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Observational and genetic evidence highlight the association of modifiable risk factors with the incidence and severity of neuroimmunological disorders

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ABSTRACT

Background: Myasthenia gravis (MG), multiple sclerosis (MS), and neuromyelitis optica spectrum disorders (NMOSD) are a heterogeneous group of rare neuroimmunological disorders whose incidence rates have increased in recent years. The relationships between modifiable risk factors and neuroimmunological disorders are not fully understood.

Methods: We utilized multiple logistic regression to estimate the relationships between 38 modifiable risk factors and two neuroimmunological diseases using data from nearly 500,000 individuals in the UK Biobank. Additionally, we applied two-sample Mendelian Randomization (MR) analyses using genetic variants as instrumental variables to investigate the causal relationships of 32 modifiable lifestyle factors with 8 outcomes, representing risk and severity across three neuroimmunological diseases. To further explore the underlying mechanisms, mediation analysis was conducted to elucidate how significant associations might be mediated by intermediate variables.

Results: Our observational and MR analyses consistently found significant associations ($P < 0.05$) indicating the number of cigarettes smoked daily, television watching, waist circumference, and BMI are all positively associated with the risk of developing MG. In contrast, moderate-to-vigorous physical activity and higher vitamin D levels are associated with a reduced risk of MS. Moreover, we discovered that the impact of television watching on the risk of MG was mediated by BMI (observational mediation analysis: 26.22%; MR mediation analysis: 9.90%).

Conclusions: These findings underscore the importance of modifiable risk factors in the development of neuroimmune diseases and support the identification of personalized intervention and prevention strategies. Notably, BMI significantly mediates the relationship between television watching and MG, indicating potential for targeted interventions to mitigate the risk of MG.

1. Introduction

Neuroimmunological disorders originate from a breakdown in self-tolerance mechanisms, resulting in the proliferation of autoreactive antibodies and lymphocytes that target the nervous system's self-antigens(Abbatemarco et al., 2021). These disorders include multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD),

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Guillain–Barré syndrome (GBS), and myasthenia gravis (MG). The incidence of these disorders has significantly increased in the last two decades(Nutma et al., 2019). Understanding the underlying causes and contributing factors of these disorders is crucial for developing effective prevention strategies. The etiology of neuroimmunological disorders involves a complex interplay of environmental triggers and genetic components. Large-scale genome-wide association studies (GWAS) have identified hundreds of genetic loci associated with MG, NMOSD, and MS. However, genetic predisposition to these disorders explains only a fraction of the disease risk (10%–40%). Identifying key modifiable factors could therefore be instrumental in enhancing prevention strategies.

Modifiable factors, defined as behavioral or environmental exposures that can be altered through individual or societal interventions, such as smoking, insufficient sun exposure, vitamin D deficiency, viral and microbial infections, obesity, and dietary habits are linked to the development of neuroimmune diseases, though the consistency and conclusiveness of these associations vary (Olsson et al., 2017; Miyazaki et al., 2023; Bjørnevik et al., 2014; Mealy et al., 2012; Munger et al., 2013; Staples et al., 2010). For instance, *Massa* et al. conducted a substantial prospective cohort study involving 95,051 women in the USA, revealing that neither caffeine nor alcohol consumption significantly influenced MS risk (Massa et al., 2013). Conversely, *Pakpoor* et al. provided evidence of a positive association between alcohol consumption and MS risk in a record-linkage study involving 6.7 million participants (Pakpoor et al., 2014). *Hedström* et al. explored the correlation between coffee consumption and MS risk via two case-control studies in Sweden (1620 cases, 2788 controls) and the US (1159 cases, 1172 controls), discovering a notably lower MS risk among those who consumed over 900 mL of coffee daily (Hedström et al., 2016a). Consequently, the role of modifiable factors as risk determinants for neuroimmunological disorders remains a subject of debate. Therefore, elucidating these relationships is essential to provide clinicians with the evidence necessary to consider modifications of these factors in reducing the risk of neuroimmunological disorders.

Several factors contribute to inconsistent findings in observational studies, including unknown confounding factors and small sample sizes. Mendelian randomization (MR) employs genetic variations as instrumental variables (IVs), specifically single nucleotide polymorphisms (SNPs), enhancing the robustness of causal inferences by reducing residual confounding and mitigating issues of reverse causality (Burgess and Thompson, 2015). Previous MR studies have examined the causal effects of several environmental risk factors and lifestyle behaviors, including vitamin D (Vandebergh et al., 2022; Wang, 2022), BMI (Harroud et al., 2021; Larsson and Burgess, 2021), and physical activity (Li et al., 2022), on the risk of MS. Integrating diverse study designs with complementary strengths to address the same core question, known as 'triangulation,' can enhance the accuracy of causal inference (Lawlor et al., 2016). To date, comprehensive research examining the causality between modifiable factors and the occurrence and progression of neuroimmune diseases is lacking.

In the current study, we performed a conventional observational analysis based on the UK Biobank (UKB) individual-level dataset and a two-sample MR analysis based on GWAS data to explore the potential causal associations of several modifiable factors with the risk and severity of neuroimmune diseases, including MS, NMOSD, and MG, along with their specific subtypes. Additionally, mediation analysis was conducted to elucidate how significant associations might be mediated by intermediate variables. Our aim is to elucidate the role of modifiable risk factors in the pathogenesis of neuroimmune diseases and to propose more targeted prevention strategies.

2. Materials and methods

2.1. Observational analysis of the UK biobank

2.1.1. Study population

The UK Biobank study enrolled over 500,000 individuals aged 40 to 69 from 22 assessment centers across the UK between 2006 and 2010 (Application 41376). During baseline appointments, participants provided informed consent and completed detailed questionnaires regarding their lifestyle, environment, and medical history. Extensive physical measurements were taken, and blood, urine, and saliva samples were collected (Bycroft et al., 2018). Researchers approved for specific health studies utilizing this resource do not require separate ethical approval.

2.1.2. Definitions of risk factors and diseases

38 modifiable risk factors were categorized into socioeconomic, behavioral, obesity, and dietary factors. Supplementary Table 1 provides a complete definition of each exposure used in the observational analysis. Participants with missing data, those who selected "Do not know" or "Prefer not to answer" for some risk factor questionnaires, and individuals of non-European genetic ancestry were excluded from downstream analyses. For the educational qualifications phenotype (UKB field ID 6138), we calculated equivalent years of education for each category as follows: 1) College or University degree = 20 years; 2) A levels/AS levels or equivalent = 13 years; 3) O levels/GCSEs or equivalent = 10 years; 4) CSEs or equivalent = 10 years; 5) NVQ or HND or HNC or equivalent = Age left schooling - 5 years; 6) Other professional qualifications (e.g., nursing, teaching) = 15 years; 7) None of the above = 7 years (Okbay et al., 2022).

The definitions of MG, MS, and NMOSD were based on ICD-10 codes (Supplementary Table 1), derived from relevant hospital inpatient data. Due to the scarcity of NMOSD cases in UKB, they were not included in the observational study analysis. Only MS and MG cases diagnosed after January 1, 2006, were included to ensure they occurred after exposures. These cohorts were compared with a randomly sampled general control group without MG or MS. To minimize the potential case-control imbalance that might arise from using the entire UK Biobank population, we selected a control sub-cohort approximately four times the number of cases. The quality control procedure is illustrated in Fig. 1.

2.2. Two sample MR analysis

2.2.1. Data source

In the two-sample MR analysis, the genetic instruments for 32 modifiable factors were selected from GWASs with large sample sizes (ranging from 66,622 to 1,331,010 participants), predominantly involving individuals of European ancestry. Outcome GWASs included MG (1873 cases and 36,370 controls, encompassing early-onset and late-onset cases) (Chia et al., 2022), MS (47,429 cases and 68,374 controls) (Patsopoulos et al., 2019), MS severity (12,584 cases) (Harroud et al., 2023), and NMOSD (215 cases and 1244 controls, inclusive of NMOSD-IgG+ and NMOSD-IgG− subtypes) (Estrada et al., 2018). Early-onset and late-onset MG were distinguished by symptom onset age ($\leq$50 years), whereas NMOSD subtypes were classified by the presence or absence of AQP4-IgG antibodies. All studies received ethical approval from their respective cohorts, negating the need for additional informed consent. Further details regarding the GWASs for exposures and outcomes are provided in Supplementary Table 1.

2.2.2. Genetic instruments selection

Independent SNPs linked to 32 modifiable risk factors were extracted from relevant GWASs datasets at the significance genome-wide threshold ($P \leq 5 \times 10^{-8}$; Supplementary Table 1). Linkage disequilibrium (LD) among these SNPs were estimated using the 1000 Genomes European reference panel, with SNPs in LD ($r2 \geq 0.1$) removed from

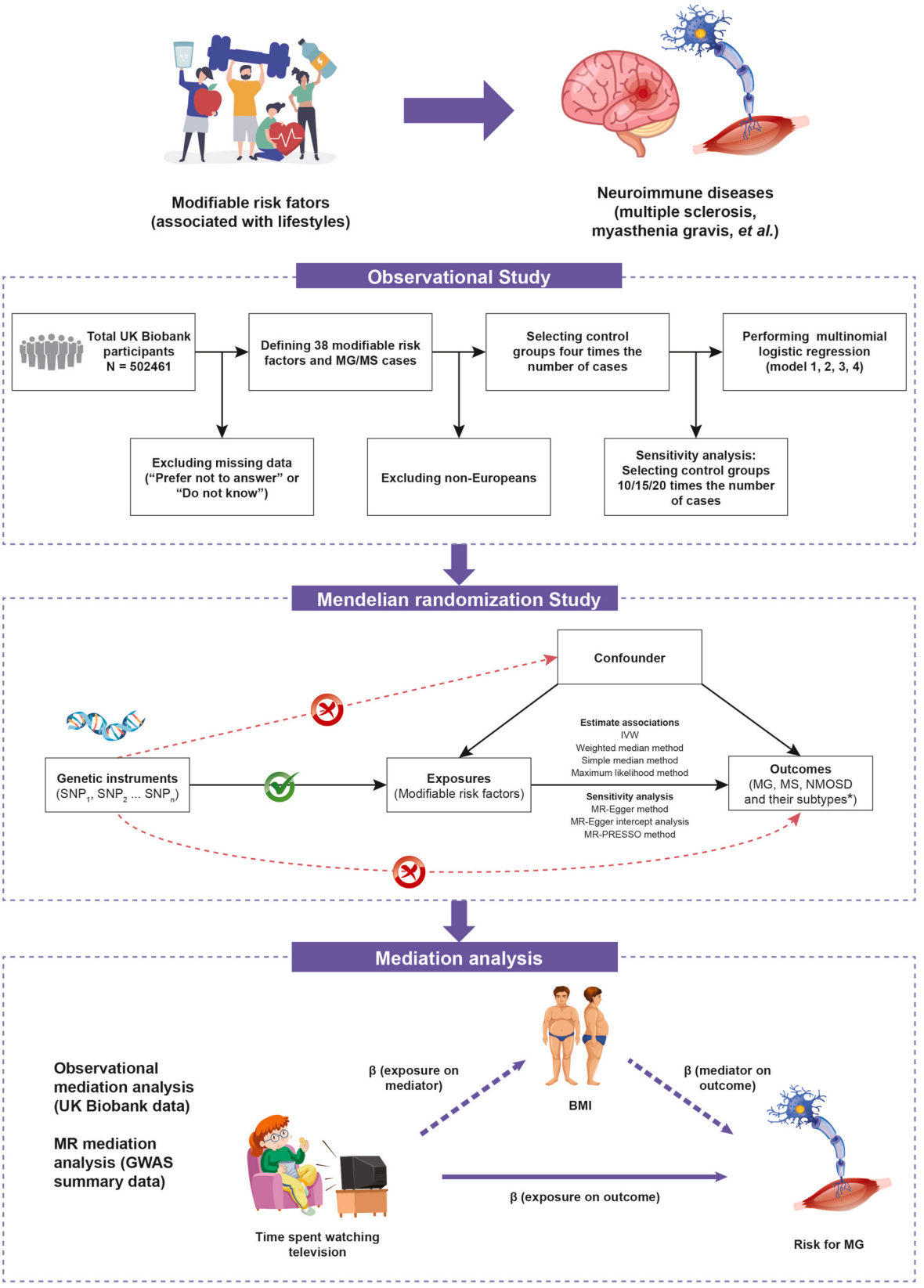

Fig. 1. Study design. SNP: single-nucleotide polymorphism. MG: myasthenia gravis; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorders; IVW: inverse-variance-weighted method; MR-PRESSO: Mendelian randomization Pleiotropy Residual Sum and Outlier; BMI: body mass index.
* Outcomes in MR include early-onset MG, late-onset MG, combined-MG, MS, MS severity, IgG + NMOSD, IgG- NMOSD, and combined-NMOSD.

further analysis. The SNPs with the lowest P value were retained as instrumental variables. Additionally, if an instrumental SNP wasn't available in the neuro-immune disorders, we performed the LDlink to search a proxy SNP in LD to replace the missing SNP ($r2 > 0.80$). Then we harmonized the exposure and outcome dataset to ensure that the instrumental variables estimate matched the same allele and excluded the possible palindromic SNPs ($0.45 < MAF < 0.55$). When lacking the effect allele frequency information, we also estimated from the 1000 Genomes European reference panel. Finally, we calculated F-statistics to assess the potency of genetic instruments (Bowden et al., 2015). Detailed information of IVs based on the GRCh37 version is displayed in Supplementary Table 5 and Supplementary Table 6.

2.3. Statistical analysis

2.3.1. Cross-sectional analysis

We utilized descriptive statistics to summarize participant characteristics and modifiable risk factors (see Supplementary Table 2). We employed multiple logistic regression to examine the relationships between modifiable risk factors and each neuroimmune disease, controlling for potential confounders. Confounders were adjusted in four models: Model 1 (including only exposure), Model 2 (Model 1 + gender), Model 3 (Model 2 + age), and Model 4 (Model 3 + BMI, excluding exposures within the 'Body size measures' category). To test the robustness of our findings, we conducted sensitivity analyses by comparing the case group with control subgroups randomly sampled at 10, 15, and 20 times the number of cases. For the unordered multinomial variables in the chronotype phenotype, we converted them into dummy variables before inclusion in the analysis.

2.3.2. Two-sample MR analysis

For each exposure, the inverse-variance weighted (IVW) method, applied within a multiplicative random-effects model, served as the primary statistical analysis, offering robust causal estimates in the absence of directional pleiotropy(Burgess et al., 2013). To ensure the robustness and validity of our findings, various sensitivity analyses were performed, including the inverse-variance weighted fixed effect model, the weighted median, the simple median, the maximum likelihood and MR-Egger methods(Bowden et al., 2015, 2016; Burgess et al., 2013; Verbanck et al., 2018). Additionally, the MR-Egger regression intercept test was utilized to evaluate directional pleiotropy, with significance set at P for intercept <0.05 (Bowden et al., 2015). We further employed the MR pleiotropy residual sum and outlier (MR-PRESSO) test to identify and prune outlier SNPs that are potentially horizontally pleiotropic and to examine the difference in estimates after removal of outliers (Verbanck et al., 2018). For certain significant causal relationships, we conducted multivariable Mendelian Randomization (MVMR) analysis to assess whether the causal relationships remained significant after controlling for BMI effects. Associations were deemed significant at $P < 0.00156$ (0.05/32 exposures), while those with $P \geq 0.00156$ and ≤ 0.05 were considered suggestive. All statistical analyses were conducted using the TwoSampleMR(Hemani et al., 2018), MR-PRESSO (Verbanck et al., 2018), and MendelianRandomization (Yavorska and Burgess, 2017) packages in R software.

2.3.3. Mediation analysis

Additionally, we conducted mediation analyses to explore whether the relationship between several risk factors (exposure) and neuroimmune diseases (outcome) could be explained, at least partially, by mediators. We performed both an observational mediation analysis and a MR mediation analysis. In the first step, using individual data from the UK Biobank or genetic instruments, we assessed the causal effect of television watching on the putative mediator (β_{EM}). In the second step, these instruments estimated the causal impact of the identified mediator on the risk of neuroimmune disorders (β_{MO}). These two estimates from the two steps were multiplied to obtain an estimate of the indirect effect of each sedentary behavior ($\beta_{EM} * \beta_{MO}$). Subsequently, the proportion of the total effect explained by each potential mediator was determined by dividing the indirect effect by the total effect. The Delta method was used to estimate the standard error (SE) and confidence interval (CI) (Carter et al., 2021).

3. Results

3.1. Observational analysis in UK biobank

In the UK Biobank cohort of 502,461 participants, 417 (0.08%) were diagnosed with MG, including 369 of European ancestry (British population), and 2070 (0.41%) were diagnosed with MS, including 1897 of European ancestry. The majority of MG patients were male (55.4%), with a mean age of 60 years (SD = 7.1) and a mean BMI of 29 kg/m^2 (SD = 5.6). Among MS patients, the majority were female (71.9%), with a mean age of 55 years (SD = 7.6) and a mean BMI of 27.1 kg/m^2 (SD = 5.2). More detailed descriptive statistics are provided in Supplementary Table 2. After adjusting for confounding factors using multiple logistic regression, the estimates from models 1, 2, 3, and 4 were generally similar (Supplementary Tables 3 and 4). The following results are based on model 3 (Fig. 2).

3.1.1. Behaviors

The number of cigarettes previously smoked daily was associated with increased risk of both MG (OR = 1.02, 95% CI: 1.002–1.044, P = 2.83×10^{-2}) and MS (OR = 1.01, 95% CI: 1.004–1.026, P = 7.09×10^{-3}). Compared to never smokers, individuals who have ever smoked have higher odds of MS (ever smoked, OR = 1.50, 95% CI: 1.31–1.72, P = 5.71×10^{-9}; smoking status, OR = 1.41, 95% CI: 1.29–1.55, P = 7.15×10^{-14}). Age stopped smoking was also associated with MS risk (OR = 1.01, 95% CI: 1.002–1.027, P = 1.96×10^{-2}). Concerning alcohol consumption, alcohol intake frequency was a risk factor for MG (OR = 1.16, 95% CI: 1.07–1.27, P = 3.94×10^{-4}) and MS (OR = 1.12, 95% CI: 1.08–1.17, P = 2.99×10^{-8}), whereas frequency of drinking alcohol (OR = 0.87, 95% CI: 0.79–0.95, P = 2.41×10^{-3}), alcohol drinker status (OR = 0.80, 95% CI: 0.69–0.92, P = 2.72×10^{-3}), amount of alcohol drunk on a typical drinking day (OR = 0.83, 95% CI: 0.72–0.96, P = 1.07×10^{-2}), and frequency of consuming six or more units of alcohol (OR = 0.81, 95% CI: 0.71–0.92, P = 1.26×10^{-3}) were protective factors for MS. Regarding sleep behaviors, insomnia was associated with increased risk of MG (OR = 1.38, 95% CI: 1.15–1.65, P = 5.15×10^{-4}) and MS (OR = 1.17, 95% CI: 1.07–1.29, P = 6.28×10^{-4}), while sleep duration was associated with increased risk of MS (OR = 1.13, 95% CI: 1.07–1.19, P = 2.44×10^{-5}). The chronotype phenotypes - more a 'morning' than 'evening' person (OR = 0.78, 95% CI: 0.61–0.99, P = 4.03×10^{-2}) and more an 'evening' than a 'morning' person (OR = 0.78, 95% CI: 0.60–0.99, P = 4.64×10^{-2}) were both linked to reduced risk of MS. Regarding physical activity, no risk factors were found to be associated with the onset of MG. However, duration of moderate activity (OR = 0.9986, 95% CI: 0.9972–0.9999, P = 3.61×10^{-2}), number of days/week of moderate physical activity 10+ minutes (OR = 0.91, 95% CI: 0.89–0.94, P = 6.39×10^{-10}), duration of other exercises (OR = 0.80, 95% CI: 0.73–0.88, P = 6.79×10^{-6}), and number of days/week of vigorous physical activity 10+ minutes (OR = 0.86, 95% CI: 0.83–0.90, P = 2.53×10^{-13}) were associated with reduced risk of MS. Concerning sedentary behaviors, time spent watching television was a risk factor for MG (OR = 1.12, 95% CI: 1.03–1.21, P = 4.99×10^{-3}) and MS (OR = 1.12, 95% CI: 1.08–1.16, P = 2.20×10^{-9}), while time spent driving was a protective factor for MS (OR = 0.86, 95% CI: 0.80–0.93, P = 7.70×10^{-5}).

3.1.2. Dietary factor and educational attainment

Vitamin D levels were associated with reduced risk of both MG (OR = 0.9919, 95% CI: 0.9852–0.9985, P = 1.70×10^{-2}) and MS (OR = 0.9933, 95% CI: 0.9900–0.9965, P = 5.37×10^{-5}). The age at which

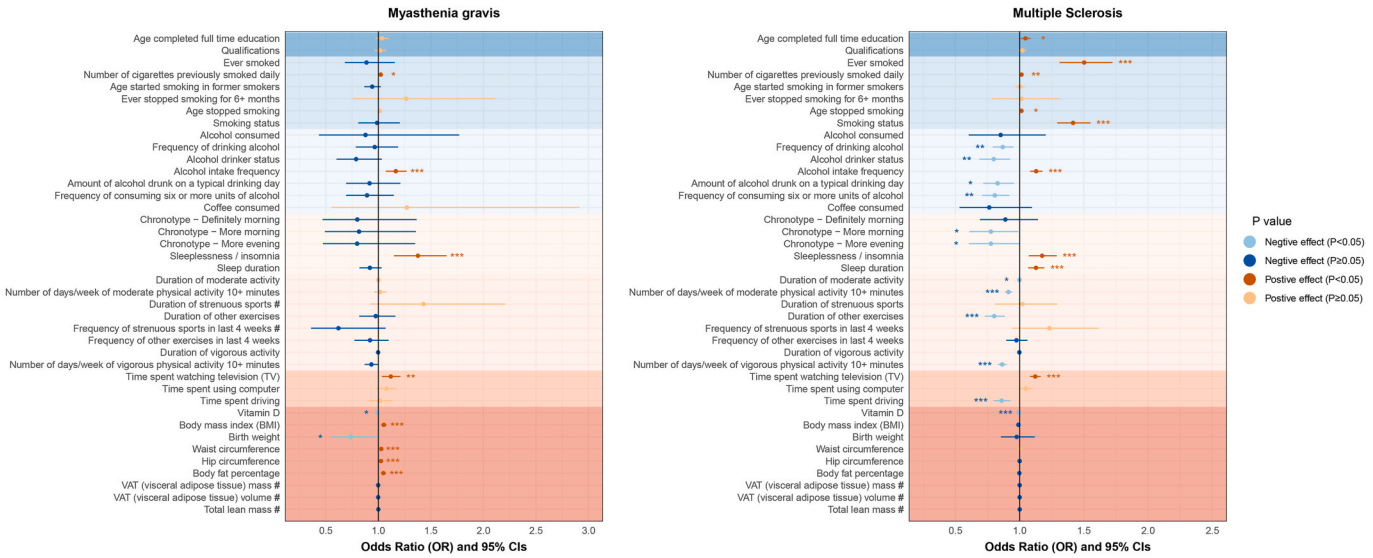

Fig. 2. Observational associations between modifiable risk factors and MG/MS.
Estimates were derived from model 3, with dots representing ORs and error bars indicating 95% CIs. All statistical tests were two-sided. P < 0.05 was considered significant.
Some exposure data had small sample sizes (less than 20) after quality control, which did not meet the Event Per Variable (EPV) requirements for logistic regression. Therefore, the results may not be robust. Considering the rarity of patient groups and the interpretability of the results, we have still chosen to present them. The reliability of these findings requires further validation through additional research.
*** p-value <0.001, ** p-value <0.01, * p-value <0.05.

participants completed full-time education was associated with an increased risk of MS (OR = 1.05, 95% CI: 1.01–1.08, P = 1.51×10^{-2}).

3.1.3. Obesity

Body Mass Index (OR = 1.05, 95% CI: 1.03–1.08, P = 6.88×10^{-5}), waist circumference (OR = 1.03, 95% CI: 1.02–1.04, P = 1.49×10^{-7}), hip circumference (OR = 1.02, 95% CI: 1.01–1.04, P = 2.60×10^{-4}), and body fat percentage (OR = 1.05, 95% CI: 1.03–1.07, P = 2.61×10^{-5}) were associated with increased risk of MG, while birth weight (OR = 0.74, 95% CI: 0.55–0.99, P = 4.33×10^{-2}) was associated with reduced risk. We did not find any evidence of such risk factors associated with MS.

3.1.4. Commonalities and heterogeneities in the observational studies

Our observational analysis revealed distinct risk factor patterns for different neuroimmune diseases (Fig. 2). Smoking, particularly with a higher number of cigarettes previously smoked daily, was a significant risk factor for both MG and MS. Alcohol consumption increased the risk for both diseases, although certain alcohol habits were protective for MS. Insomnia increased the risk for both MG and MS, while sleep duration specifically increased the risk of MS. No physical activity factors were linked to MG, but moderate and vigorous activities reduced the risk of MS. Television watching increased the risk for both MG and MS, whereas driving was protective for MS. Body size measures, including BMI, waist circumference, hip circumference, and body fat percentage, were linked to a higher risk of MG but not MS. Vitamin D levels were associated with reduced risks for both diseases. Sensitivity analyses using control subgroups sampled at 10, 15, and 20 times the number of cases showed similar results (Supplementary Tables 3 and 4).

3.2. MR estimates of modifiable risk factors on neuroimmune disorders

The F statistics for all instrumental variables (IVs) are presented in Supplementary Table 5, with values ranging from 23.48 to 363.21, indicating a valid strength of the genetic instruments used. Detailed MR results are illustrated in Fig. 3.

3.2.1. Behaviors

Suggestive evidence indicated that genetically predicted increases in daily cigarette consumption were associated with a higher risk of combined MG (OR = 1.84 per one SD increase, 95% CI: 1.11–3.05; P = 1.76×10^{-2}), which was consistent with the results from observational study. Genetically predicted older age at initiation of regular smoking was associated with a lower risk of MS (OR = 0.36 per one SD increase, 95% CI: 0.16–0.82; P = 1.46×10^{-2}; Fig. 3). A suggestive association was detected between a higher genetically predicted lifetime smoking index and increased MS severity (OR = 1.21 per one SD increase, 95% CI: 1.03–1.42; P = 1.71×10^{-2}). Additionally, genetic predispositions towards regular smoking were associated with a reduced risk of developing the NMOSD-IgG + subtype (OR = 0.36 per doubling in odds of smoking initiation, 95% CI: 0.15–0.85; P = 2.04×10^{-2}; Fig. 3) compared to non-smokers, with no observed association for combined NMOSD or its IgG− subtype.

Regarding drinking behaviors, genetically predicted alcohol drinking per week showed a positive association with MS severity (OR = 1.25 per one SD increase, 95% CI: 1.04–1.51; P = 1.97×10^{-2}). However, the IVW model indicated that alcohol drinking was suggestively inversely associated with the risk of late-onset MG (OR = 0.44, 95% CI: 0.21–0.89; P = 2.31×10^{-2}), combined NMOSD (OR = 0.07, 95% CI: 0.01–0.46; P = 5.19×10^{-3}), NMOSD-IgG + subtype (OR = 0.05, 95% CI: 0.004–0.61; P = 1.87×10^{-2}), and NMOSD-IgG− subtype (OR = 0.04, 95% CI: 0.002–0.71; P = 2.79×10^{-2}). These associations remained overall concordant in sensitivity analyses. These findings implicated low to moderate alcohol consumption as a potential protective factor against the development of certain neuroimmune disorders. However, there is no evidence of inverse correlations between alcohol use disorder (resulting from excessive alcohol consumption) and susceptibility to any neuroimmune diseases.

Regarding sleep behaviors, a statistically significant correlation was observed between genetically determined sleep duration and decreased MG risk (OR = 0.98 per one SD increase, 95% CI: 0.97–0.99; P = 2.56×10^{-4}; Fig. 3). Subgroup analyses revealed suggestive negative associations with habitual self-reported sleep duration for both early-onset MG and late-onset MG (early-onset MG: OR = 0.97, 95% CI: 0.95–1.00, P =

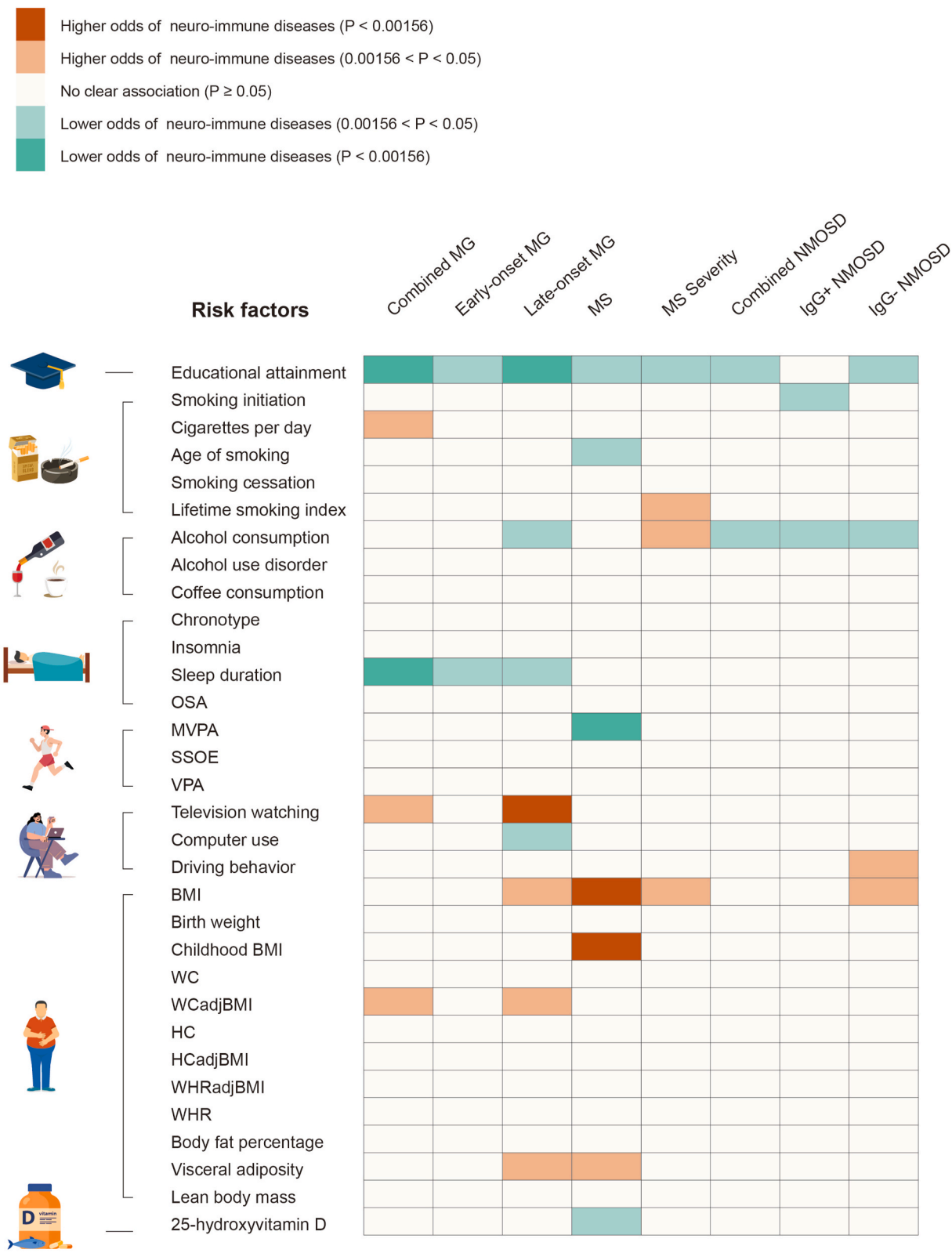

Fig. 3. MR associations of modifiable risk factors with neuroimmune diseases using random effect inverse-variance weighted method. OSA: obstructive sleep apnea; MVPA: moderate-to-vigorous physical activity; SSOE: strenuous sports or other exercises; VPA: vigorous physical activity; BMI: body mass index; SNP: single nucleotide polymorphism; WC: waist circumference; WCadjBMI: BMI-adjusted waist circumference; HC: hip circumstance; HCadjBMI: BMI-adjusted hip circumstance; WHR: waist-to-hip ratio; WHRadjBMI: BMI-adjusted waist-to-hip ratio.

1.78×10^{-2}; late-onset MG: OR = 0.98, 95% CI: 0.97–1.00, $P = 1.03 \times 10^{-2}$; Supplementary Tables 8 and 9).

Concerning physical activity, a significant association was observed between moderate-to-vigorous physical activity (MVPA) and a decreased likelihood of MS (OR = 0.24 per one SD increase, 95% CI: 0.13–0.45; $P = 7.58 \times 10^{-6}$; Fig. 3), which was validated in observational studies. The inverse-variance weighted (IVW) model revealed no significant effects from strenuous sports or other exercises (SSOE) and vigorous physical activity (VPA) on the risk and severity of neuroimmunological disorders and their subtypes.

Regarding leisure sedentary behaviors, genetically associated prolonged television watching was linked to a higher risk of MG (OR = 2.11 per one SD increase, 95% CI: 1.30–3.41; $P = 2.33 \times 10^{-3}$), particularly for its late-onset subtype (OR = 2.54, 95% CI: 1.45–4.45; $P = 1.15 \times 10^{-3}$; Fig. 3). This finding aligned with our observational study results. Genetically inferred leisure computer use was associated with reduced odds of late-onset MG (OR = 0.25 per one SD increase, 95% CI: 0.07–0.87; $P = 2.97 \times 10^{-2}$). Additionally, we noted a suggestive association between genetically predicted leisure driving and the increased risk of NMOSD-IgG− subtype. Causal estimate was consistent in several alternative MR algorithms.

3.2.2. Dietary factor and educational attainment

Higher genetically predicted circulating 25-hydroxyvitamin D levels were suggestively and inversely associated with susceptibility to MS (OR = 0.58 per one SD increase, 95% CI: 0.41–0.82; $P = 1.86 \times 10^{-3}$). This association was also observed in our observational analysis. No other significant associations were identified between serum 25-hydroxyvitamin D concentrations and any other neuroimmunological disorders in this MR analysis (Fig. 3). We observed a significant inverse association of genetically predicted educational attainment with MG (Fig. 3). The odds ratio (OR) for MG was 0.64 (95% CI: 0.52–0.80; $P = 1.02 \times 10^{-4}$) for one standard deviation (SD) increase in years of schooling. Similarly, genetically predicted higher educational level also showed a significantly negative associations with both the early-onset MG subtype and late-onset MG subtype (OR = 0.59, 95% CI: 0.39–0.91, $P = 1.63 \times 10^{-2}$; OR = 0.65, 95% CI: 0.50–0.85, $P = 1.38 \times 10^{-3}$, respectively, Fig. 3). Furthermore, suggestive evidence was found for an inverse association between genetically predicted higher educational levels and MS (OR = 0.83, 95% CI: 0.72–0.94; $P = 5.11 \times 10^{-3}$), MS severity (OR = 0.90, 95% CI: 0.84–0.96; $P = 1.85 \times 10^{-3}$), combined NMOSD (OR = 0.50, 95% CI: 0.27–0.93; $P = 2.77 \times 10^{-2}$), and its IgG− subtype (OR = 0.30, 95% CI: 0.12–0.78; $P = 1.35 \times 10^{-2}$).

3.2.3. Obesity

Increased genetically predicted body mass index (BMI) and childhood BMI were found to be significantly associated with a greater susceptibility to MS (BMI: OR = 1.30 per one SD increase, 95% CI: 1.18–1.43; $P = 1.71 \times 10^{-7}$; childhood BMI: OR = 1.33 per one SD increase, 95% CI: 1.13–1.57; $P = 5.28 \times 10^{-4}$; Fig. 3). Similarly, genetically predicted BMI was also positively associated with MS severity (OR = 1.09, 95% CI: 1.03–1.15; $P = 1.61 \times 10^{-3}$), late-onset MG (OR = 1.27, 95% CI: 1.02–1.56; $P = 2.89 \times 10^{-2}$) and IgG− NMOSD (OR = 2.33, 95% CI: 1.08–5.06; $P = 3.16 \times 10^{-2}$). The IVW model indicated a suggestive causal effect of increased BMI-adjusted waist circumference (WCadjBMI) on the risk of MG (OR = 1.80 per one SD increase, 95% CI 1.14–2.85; $P = 1.18 \times 10^{-2}$) and its late-onset subtype (OR = 1.78 per one SD increase, 95% CI 1.04–3.04; $P = 3.47 \times 10^{-2}$; Fig. 3), which was verified by our observational study. Moreover, suggestive positive associations were demonstrated between genetically proxied visceral adiposity and MS (OR = 1.33 per one SD increase, 95% CI: 1.10–1.61; $P = 3.73 \times 10^{-3}$) and late-onset MG (OR = 1.48, 95% CI: 1.03–2.11; $P = 3.19 \times 10^{-2}$) were demonstrated.

3.2.4. Commonalities and heterogeneities in the MR causal relationships

Our MR results demonstrated overlapping causal relationships among various modifiable risk factors and neuroimmune diseases (Fig. 4). Notably, genetically predicted educational attainment emerged as a shared causal risk factor among MG, MS, NMOSD, and MS Severity. Genetically predicted BMI was associated with both MS and MS Severity, while genetically predicted alcohol consumption was correlated with MS Severity and NMOSD. Additionally, we identified daily cigarette consumption, sleep duration, television watching, and WC-adjusted BMI as unique contributors to MG; age of smoking, MVPA, 25-hydroxyvitamin D, childhood BMI, and visceral adiposity as contributors to MS; and lifetime smoking index as a contributor to MS Severity.

3.3. Consistencies between observational and MR studies

Both observational and MR analyses consistently identified the same key modifiable risk factors for neuroimmune diseases (Figs. 2 and 3). For instance, higher BMI, the number of cigarettes smoked daily, and television watching were all linked to increased risks of MG. Conversely, moderate and vigorous physical activity, as well as higher vitamin D levels, were found to reduce the risk of MS. These consistent findings underscore the importance role of these modifiable risk factors in the development of neuroimmune diseases.

3.4. BMI mediated the effect of television watching on MG

Both observational study and MR analysis demonstrated a significant association between time spent watching television and an increased risk of MG. However, when BMI was included as an additional covariate (model 4), this association became non-significant (OR = 1.03, 95% CI: 0.95–1.12, P = 0.44; Fig. 5a). Similarly, the significant association observed in the univariable MR analysis disappeared when BMI was incorporated in the MVMR analysis (Fig. 5b). Therefore, we conducted both observational mediation analysis and MR mediation analysis to explore whether the relationship between watching television and MG could be at least partially explained by BMI. The observational mediation analysis indicated that 26.2% of the effect of watching television on MG was mediated by BMI (Fig. 5c), while the MR mediation analysis found that BMI mediated 9.9% of the effect (Fig. 5d). Interestingly, the mediating role of BMI in the relationships between other risk factors (such as daily smoking, MVPA, and vitamin levels) and MG/MS was not consistently validated in observational and MR mediation analyses. Notably, we cannot entirely exclude the possibility of other mediators involved in the relationship between television watching and MG. Leisure television watching has also been reported to be associated with educational attainment, smoking, inflammatory markers, and metabolic changes (Frydenlund et al., 2012; Huang et al., 2023; Pischon et al., 2003). To further explore these potential pathways, we conducted additional mediation analyses and found that educational attainment (via MR analysis), the number of cigarettes previously smoked daily (via observational analysis), and C-reactive protein levels (via observational analysis) mediated the relationship between television watching and MG (Supplementary Tables 15 and 16).

4. Discussion

To our best knowledge, this is the first comprehensive study combining observational analyses and MR analysis utilizing individual-level data from the UK Biobank and the large-scale GWAS data on neuroimmunological diseases to systematically identify modifiable factors that can trigger and exacerbate these conditions. Triangulating evidence from observational and MR analyses, we confirmed robust causal relationships between smoking (number of cigarettes previously smoked daily), exercise (moderate to vigorous physical activity), sedentary behavior (television watching), waist circumference, and vitamin D levels with specific neuroimmunological diseases. Moreover, mediation analysis revealed that the impact of watching television on the risk of MG was mediated by BMI.

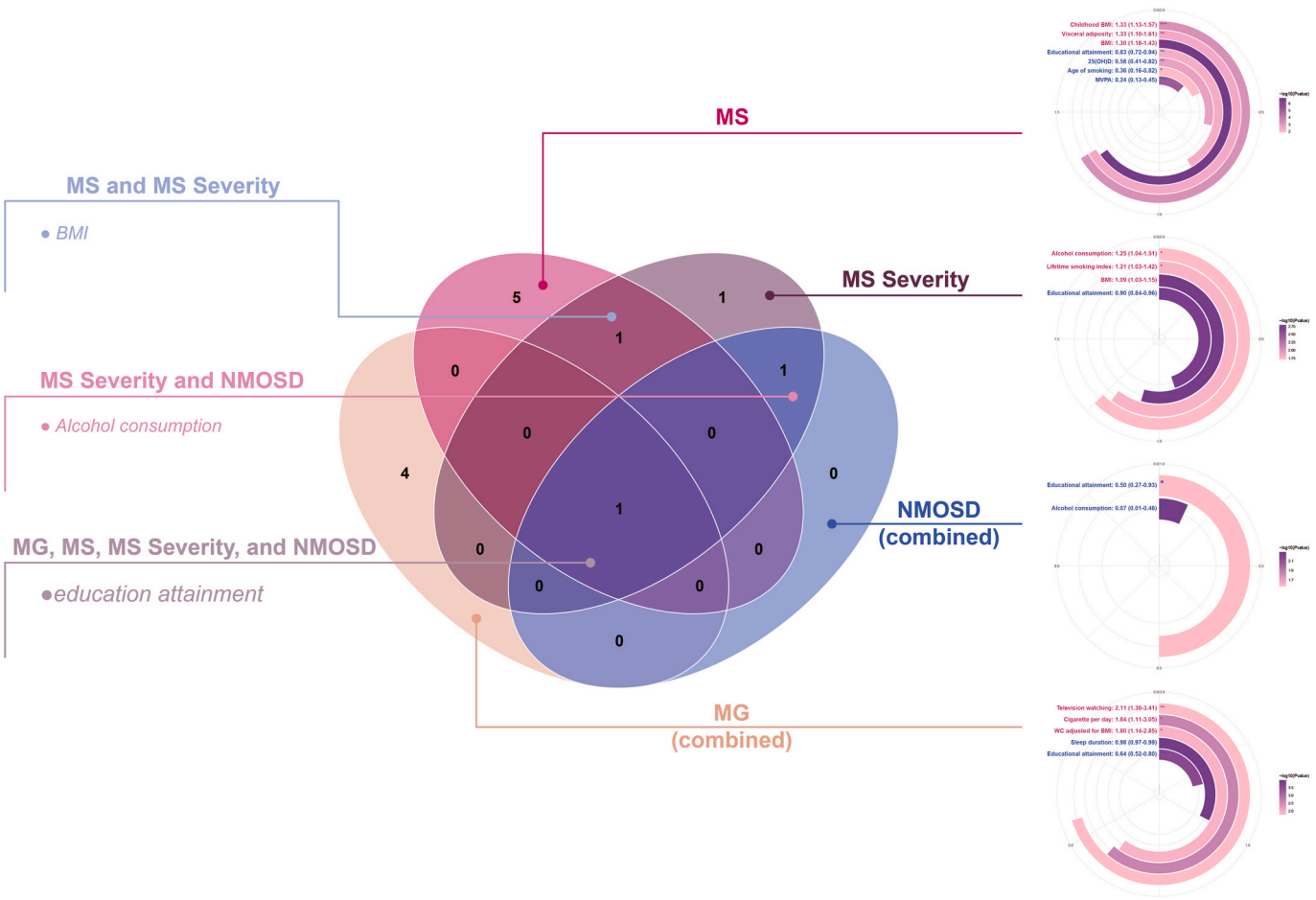

Fig. 4. Commonalities and heterogeneities in the MR causal relationships between modifiable risk factors and neuroimmune diseases. Venn diagram illustrates the overlapping and distinct causal associations of environmental factors with MS, MS Severity, combined MG and combined NMOSD. Radial histograms on the right depict all significant causal relationships, with p-values represented by color gradients and odds ratios (ORs) by bar lengths. Modifiable risk factors are highlighted in blue or red to indicate decreased or increased risks of neuroimmune disorders, respectively. Shared causal impacts are shown on the left. Significant causal relationships are indicated by asterisks (*p-value <0.05; **p-value <0.01; ***p-value <0.00156). MG: myasthenia gravis; MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorders; BMI: body mass index; 25(OH)D: 25-hydroxyvitamin D.

Numerous studies have indicated that smoking impacts the development and progression of neuroimmune diseases across various populations. A systematic review has documented that smoking serves as an additional risk factor for both the onset and progression of MS (Arneth, 2020). Additionally, several observational studies have demonstrated an inverse association between cigarette smoking and the onset of MG (Miyazaki et al., 2023; Maniaol et al., 2013). In our study, observational and genetic evidence supports the effects of smoking-related factors on both MG and MS. Specifically, both observational and genetic evidence suggested that the number of cigarettes previously smoked daily is significantly associated with an increased risk of MG. A possible mechanism to explain this phenomenon involves tobacco components, including nicotine, which impact nervous system function through various mechanisms such as immunomodulation, inflammation, and disruption of the blood-brain barrier (Arneth, 2020).

Physical activity has been proposed as beneficial in mitigating vulnerability to and manifestations of MS(Li et al., 2022; Gunnarsson et al., 2015; Wesnes et al., 2018). Our observational and MR study, which focused on physical activity of varying intensities, provided more robust evidence supporting the protective effect of physical activity, particularly moderate to vigorous physical activity (MVPA), on MS risk. A potential mechanism for this protective effect may involve the upregulation of T-regulatory cells, reduction in immunoglobulin secretion, increase in neuroactive protein expression, and enhancement of the anti-inflammatory response, all mediated by physical activity, potentially reducing inflammatory events (Gleeson et al., 2011; Krüger et al., 2016; White and Castellano, 2008).

Multiple observational studies have identified an association between sedentary behavior and the occurrence of comorbidities in certain neuroimmune disorders (Hensman et al., 2020; Klaren et al., 2014; Veldhuijzen van Zanten et al., 2016). However, most have primarily focused on overall sedentary time, neglecting the specific impact of each sedentary behavior subtype on the risk and severity of neuroimmune diseases. Various forms of sedentary behavior may yield distinct impacts on health. In the current study, robust observational and genetic evidence is provided that leisure television watching constitutes a risk factor for MG. Similar detrimental impacts of leisure television watching have been observed in several studies (Huang et al., 2023; Chen et al., 2022; Nang et al., 2013; Raichlen et al., 2022). Several potential explanations for this causal relationship are linked to obesity-related phenotypes, including type 2 diabetes, triglycerides, and BMI, coinciding with the observational and MR mediation effects identified (Huang et al., 2023; Hu et al., 2003). Leisure television watching has been reported to lead to excessive food and total energy intake, as well as reduced physical activity (Frydenlund et al., 2012; Hu et al., 2003; Otten et al., 2009; Lyons et al., 2012), all directly associated with a heightened risk of several neuroimmune disorders. This was further verified by the fact that the association became non-significant after incorporating BMI as a covariate in the analyses. Furthermore, the mediation proportion of BMI is 26.2% in observational studies and 9.9%

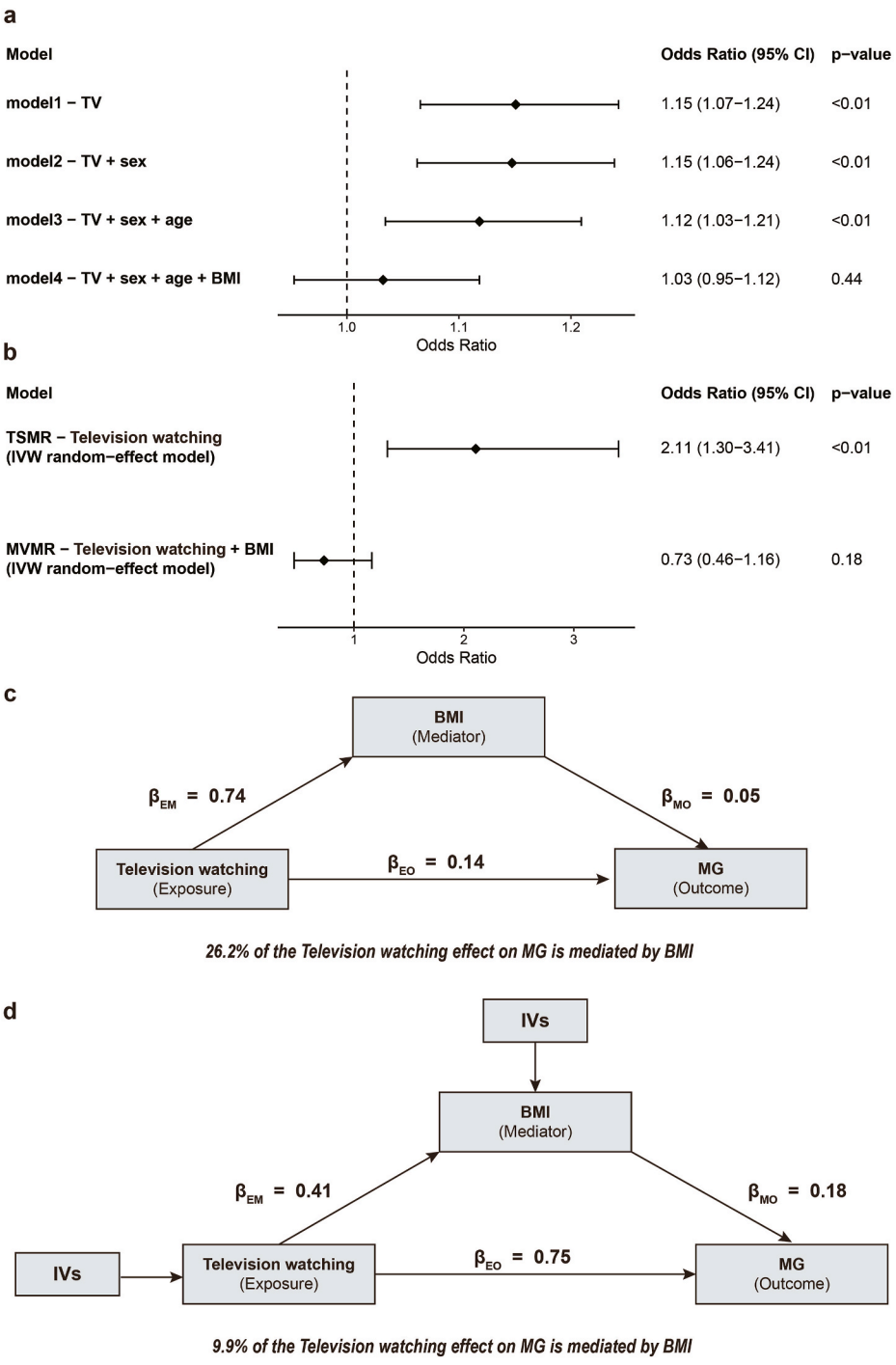

Fig. 5. BMI mediated the effect of television watching on MG. a, Summary of effect estimates from different models in observational study assessing the impact of time spent watching television on MG. **b,** Summary of effect estimates in MR analyses assessing the impact of television watching on MG. **c,** Observational mediation analysis to assess the effect of television watching on MG via BMI. **d,** MR mediation analysis to assess the effect of television watching on MG via BMI. β_{EO}: effects of exposure on outcome, β_{EM}: effects of exposure on mediator, β_{MO}: effects of mediator on outcome, IVs: instrumental variables, MG: myasthenia gravis, TV: time spent watching television, BMI: body mass index, TSMR: two-sample Mendelian Randomization, MVMR: multivariable Mendelian Randomization.

in MR studies, indicating that BMI does not fully mediate the effect, suggesting the involvement of additional mediators. Further mediation analyses revealed that educational attainment, the number of cigarettes previously smoked daily, and C-reactive protein levels also mediated the relationship between television watching and MG (Supplementary Tables 15 and 16), which are in line with previous studies (Frydenlund et al., 2012; Huang et al., 2023; Pischon et al., 2003). Future research should explore how other mediators, such as socioeconomic factors, additional inflammatory markers, and metabolic changes, might affect the relationship between watching television and MG risk.

Growing evidence has identified obesity as a risk factor for the development of several neuroimmune disorders (Olsson et al., 2017; Munger et al., 2013; Hedström et al., 2016b; Misicka et al., 2023). In line with this finding, our study provides more robust evidence for the deleterious effects of high waist circumference (BMI-adjusted or not) on the risk of MG. The mechanistic pathways are related to inflammation and adaptive immunity, as well as reduced bioavailability of vitamin D (Wortsman et al., 2000; Lumeng et al., 2007; Matarese et al., 2005).

Vitamin D deficiency is known to play a crucial role in the pathogenesis of MS(Olsson et al., 2017). This association was replicated by our observational and MR findings, indicating that vitamin D intake or sun exposure in adolescence should be advocated to reduce subsequent MS risk.

Notably, our observational and MR study results showed inconsistent associations between diseases and various risk factors, such as educational attainment, alcohol consumption, coffee drinking, sleep behaviors, other sedentary behaviors, and other obesity-related phenotypes. This inconsistency may be due to residual confounding or limited disease sample sizes in cross-sectional analysis. Previous research on these risk factors has yielded controversial findings (Massa et al., 2013; Harroud et al., 2023; Riise et al., 2011; Kleerekooper et al., 2022; Topiwala et al., 2017, 2021; Stepansky and Zeitlhofer, 2001; Kalita et al., 2021; Yeşil Demirci et al., 2024), and their inconsistent associations with diseases in our study warrant further validation using alternative research designs to strengthen evidence for causality and reproducibility.

Interestingly, our MR analysis identified consistent effects of education, alcohol consumption, and obesity on these diseases, suggesting potential commonalities and shared immunopathogenic mechanisms among neuroimmunological diseases from a genetic perspective. This observation highlights the need for further exploration of these potential mechanisms and the identification of common therapeutic targets. Additionally, both our observational and MR results revealed that the impacts of identical modifiable risk factors, such as BMI, time spent driving and sleep duration, on different neuroimmunological diseases were not entirely consistent. This highlighted the multifaceted nature of the relationships between environmental factors and neuroimmunological diseases, suggesting that prevention or intervention strategies for various neuroimmunological diseases may need to be more specific and tailored.

NMOSD and MS, as central nervous system demyelinating diseases, share certain clinical symptoms, raising the question of whether they also share similar modifiable risk factors. Including NMOSD in the MR analysis provides complementary evidence, contributing to a more comprehensive understanding of the shared or unique etiological mechanisms underlying neuroimmunological diseases. In our study, we observed both overlaps and differences in the associations of modifiable risk factors between NMOSD and MS. For example, higher levels of education were protective for both diseases, and BMI was identified as a common risk factor. However, the associations of vitamin D levels, physical activity, and alcohol consumption differed between the two conditions. Notably, the small sample size for NMOSD cases limited the statistical power, making it challenging to discern whether the absence of significant findings was due to a genuine lack of association or insufficient power. These limitations call for caution when interpreting the results. Therefore, future studies with larger sample sizes or meta-analyses combining multiple datasets are warranted to further elucidate the potential roles of these shared and unique risk factors.

The strengths of the study include representative and comprehensive environmental risk factors, detailed consideration of candidate outcomes, and the integration of both cross-sectional and MR approaches. Observational analysis benefited from large sample sizes and statistical power without determining causality. MR aided in inferring causality and was more robust against confounding factors. Additionally, the potential horizontal pleiotropy was assessed using the MR-Egger regression intercept test. For all exposures, except educational attainment and early-onset as well as late-onset MG, the MR-Egger intercept did not reach statistical significance, indicating no evidence of significant horizontal pleiotropy (Supplementary Tables 7–14). The associations between educational attainment and early-onset MG, as well as late-onset MG, remained significant after removing outlier SNPs that may exhibit horizontal pleiotropy, and were consistent with the results from the IVW method, further supporting the robustness of our findings. Furthermore, the results of various sensitivity analyses were consistent with main findings from both the observational study and MR analysis (Supplementary Tables 3-4, 7-14), further strengthening the robustness and reliability of the results. However, limitations require careful consideration when interpreting our results. Firstly, due to the sample size of the UK Biobank disease cohort and availability of genetic instruments, we only investigated MG and MS in observational study and MG, MS, and NMOSD along with their subtypes or severity levels in MR studies. Future research could explore disease subtype classification or extend to other neuroimmune disorders. Secondly, despite consistent results from multiple MR sensitivity analyses aligning with the main findings, indicating minimal impact from weak instrument bias, horizontal pleiotropy, or outliers on our causal estimates, caution is still warranted in interpreting causality. Thirdly, our study could not fully encompass all potential intermediate pathways, future research should explore additional mediators, such as socioeconomic factors, additional inflammatory markers, and metabolic changes, to better understand how these factors influence the relationship between modifiable risk factors and neuroimmune diseases. Fourthly, our findings were based on individual-level data and GWAS summary data from individuals of European ancestry. Further studies incorporating non-European cohorts are needed to assess the generalizability of our findings to other genetic ancestry populations. Finally, we included only MS and MG cases diagnosed after January 1, 2006, to ensure that these cases occurred after the exposures. While this restriction reduced the likelihood of reverse causation, it could not fully resolve the inherent temporal limitations of observational study. Future research should prioritize longitudinal cohort studies to enhance the robustness of causal inferences and provide a more comprehensive understanding of disease progression.

5. Conclusion

The current study employed both observational and genetic epidemiological designs to reveal the impact of various modifiable risk factors on neuroimmune diseases. Robust causal relationships were confirmed between the number of cigarettes previously smoked daily, moderate to vigorous physical activity, television watching, waist circumference, and vitamin D levels with several neuroimmune diseases. Furthermore, the influence of television watching on the risk of myasthenia gravis was partially mediated by BMI. This research underscores the importance of environmental factors in the onset of neuroimmune diseases and could facilitate the identification of tailored intervention and prevention strategies of these diseases.

CRediT authorship contribution statement

Jiang-wei Xia: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jia-jian Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yu Qian:** Writing – review & editing, Methodology, Data curation. **Jinmin Han:** Writing – review & editing, Visualization. **Ming Lin:** Writing – review & editing, Formal analysis, Investigation. **Ming-yang Wang:** Writing – review & editing, Validation. **Teng Chen:** Writing – review & editing, Investigation. **Guo-liang Chai:** Writing – review & editing. **Yi-nan Zhao:** Writing – review & editing, Formal analysis, Visualization, Validation, Methodology, Investigation. **Jun-wei Hao:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

I have nothing to declare.

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Abbreviations

MR: Mendelian randomization
GWAS: genome-wide association study
MS: multiple sclerosis
NMOSD: neuromyelitis optica spectrum disorders
MG: myasthenia gravis
MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease
GBS: Guillain–Barré syndrome
OR: odds ratio
CI: confidence interval
UKB: UK Biobank
RCT: randomized controlled trial
TSMR: two-sample Mendelian Randomization
MVMR: multivariable Mendelian Randomization
SNP: single nucleotide polymorphism
IV: instrumental variable
BMI: body mass index
IVW: inverse-variance-weighted method
LD: Linkage Disequilibrium
EAF: effect allele frequency
OSA: Obstructive sleep apnea
MVPA: moderate to vigorous physical activity
SSOE: strenuous sports or other exercises
VPA: vigorous physical activity
25(OH)D: 25-hydroxyvitamin D
WC: Waist circumstance
HC: Hip circumstance
WHR: Waist-to-hip ratio
WCadjBMI: BMI-adjusted waist circumference
HCadjBMI: BMI-adjusted hip circumstance
WHRadjBMI: BMI-adjusted waist-to-hip ratio

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.100975.

Data availability

Data will be made available on request.

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