questions. Importantly, the present study does not provide evidence of a health benefit for patients with MS to refrain from alcohol consumption.

Table 2. Univariable and Multivariable GEEs Investigating Associations With mGCIPL Thickness in MS Among 164 Individuals

	Univariable analysis[a]				Multivariable analysis[b]		
Characteristic	β (95% CI)	*P* value	*P* value for trend	No. of observations	Adjusted β (95% CI)	*P* value	*P* value for trend
Sex							
Women	NA	NA	NA	179	NA	NA	NA
Men	−1.37 (−1.12 to 3.26)	.20			−1.02 (−1.22 to 3.25)	.37	
Age per unit increase	0.00 (−0.15 to 0.10)	.99	NA	179	−0.04 (−0.17 to 0.07)	.36	NA
Smoking status							
Never	NA	NA	.33	177	NA	NA	NA
Previous	−0.34 (−2.36 to 2.02)	.75			0.37 (−1.83 to 2.57)	.74	
Current	−1.26 (−4.14 to 0.93)	.30			−0.66 (−3.21 to 1.89)	.61	
Alcohol consumption[c]							
Low	NA	NA	.02	177	NA	NA	.02
Moderate	−0.15 (−2.62 to 2.05)	.90			−0.56 (−2.82 to 1.71)	.63	
High	−2.94 (−5.49 to −0.68)	.02			−3.09 (−5.70 to −0.48)	.02	
Townsend deprivation index[d]							
Lowest quartile	NA	NA	.88	179	NA	NA	NA
Low-middle quartile	−0.91 (−3.34 to 2.63)	.54			−0.32 (−3.33 to 2.69)	.84	
High-middle quartile	−1.34 (−4.58 to 1.67)	.39			−1.45 (−4.70 to 1.79)	.38	
Highest quartile	−0.34 (−3.15 to 2.85)	.82			−0.30 (−343 to 2.83)	.85	
BMI group							
Low/normal weight (<18.0 to 24.9)	NA	NA	NA	170	NA	NA	NA
Overweight (25.0-30.0)	−0.41 (−3.34 to 2.63)	.72			NA	NA	
Obesity (>30.0)	−0.41 (−4.58 to 1.67)	.77			NA	NA	
IOP per unit increase	1.61 (−3.15 to 2.85)	.29	NA	167	0.21 (−0.09 to 0.51)	.17	NA
Household passive smoking							
No	NA	NA	NA	156	NA	NA	NA
Yes	−0.76 (−2.43 to 2.01)	.61			NA	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GEEs, generalized estimating equations; IOP, intraocular pressure; mGCIPL, macular ganglion cell and inner plexiform layer; MS, multiple sclerosis; NA, not applicable.

[a] Investigates associations with explanatory variables (alcohol consumption and smoking status) and other covariates with mGCIPL thickness in individuals diagnosed with MS.

[b] Investigates the associations between alcohol consumption and smoking status with mGCIPL thickness in individuals diagnosed with MS, adjusted for confounders.

[c] Defined as never or special occasions only (low), drinking once per month to no more than 4 times per week (moderate), or daily or almost daily (high).

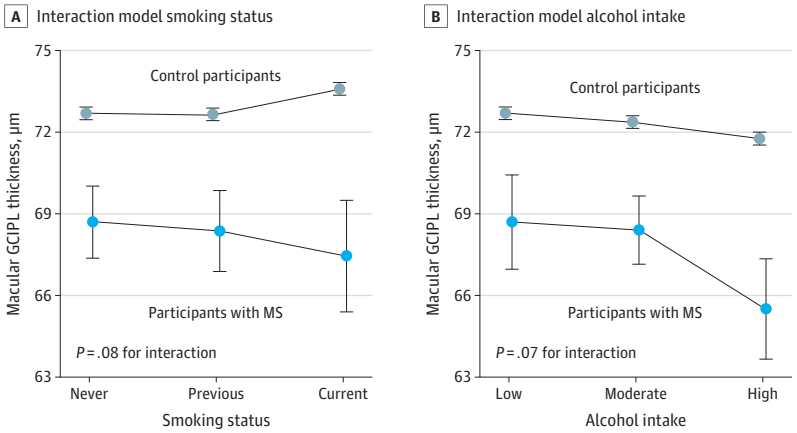
[d] Scores range from −6.3 to 9.4, with higher scores indicating higher levels of deprivation.

The data reported in this study suggest that associations of both smoking and alcohol intake with mGCIPL thickness may be different for individuals with MS compared with control individuals, with individuals diagnosed with MS appearing to be more susceptible to the neurodegenerative effects of these adverse health behaviors. Although these findings did not reach statistical significance and need to be interpreted with caution, these may still represent clinically important processes, given their large effect sizes. These findings will need to be replicated in an independent cohort to be confirmed. Our findings suggest that neurodegenerative processes occurring in MS may interact with neurotoxic effects of alcohol and smoking, resulting in greater neuronal cell death and axonal loss. Ethanol and its metabolite acetaldehyde are directly neurotoxic.[52,53] In addition, both alcohol and smoking are related to microvascular dysfunction and oxidative stress,[54,55] which could aggravate MS pathophysiological processes, because mitochondrial failure may play an important role.[56,57] However, the association of thinner mGCIPL with high alcohol intake could also be related to retinal mechanisms instead of neuroaxonal loss. For example, the high energy use of the retina may make it sensitive to damage due to alcohol-related increases in oxidative stress,[58] and higher alcohol intake has been found to be associated with increased risk of glaucoma.[59] This might have influenced our results, although our analysis was adjusted for IOP.

Strengths and Limitations

The strengths of this study include the large community-based data set that provided extensive and high-quality data. This study also has some limitations. Although the questionnaire on exposure status has not been formally validated, previous studies[38,39] demonstrated good performance. However, the self-reported nature of exposure status classification could have caused misclassification. This would have most likely been nondifferential misclassification, biasing effect estimates to zero, although individuals with MS may have had different likelihoods of overestimating and underestimating their health behaviors compared with healthy control individuals. Furthermore, alcohol consumption in this study was not determined with regard to quantity of alcohol units consumed, because this information was missing for a large proportion. This means we were not able to quantify alcohol intake more precisely, identify binge-drinking behaviors, or distinguish the effects of various alcoholic beverage types, which might have shown distinctive health effects of red wine, as was shown before in relation to cataract.[39] A further limitation was the low response rate of the UKBB, with an underrepresentation of individuals who belong to ethnic minority groups or have a lower socioeconomic status. In particular, individuals with MS who participated in the UKBB may not have been representative of the general population with MS because they were aged 40 to 69 years and may have had milder disease, enabling them to travel to study centers. In addition, we did not

Figure 3. Differences in Associations With Macular Ganglion Cell and Inner Plexiform Layer (mGCIPL) Thickness Based on Multiple Sclerosis (MS) Diagnosis Status



Modeled estimates of the associations of mGCIPL with alcohol consumption and smoking status for the entire cohort, plotted for individuals with MS and control individuals separately. A, Interaction model including interaction term for smoking status and MS diagnosis. B, Interaction model including interaction term for alcohol intake and MS diagnosis. Whiskers represent 95% CIs.

have sufficiently reliable information on optic neuritis status, disease duration, or disability to take these factors into account, which could have caused residual confounding.

Conclusions

This cross-sectional study found that high alcohol consumption was associated with more pronounced retinal features of neurodegeneration, although moderate alcohol consumption was associated with lower odds of being diagnosed with MS. Smoking was associated with increased odds of having an MS diagnosis. Further research is necessary to confirm the results of this study, in particular the complex associations of alcohol consumption with MS severity. The presented findings suggest that current recommendations for the general population regarding smoking and moderating alcohol consumption may be particularly relevant for individuals who have been diagnosed with MS or who are at risk for the disease.

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Author Contributions: Dr Kleerekooper had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Kleerekooper, Petzold.

Obtained funding: Foster.

Administrative, technical, or material support: Chua, Trip.

Supervision: Foster, Trip, Plant, Petzold, Patel.

Other (had the original idea for this study): Petzold.

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REFERENCES

1. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. 2018;391(10130):1622-1636. doi:10.1016/S0140-6736(18)30481-1

2. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol*. 2017;13(1):25-36. doi:10.1038/nrneurol.2016.187

3. Jacobs BM, Noyce AJ, Bestwick J, Belete D, Giovannoni G, Dobson R. Gene-environment interactions in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(4):e1007. doi:10.1212/NXI.0000000000001007

4. Pakpoor J, Goldacre R, Disanto G, Giovannoni G, Goldacre MJ. Alcohol misuse disorders and multiple sclerosis risk. *JAMA Neurol*. 2014;71(9):1188-1189. doi:10.1001/jamaneurol.2014.1795

5. Rosso M, Chitnis T. Association between cigarette smoking and multiple sclerosis: a review. *JAMA Neurol*. 2020;77(2):245-253. doi:10.1001/jamaneurol.2019.4271

6. Manouchehrinia A, Tench CR, Maxted J, Bibani RH, Britton J, Constantinescu CS. Tobacco smoking and disability progression in multiple sclerosis: United Kingdom cohort study. *Brain*. 2013;136(pt 7):2298-2304. doi:10.1093/brain/awt139

7. Brownlee WJ, Miller DH. Clinically isolated syndromes and the relationship to multiple sclerosis. *J Clin Neurosci*. 2014;21(12):2065-2071. doi:10.1016/j.jocn.2014.02.026

8. Chard DT, Griffin CM, Parker GJM, Kapoor R, Thompson AJ, Miller DH. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. *Brain*. 2002;125(pt 2):327-337. doi:10.1093/brain/awf025

9. Popescu V, Agosta F, Hulst HE, et al; MAGNIMS Study Group. Brain atrophy and lesion load predict long term disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1082-1091. doi:10.1136/jnnp-2012-304094

10. Lema Dopico A, Choi S, Hua J, Li X, Harrison DM. Multi-layer analysis of quantitative 7 T magnetic resonance imaging in the cortex of multiple sclerosis patients reveals pathology associated with disability. *Mult Scler*. 2021;27(13):2040-2051. doi:10.1177/1352458521994556

11. Riccitelli G, Rocca MA, Pagani E, et al. Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. *Hum Brain Mapp*. 2011;32(10):1535-1543. doi:10.1002/hbm.21125

12. Kappos L, De Stefano N, Freedman MS, et al. Inclusion of brain volume loss in a revised measure of "no evidence of disease activity" (NEDA-4) in relapsing-remitting multiple sclerosis. *Mult Scler*. 2016;22(10):1297-1305. doi:10.1177/1352458515616701

13. Mejia-Vergara AJ, Karanjia R, Sadun AA. OCT parameters of the optic nerve head and the retina as surrogate markers of brain volume in a normal population, a pilot study. *J Neurol Sci*. 2021;420:117213. doi:10.1016/j.jns.2020.117213

14. Saidha S, Al-Louzi O, Ratchford JN, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: a four-year study. *Ann Neurol*. 2015;78(5):801-813. doi:10.1002/ana.24487

15. Petzold A, Balcer LJ, Calabresi PA, et al; ERN-EYE IMSVISUAL. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol*. 2017;16(10):797-812. doi:10.1016/S1474-4422(17)30278-8

16. Chua SYL, Lascaratos G, Atan D, et al; UK Biobank Eye, Vision Consortium. Relationships between retinal layer thickness and brain volumes in the UK Biobank cohort. *Eur J Neurol*. 2021;28(5):1490-1498. doi:10.1111/ene.14706

17. Pietroboni AM, Dell'Arti L, Caprioli M, et al. The loss of macular ganglion cells begins from the early stages of disease and correlates with brain atrophy in multiple sclerosis patients. *Mult Scler*. 2019;25(1):31-38. doi:10.1177/1352458517740214

18. Martinez-Lapiscina EH, Arnow S, Wilson JA, et al; IMSVISUAL consortium. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. *Lancet Neurol*. 2016;15(6):574-584. doi:10.1016/S1474-4422(16)00068-5

19. Birkeldh U, Manouchehrinia A, Hietala MA, et al. Retinal nerve fiber layer thickness associates with cognitive impairment and physical disability in multiple sclerosis. *Mult Scler Relat Disord*. 2019;36:101414. doi:10.1016/j.msard.2019.101414

20. Jiang N, Lee YO, Ling PM. Association between tobacco and alcohol use among young adult bar patrons: a cross-sectional study in three cities. *BMC Public Health*. 2014;14(1):500. doi:10.1186/1471-2458-14-500

21. Beard E, West R, Michie S, Brown J. Association between smoking and alcohol-related behaviours: a time-series analysis of population trends in England. *Addiction*. 2017;112(10):1832-1841. doi:10.1111/add.13887

22. Paul CA, Au R, Fredman L, et al. Association of alcohol consumption with brain volume in the Framingham Study. *Arch Neurol*. 2008;65(10):1363-1367. doi:10.1001/archneur.65.10.1363

23. Anstey KJ, Jorm AF, Réglade-Meslin C, et al. Weekly alcohol consumption, brain atrophy, and white matter hyperintensities in a community-based sample aged 60 to 64 years. *Psychosom Med*. 2006;68(5):778-785. doi:10.1097/01.psy.0000237779.56500.af

24. Kubota M, Nakazaki S, Hirai S, Saeki N, Yamaura A, Kusaka T. Alcohol consumption and frontal lobe shrinkage: study of 1432 non-alcoholic subjects. *J Neurol Neurosurg Psychiatry*. 2001;71(1):104-106. doi:10.1136/jnnp.71.1.104

25. Taki Y, Goto R, Evans A, et al. Voxel-based morphometry of human brain with age and cerebrovascular risk factors. *Neurobiol Aging*. 2004;25(4):455-463. doi:10.1016/j.neurobiolaging.2003.09.002

26. Mukamal KJ, Longstreth WT Jr, Mittleman MA, Crum RM, Siscovick DS. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the Cardiovascular Health Study. *Stroke*. 2001;32(9):1939-1946. doi:10.1161/hs0901.095723

27. Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ*. 2017;357:j2353. doi:10.1136/bmj.j2353

28. Dougherty RJ, Moonen J, Yaffe K, et al. Smoking mediates the relationship between SES and brain volume: The CARDIA study. *PLoS One*. 2020;15(9):e0239548. doi:10.1371/journal.pone.0239548

29. Ning K, Zhao L, Matloff W, Sun F, Toga AW. Association of relative brain age with tobacco smoking, alcohol consumption, and genetic variants. *Sci Rep*. 2020;10(1):10. doi:10.1038/s41598-019-56089-4

30. Topiwala A, Ebmeier K, Maullin-Sapey T, Nichols T. No safe level of alcohol consumption for brain health: observational cohort study of 25,378 UK Biobank participants. *medRxiv*. Preprint posted online May 12, 2021. doi:10.1101/2021.05.10.21256931

31. Ashina H, Li XQ, Olsen EM, Skovgaard AM, Larsen M, Munch IC. Association of maternal smoking during pregnancy and birth weight with retinal nerve fiber layer thickness in children aged 11 or 12 years: the Copenhagen Child Cohort 2000 Eye Study. *JAMA Ophthalmol*. 2017;135(4):331-337. doi:10.1001/jamaophthalmol.2017.0043

32. Khawaja AP, Chua S, Hysi PG, et al; UK Biobank Eye and Vision Consortium. Comparison of associations with different macular inner retinal thickness parameters in a large cohort: the UK Biobank. *Ophthalmology*. 2020;127(1):62-71. doi:10.1016/j.ophtha.2019.08.015

33. Kvistad S, Myhr KM, Holmøy T, et al. No association of tobacco use and disease activity in multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(4):e260. doi:10.1212/NXI.0000000000000260

34. Rosso M, Kimbrough DJ, Gonzalez CT, et al. Cross-sectional study of smoking exposure: no differential effect on OCT metrics in a cohort of MS patients. *Mult Scler J Exp Transl Clin*. 2019;5(1):2055217319828400. doi:10.1177/2055217319828400

35. Hedström AK, Hillert J, Olsson T, Alfredsson L. Alcohol as a modifiable lifestyle factor affecting multiple sclerosis risk. *JAMA Neurol*. 2014;71(3):300-305. doi:10.1001/jamaneurol.2013.5858

36. Weiland TJ, Hadgkiss EJ, Jelinek GA, Pereira NG, Marck CH, van der Meer DM. The association of alcohol consumption and smoking with quality of life, disability and disease activity in an international sample of people with multiple sclerosis. *J Neurol Sci*. 2014;336(1-2):211-219. doi:10.1016/j.jns.2013.10.046

37. Abdollahpour I, Nedjat S, Mansournia MA, Sahraian MA, van der Mei I. Lifestyle factors and multiple sclerosis: a population-based incident case-control study. *Mult Scler Relat Disord*. 2018;22:128-133. doi:10.1016/j.msard.2018.03.022

38. Wood AM, Kaptoge S, Butterworth AS, et al; Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet*. 2018;391(10129):1513-1523. doi:10.1016/S0140-6736(18)30134-X

39. Chua SYL, Luben RN, Hayat S, et al; UK Biobank Eye and Vision Consortium. Alcohol consumption and incident cataract surgery in two large UK cohorts. *Ophthalmology*. 2021;128(6):837-847. doi:10.1016/j.ophtha.2021.02.007

40. Chua SYL, Thomas D, Allen N, et al; UK Biobank Eye & Vision Consortium. Cohort profile: design and methods in the eye and vision consortium of UK Biobank. *BMJ Open*. 2019;9(2):e025077. doi:10.1136/bmjopen-2018-025077

41. Petzold A, Chua SYL, Khawaja AP, et al; UK Biobank Eye and Vision Consortium. Retinal asymmetry in multiple sclerosis. *Brain*. 2021;144(1):224-235. doi:10.1093/brain/awaa361

42. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, et al; IMSVISUAL consortium. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Neurology*. 2016;86(24):2303-2309. doi:10.1212/WNL.0000000000002774

43. Aytulun A, Cruz-Herranz A, Aktas O, et al. The APOSTEL 2.0 recommendations for reporting quantitative optical coherence tomography studies. *Neurology*. 2021;97(2):68-79. doi:10.1212/WNL.0000000000012125

44. Patel PJ, Foster PJ, Grossi CM, et al; UK Biobank Eyes and Vision Consortium. Spectral-domain optical coherence tomography imaging in 67 321 adults: associations with macular thickness in the UK biobank study. *Ophthalmology*. 2016;123(4):829-840. doi:10.1016/j.ophtha.2015.11.009

45. Tewarie P, Balk L, Costello F, et al. The OSCAR-IB consensus criteria for retinal OCT quality assessment. *PLoS One*. 2012;7(4):e34823. doi:10.1371/journal.pone.0034823

46. Jordan H, Roderick P, Martin D. The Index of Multiple Deprivation 2000 and accessibility effects on health. *J Epidemiol Community Health*. 2004;58(3):250-257. doi:10.1136/jech.2003.013011

47. Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. High frequency of adverse health behaviors in multiple sclerosis. *Mult Scler*. 2009;15(1):105-113. doi:10.1177/1352458508096680

48. Davis BJK, Vidal JS, Garcia M, et al. The alcohol paradox: light-to-moderate alcohol consumption, cognitive function, and brain volume. *J Gerontol A Biol Sci Med Sci*. 2014;69(12):1528-1535. doi:10.1093/gerona/glu092

49. Hedström AK, Hillert J, Olsson T, Alfredsson L. Factors affecting the risk of relapsing-onset and progressive-onset multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2021;92(10):1096-1102. doi:10.1136/jnnp-2020-325688

50. Ivashynka A, Copetti M, Naldi P, D'Alfonso S, Leone MA. The impact of lifetime alcohol and cigarette smoking loads on multiple sclerosis severity. *Front Neurol*. 2019;10:866. doi:10.3389/fneur.2019.00866

51. Diaz-Cruz C, Chua AS, Malik MT, et al. The effect of alcohol and red wine consumption on clinical and MRI outcomes in multiple sclerosis. *Mult Scler Relat Disord*. 2017;17(May):47-53. doi:10.1016/j.msard.2017.06.011

52. Arendt T, Allen Y, Sinden J, et al. Cholinergic-rich brain transplants reverse alcohol-induced memory deficits. *Nature*. 1988;332(6163):448-450. doi:10.1038/332448a0

53. McIntosh C, Chick J. Alcohol and the nervous system. *J Neurol Neurosurg Psychiatry*. 2004;75(suppl 3):iii16-iii21. doi:10.1136/jnnp.2004.045708

54. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004;43(10):1731-1737. doi:10.1016/j.jacc.2003.12.047

55. Das SK, Vasudevan DM. Alcohol-induced oxidative stress. *Life Sci*. 2007;81(3):177-187. doi:10.1016/j.lfs.2007.05.005

56. Desai RA, Smith KJ. Experimental autoimmune encephalomyelitis from a tissue energy perspective. *F1000Res*. 2017;6:1973. doi:10.12688/f1000research.11839.1

57. Su K, Bourdette D, Forte M. Mitochondrial dysfunction and neurodegeneration in multiple sclerosis. *Front Physiol*. 2013;4:169. doi:10.3389/fphys.2013.00169

58. Kleerekooper I, Petzold A, Trip SA. Anterior visual system imaging to investigate energy failure in multiple sclerosis. *Brain*. 2020;143(7):1999-2008. doi:10.1093/brain/awaa049

59. Han YS, Kim YW, Kim YJ, Park KH, Jeoung JW. Alcohol consumption is associated with glaucoma severity regardless of ALDH2 polymorphism. *Sci Rep*. 2020;10(1):17422. doi:10.1038/s41598-020-74470-6

SUPPLEMENT 1.

eTable 1. Univariable and Multivariable Logistic Regression—Odds of Multiple Sclerosis Case Status

eTable 2. Testing for Multiplicative Interactions of Alcohol and Smoking in Multiple Sclerosis

eTable 3. Effect Modification of Alcohol and Smoking Effects by Multiple Sclerosis Diagnosis

eFigure. Directed Acyclic Graph (DAG) Visualizing the Assumed Associations Among the Exposures, Outcomes and Potential Confounders in This Study

SUPPLEMENT 2.

Nonauthor Collaborators