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Original Article

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Celiac Disease Increases the Risk of Multiple Sclerosis: Evidence from Mendelian Randomization and the Role of CCL19

Seongjin Lim[1†], Junhua Wu[2†], Yeon Woo Kim[1], Sun Woo Lim[1], Juhee Shin[3], Hyo Jung Shin[4], Sang Ryong Kim[5] and Dong Woon Kim[1*]

[1]Department of Oral Anatomy & Developmental Biology, Kyung Hee University College of Dentistry, Seoul 02447, Korea, [2]Department of Neurology, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing 400038, China, [3]Center for Cognition and Sociality, Institute for Basic Science (IBS), Daejeon 34824, [4]Department Biochemistry, Eulji University School of Medicine, Daejeon 34824, [5]School of Life Sciences, Kyungpook National University, Daegu 41566, Korea

Celiac disease (CeD) is an autoimmune disorder triggered by gluten, primarily affecting the small intestine but potentially impacting other systems, including the nervous system through the gut-brain axis. This study employed Mendelian randomization (MR) to explore the causal relationships between CeD and several neurological disorders, with a particular focus on multiple sclerosis (MS). Utilizing genetic data from the OpenGWAS and Finngen databases, we applied various MR methods, including Inverse Variance Weighted (IVW), IVW-multiplicative random effects (MRE), weighted median (WM), MR-Egger, and robust adjusted profile score (RAPS), to investigate these associations. The analysis revealed no significant causal relationship between CeD and several other neurological disorders, but a significant positive association with MS was found (IVW OR=1.1919, 95% CI: 1.0851~1.3092, p=0.0002). Further analysis indicated that the mediator CCL19 plays a significant role in the pathway from CeD to MS, suggesting that CCL19 may be a key factor in the immune response linking these conditions. This mediation effect highlights the potential mechanism through which CeD increases the risk of developing MS. These findings emphasize the complexity of the relationship between CeD and MS, indicating the need for further research to understand these connections better and their clinical implications.

Key words: Celiac disease, Alzheimer's disease, Gut-brain axis, Mendelian randomization, Gluten-free diet

INTRODUCTION

Celiac disease (CeD) is an autoimmune disorder characterized by inflammation primarily in the small intestine, caused by abnormal immune response to gluten ingestion [1]. Although CeD primarily manifests its symptoms within the gastrointestinal region, the disease does not limit itself to digestive issues; it also has significant effects on other systems of the body, including the nervous system [2]. This broader impact can be partially illustrated through the concept of the gut-brain axis, a bidirectional communication network linking the gut and the brain. This so-called gut-brain axis follows the intricate interactions between the gut and the brain, which connects the enteric and central neurological systems through a complex communication network [3]. Recent studies show that CeD's neurological involvement lies primarily in the gut-liver-brain axis and may related to gluten-mediated pathogenesis, including antibody cross-reaction, deposition of immune-complex, direct neurotoxicity, and in extreme cases, vitamins or nutrients deficiency [4].

Neurological disorders associated with CeD encompass a broad range of conditions, including but not limited to ataxia, cognitive impairment, epilepsy, headache, and neuropathy [5]. Addition-

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*To whom correspondence should be addressed.
TEL: 82-2-961-9298, FAX: 82-2-961-9594
e-mail: visnu528@khu.ac.kr
†These authors contributed equally to this article.

ally, bacterial metabolites produced by CeD progression can seep into the bloodstream from the intestinal lumen and may enter the brain, triggering localized neuroinflammatory reactions [6]. The exact mechanisms underlying these associations remain controversial, raising questions about whether these neurological disorders are directly caused by CeD or if they arise from secondary effects as in gluten-mediated pathogenesis.

To address these questions, Mendelian randomization (MR) provides a potent method for elucidating causal links by using genetic differences linked to CeD as instrumental variables (IVs). MR aims to minimize confounding factors and reverse causation, providing insights into whether CeD is a causal factor for neurological disorders or if observed associations are due to other underlying reasons [7]. By leveraging genetic variations that are actively linked to CeD, MR can help distinguish between direct causal effects and those resulting from correlated but separated processes. It serves as a valuable tool, particularly in situations in which randomized controlled trials are deemed impractical and observational studies may yield biased results due to confounding or reverse causation [8].

Therefore, we conduct to investigate the causal relationship between CeD and various neurological disorders, including dementia, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), status epilepticus (SE), stroke, and multiple sclerosis (MS), using MR analysis. These disorders are selected due to their significant neurological impacts and potential links to systemic inflammation and autoimmune processes triggered by CeD. By exploring these connections, we seek to clarify how CeD may contribute to these disorders and thereby enhancing our understanding of the gut-brain axis and its implications for both diagnosis and treatment strategies in CeD and related neurological conditions.

MATERIALS AND METHODS

Mendelian randomization and assumptions

This study is based on a multiple two-directional two-sample MR using single-nucleotide polymorphisms (SNPs) to evaluate the potential relationship between CeD as exposure and various neurological disorders as outcomes, using the latest data from GWAS (Genome Wide Association Study) and Finngen. Three underlying hypotheses underpin MR: first, that genetic exposure predictors are highly correlated with the exposure of interest; second, that genetic exposure predictors are unaffected by confounders in the exposure-outcome relation; and third, that genetic predictors are only related to the outcome by directly influencing the exposure of interest (i.e., the exclusion-restriction assumption) [9].

Data source for exposure and outcome

The data for exposure CeD was obtained from the OpenGWAS database (GWAS ID: ieu-a-1058). There were 24,269 samples and 38,037 single-nucleotide polymorphisms, of which 97% were part of the European demographic (cases: 12,041; controls: 12,228) [10]. The dataset for outcomes of various neurological disorders were collectively acquired from Finngen database, which only studies European population; the data include dementia (finngen_R11_F5_DEMENTIA), AD (finngen_R11_G6_ALZHEIMER), PD (finngen_R11_G6_PARKINSON), ALS (finngen_R11_G6_ALS), SE (finngen_R11_G6_STATUSEPI), stroke (finngen_R11_C_STROKE), and MS (finngen_R11_G6_MS). All genomic data used for this research are the most up-to-date and have been made publicly available online.

Statistical analysis

In this study, MR, performed by R (version4.4.1) through the TwoSampleMR package, was employed to investigate the causal relationship between CeD and various neurological disorders, using genetic variations as instrumental variables (IV). Establishing CeD as the exposure and neurological disorders as outcomes, MR leverages genetic variants, primarily SNPs, as proxies to estimate the causal effects. We selected SNPs that were independent (R2<0.001) and had a strong association with the exposure factor (p<5×10-8); then, to enhance the precision and integrity of the analysis, any SNPs that were common to both the exposure (CeD) and the outcomes (neurological disorders) were carefully identified and excluded to prevent potential confounding effects using the PhenoScanner database V2 [11]. While 5×10^(-8) has become the conventional genome-wide significance p-value threshold for common-variant GWAS, since the dataset for CD had only few independent SNPs at genome-wide significance, SNPs with p-values <5×10^(−6) and p-values <5×10^(−5) that have higher cut-offs were chosen to ensure the relevance and validity of the IVs [12].

The primary method in this study was the inverse-variance weighted (IVW) approach, assuming all IVs are valid and free from pleiotropy, which provides strong causal estimates under these conditions [13]. It provides a consistent estimate of the causal effect of the exposure on the outcome by combining the Wald ratio estimates of the causal effect obtained from different SNPs using a meta-analysis approach [14]. To further enhance robustness, complementary MR methods were used, including IVW-multiplicative random effects (MRE), weighted median (WE), and MR-Egger. The IVW(MRE) method accounts for heterogeneity among IVs, improving reliability when assumptions are partially violated. The weighted median method is robust even if up to 50% of IVs are invalid [15], while MR-Egger not only does not rely on

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non-zero pleiotropy but detects and controls bias from directional pleiotropy, offering unbiased estimates more efficiently [16, 17].

Further reliability of the study was assessed using the MR robust adjusted profile score (MR-RAPS) method, which provides unbiased estimates even with numerous weak instruments and validation to both systematic and idiosyncratic pleiotropy [18]. This comprehensive analysis allowed us to rigorously test for causal relationships, correct for biases, and confirm the reliability of the findings, thereby enhancing the overall strength and reliability of our results and highlighting valuable insights of the genetic links between CeD and neurological disorders.

Mediation analysis

We conducted a mediation analysis to connect CeD with neurological disorders through circulating inflammatory proteins. After performing a bidirectional MR, we found positive associations between CeD and inflammation-related circulating proteins [19]. Next, we investigated the correlations between 91 circulating inflammatory proteins with the outcome factor MS. Mediation analysis is to determine whether the effect of the exposure (CeD) on the outcome (MS) is direct or is mediated through the mediator. This helps in understanding the pathway and potential mechanisms. MR mediation analysis involves using genetic variants as instrumental variables to assess the causal effect of the exposure on the mediator, and subsequently, the mediator on the outcome. This is done to estimate the indirect effect (through the mediator) and the direct effect (not through the mediator) [20]. If a significant mediation effect is found, it suggests that part of the effect of the exposure on the outcome is explained by the mediator. This can identify potential targets for intervention to prevent or treat the outcome. We selected the circulating proteins that showed positive associations for further analysis. These selected proteins were then analyzed to determine their correlation with exposure factor CeD when considered as outcome factors MS. When intermediary substances were found to be correlated with both exposure and outcome factors, we calculated the proportion of the mediating effect attributable to each intermediary substance using delta method [21]. We calculated the proportion of mediation using the delta method, which involves estimating the indirect effect of CeD on MS through CCL19 and comparing it to the total effect. Specifically, we utilized the formula: [\text{Proportion of Mediation}=\frac{\text{Beta1} \times \text{Beta2}}{\text{Beta all}}] where Beta1 represents the effect of CeD on the mediator (CCL19), Beta2 represents the effect of the mediator on MS, and Beta all is the total effect of CeD on MS.

RESULTS

CeD on MS

In order to investigate the potential causal relationship between CeD and MS, a two-way MR analysis was conducted. A total of 23 SNPs were carefully chosen for this study, with some SNPs excluded due to their confounding effects to ensure more accurate results. The results shown in Fig. 1A, together with the scatterplots of SNP effect sizes for CeD and MS in Fig. 1B, offer detailed insights: the IVW method reveals an OR of 1.1919 with a 95% CI of 1.0851 to 1.3092, and a p-value of 0.0002, making it abundantly clear that there's a significant positive association between CeD and MS. The IVW(MRE) method echoes this conclusion with identical results (OR=1.1919, 95% CI=1.0851~1.3092, p=0.0002). The WM method also backs this up, with an OR of 1.0992 (95% CI=1.0266~1.1769, p=0.0067), affirming the positive impact of CeD on MS. The MR Egger method shows a slightly different outcome, with an OR of 1.1730 (95% CI=1.0270~1.3399, p=0.0285). Although the CIs are wider due to the method's sensitivity to pleiotropy, it still suggests a significant association. The RAPS method, yielding an OR of 1.2189 (95% CI=1.0474~1.4184, p=0.105), further reinforces the presence of a positive association. Despite the methodological differences between MR Egger and RAPS, which are inherently designed to be more cautious due to their sensitivity to specific biases and outliers, the overall message is consistent: there is a positive causal link between CeD and MS.

The slight difference in the results from the MR Egger and RAPS methods can be attributed to the unique characteristics and assumptions underlying these approaches. The MR Egger method is particularly sensitive to directional pleiotropy, where genetic variants influence the outcome through pathways other than the exposure, which may lead to more conservative estimates and wider CIs. Similarly, the RAPS method is designed to be robust against weak instruments and outliers, which can also lead to more cautious estimates. These differences in methodology can result in slightly lower significance levels, but they still support the overall conclusion of a positive association between CeD and MS.

Considering the findings from all the applied methods, the results consistently indicate a significant causal relationship between CeD and MS. The odds ratios across the board are substantially above 1, with p-values that consistently reach statistical significance and CIs that do not cross 1. These findings strongly suggest that CeD significantly increases the risk of developing MS, raising the possibility that CeD could be a contributing factor in the onset of MS.

Next we, we used the MR method to analyze the connection between 91 circulating inflammatory proteins with MS [19].

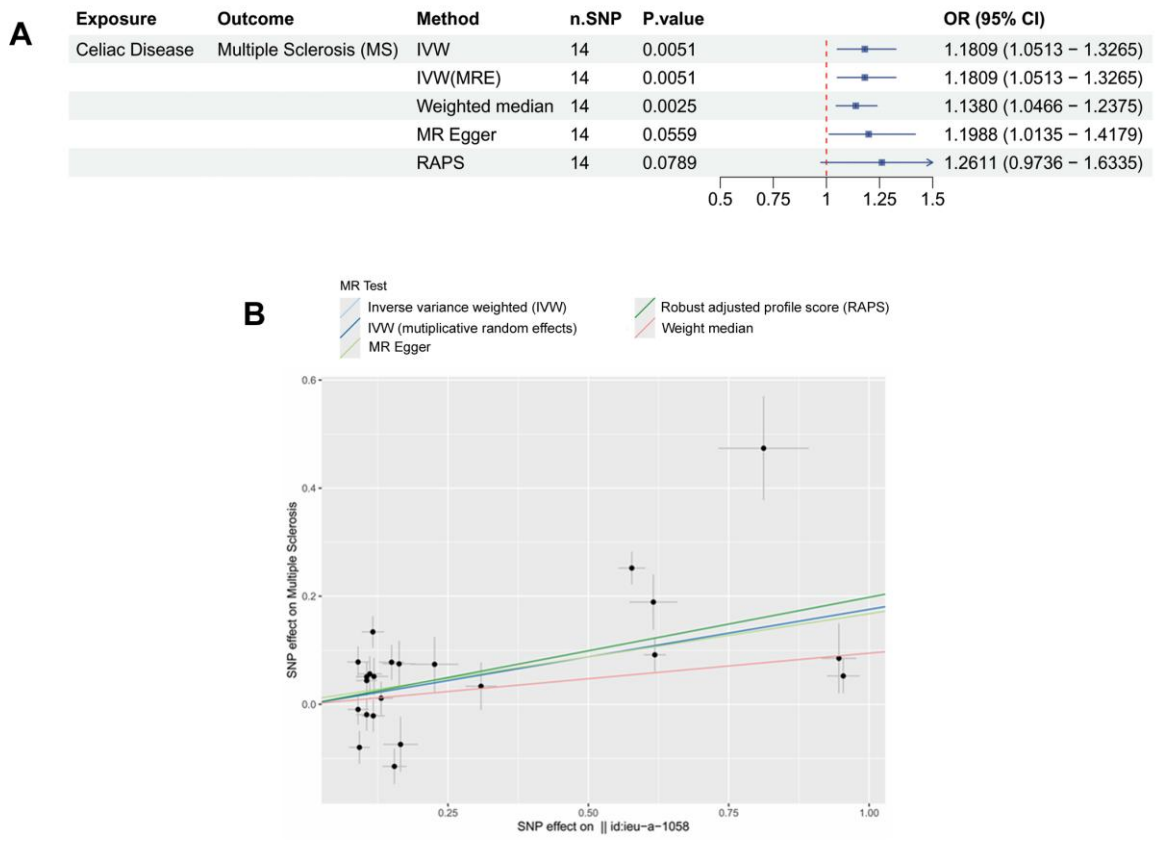

Fig. 1. (A) Mendelian randomization (MR) analysis of the association between celiac disease (CeD) and multiple sclerosis (MS). The analysis incorporates various MR methods, including inverse variance weighted (IVW) for primary analysis, and sensitivity analyses using IVW-multiplicative random effects (MRE), weighted median, MR-Egger, and robust adjusted profile score (RAPS). Results are presented as odds ratios (OR) with 95% confidence intervals (CI) per log-odds increment in MS risk, indicating the strength and direction of the association. (B) Scatterplot illustrating the potential effects of the targeted single nucleotide polymorphisms (SNPs) on CeD versus MS. Each line's slope in the scatterplot represents the estimated MR effect for a given method: a positive slope suggests a positive correlation, indicating that CeD may increase MS risk, while a negative slope would suggest a negative correlation.

Table 1. Mediation analysis of CeD on MS through circulating inflammatory proteins

Exposure	CeD	ieu-a-1058	Beta (SE), p value		
			Exposure-outcome (Beta all)	Mediator-outcome (Beta 2)	Exposure-Mediator (Beta 1)
Mediator Outcome	CCL19 MS	GCST90274765 finngen_R11 _G6_MS	0.169297 (0.040066), 2.39E-05	0.126806 (0.0593), 0.032487	0.057913 (0.015971), 0.000288

Beta mediation%=Beta1*Beta2/Beta all=4.17.
Upper CI 95%=Upper CI 95%/Beta all=0.13109. Lower CI 95%=Lower CI 95%/Beta all=-0.04433.

We identified that a total of potential circulating inflammatory proteins were associated with CeD, with positively or negatively correlated. We then analyzed the correlation between these circulating inflammatory proteins as the outcome factor with MS as the exposure factor. We also calculated the mediating effect ratios. After completing these steps, we identified a CCL19 as potential mediators that reduce the likelihood of MS. Standard error (se), Upper CI and Lower CI was calculated; se=sqrt(Beta 1 ^2*se1^2+ Beta 2 ^2*se2^2), Upper CI=Beta mediation (Beta1*Beta2)+ 1.96*se, Lower CI=Beta mediation (Beta1*Beta2)-1.96*se. Z score is 23.838 suggested that the effect is statistically significant, meaning it is unlikely to have occurred by chance (Table 1).

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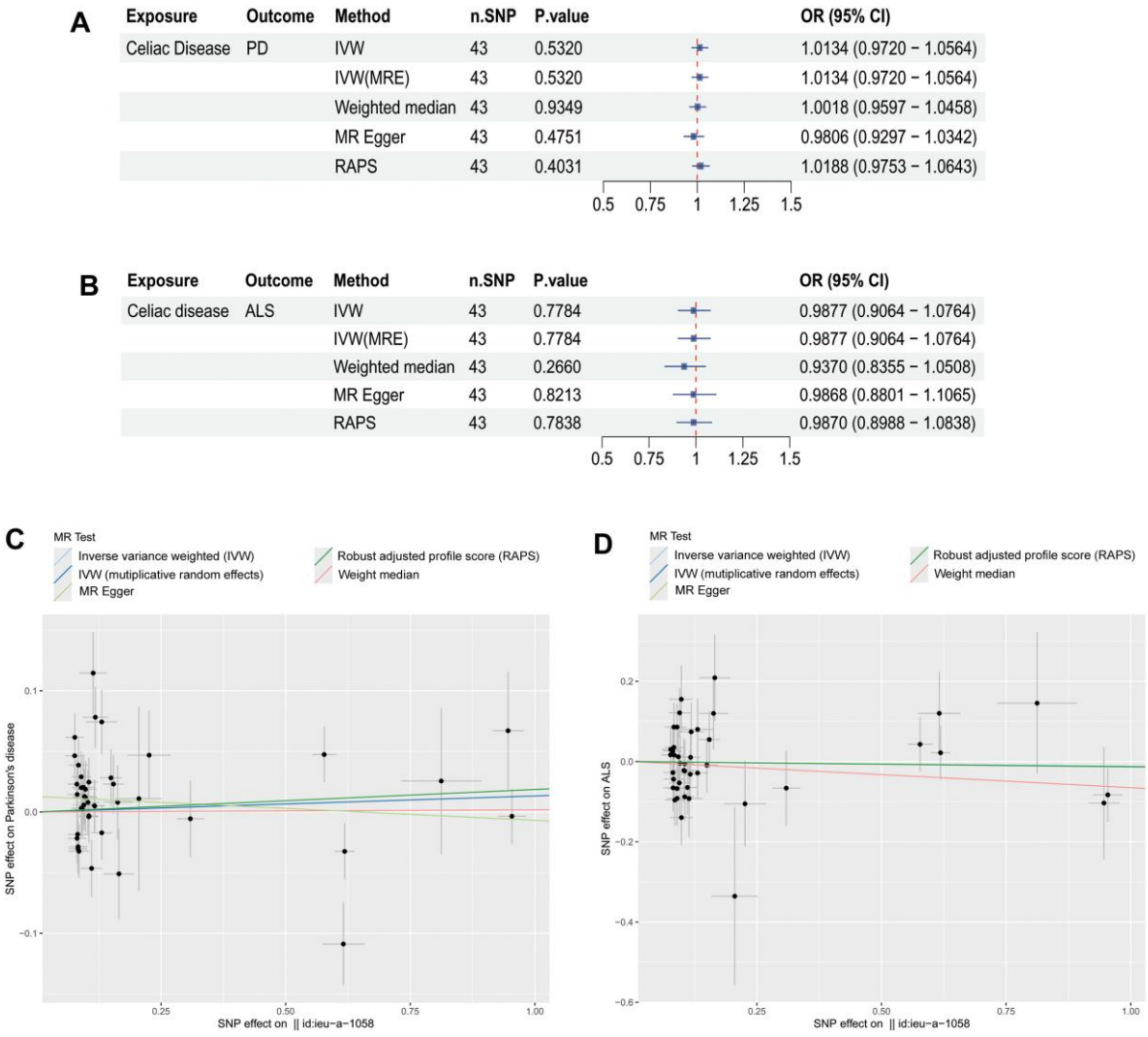

Fig. 2. (A, B) Mendelian randomization (MR) estimates between A celiac disease (CeD) and Parkinson's disease (PD) and B celiac disease (CeD) and amyotrophic lateral sclerosis (ALS). Primary analysis (IVW) and sensitivity analysis (IVW-MRE, weighted median, MR-Egger, and RAPS were utilized. Data are displayed as odds ratio (OR) and 95% confidence interval (CI) per log-odds increment in PD/ALS risk. (C, D) Scatterplot of potential effects of the targeted SNPs on C CeD vs PD and D CeD vs ALS. The slope of each line corresponds to the estimated MR effect for each method used. Positive slope indicates a positive correlation, and negative slope indicates a negative correlation.

CeD on PD and ALS

CeD on Parkinson's disease

For this two-way MR analysis, 43 SNPs were selected to explore the causal relationship between CeD (CeD) and Parkinson's disease (PD). The findings from these methods are shown in Fig. 2A, and the scatterplots of SNP effect sizes for CeD and PD can be seen in Fig. 2C. The results portrayed the following: The IVW method yielded an OR of 1.0134 (95% CI=0.9720~1.0564, p=0.5320). This result suggests no significant causal effect of CeD on PD, as the CI crosses 1 and the p-value is not statistically significant. The IVW(MRE) method produced identical results (OR=1.0134, 95% CI=0.9720~1.0564, p=0.5320), corroborating the findings of the IVW method. The WM method resulted in an OR of 1.0018 (95% CI=0.9597~1.0458, p=0.9349), indicating no significant relationship between CeD and PD. Similarly, the MR-Egger method yielded an OR of 0.9806 (95% CI=0.9297~1.0342, p=0.4751), which also indicates no significant effect of CeD on PD. Finally, the RAPS method provided an OR of 1.0188 (95% CI=0.9753~1.0643, p=0.4031), further suggesting that there is no significant association.

In summary, all MR methods used in this analysis, including IVW, IVW-MRE, weighted median, MR Egger, and RAPS, consistently indicate that there is no significant causal relationship between CeD and PD. The odds ratios across all methods are near

1, and none of the CIs exclude 1, reinforcing the conclusion that CeD does not significantly affect the risk of developing PD.

CeD on amyotrophic lateral sclerosis

A total of 43 SNPs were employed to carry out the two-way MR analysis between CeD as exposure and ALS as outcome. The results are illustrated in Fig. 2B alongside the scatterplots of SNP effect sizes for CeD and ALS in Fig. 2D. The IVW method resulted in an OR of 0.9877 (95% CI=0.9064~1.0764, p=0.7784). The IVW(MRE) method produced identical results (OR=0.9877, 95% CI=0.9064~1.0764, p=0.7784), indicating no significant causal relationship between CeD and ALS. The WM method provided an OR of 0.9370 (95% CI=0.8355~1.0508, p=0.2660), and the MR-Egger method gave an OR of 0.9868 (95% CI=0.8801~1.1065, p=0.8213); both methods suggest no significant association between CeD and ALS. The RAPS method also showed consistent results with an OR of 0.9870 (95% CI=0.8988~1.0838, p=0.7838).

In total, all MR methods consistently indicate that there is no significant causal relationship between CeD and ALS. The odds ratios across all methods are close to 1, and the CIs do not exclude 1, reinforcing the conclusion that CeD does not significantly influence the risk of developing ALS.

CeD on status epilepticus and stroke

CeD on status epilepticus

A total of 43 SNPs were selected for this two-way MR analysis, which aimed to investigate the potential causal relationship between CeD and SE. The results outlined in Fig. 3A, combined with the scatterplots of SNP effect sizes for CeD and SE shown in Fig. 3C, illustrate the findings comprehensively. The IVW method produced an OR of 1.0098 with a 95% CI of 0.9540 to 1.0689 and a non-significant p-value of 0.7359, indicating no significant association between CeD and SE. The IVW(MRE) method provided nearly identical results (OR=1.0098, 95% CI=0.9590~1.0633, p=0.7102), reinforcing the conclusion that there is no significant causal relationship between CeD and SE. Similarly, the WM method showed an OR of 1.0230 (95% CI=0.9411~1.1120, p=0.5938), and the MR Egger method resulted in an OR of 1.0455 (95% CI=0.9701~1.1268, p=0.2505). Finally, while the RAPS method yielded an OR of 0.9994 (95% CI=0.9422~1.0599, p=0.9829). All these methods suggest no significant association.

Taking all the methods into account, the results consistently indicate no significant causal relationship between CeD and SE. Although several of the OR are slightly above 1, the p-values across all methods are far from statistically significant, with CIs consistently including 1. This suggests that CeD does not significantly affect the risk of developing SE, and any observed associations are likely due to chance rather than a true causal effect.

CeD on stroke

In the two-way MR analysis, 42 SNPs were selected with CeD as the exposure and stroke as the outcome to investigate whether having CeD could affect the risk of developing stroke. Certain SNPs were excluded to minimize confounding effects and enhance the reliability of the results. The results detailed in Fig. 3B and the corresponding scatterplots of SNP effect sizes for CeD and Stroke in Fig. 3D provide a thorough analysis. The IVW method reported an OR of 1.0159 (95% CI=1.0011~1.0310, p=0.0350), suggesting a statistically significant but small association between CeD and stroke. The IVW(MRE) method produced identical results (OR=1.0159, 95% CI=1.0011~1.0310, p=0.0350), supporting the IVW findings. However, the significance of these results is borderline, and the effect size is small, which might limit the clinical relevance. The weighted median method yielded an OR of 1.0091 (95% CI=0.9909~1.0276, p=0.3293), indicating no significant association. Similarly, the MR Egger method reported an OR of 1.0117 (95% CI=0.9922~1.0316, p=0.2476), which also suggests no significant effect of CeD on stroke. Interestingly, the RAPS method resulted in an OR of 1.0242 (95% CI=1.0083~1.0403, p=0.0027), showing a statistically significant association. The RAPS method is particularly robust against weak instruments and the influence of outliers, making it more sensitive to subtle associations. Despite the statistically significant result from the RAPS method, the small effect size and the CI close to 1 suggest that the practical or clinical significance of this finding may be limited.

In conclusion, while the majority of methods do not show a significant causal relationship between CeD and stroke, the RAPS method does detect a marginally significant association. However, the effect size is small, and the CI is narrow, indicating that even though the association is statistically significant, it may not translate into a substantial impact on stroke risk for individuals with CeD. Therefore, these findings should be interpreted with caution.

CeD on dementia and Alzheimer's disease

CeD on dementia

In the two-way MR analysis, 43 SNPs were obtained with CeD as the exposure and dementia as the outcome to explore whether having CeD could influence the risk of developing AD. The results of these methods reflected in Fig. 4A, and the scatterplots of SNP effect sizes for CeD and dementia are shown in Fig. 4C. The IVW method as well as the IVW(MRE) method yielded an OR of 0.9881, with a 95% CI ranging from 0.9675 to 1.0091. Since the CI includes 1 and the p-value of 0.2638 is higher than 0.05, these methods suggest no significant causal effect of CeD on dementia.

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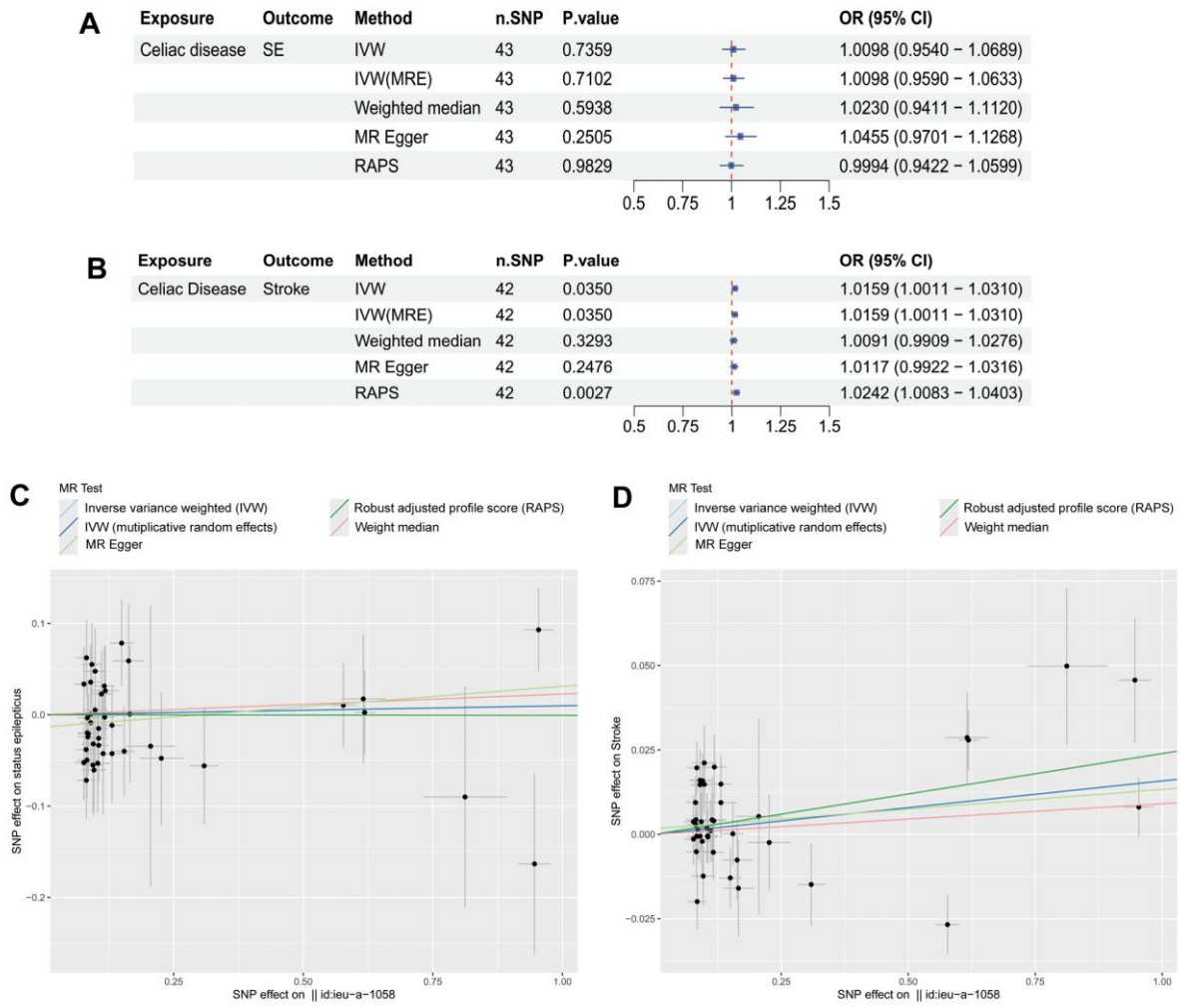

Fig. 3. (A, B) Mendelian randomization (MR) estimates between A celiac disease (CeD) and status epilepticus (SE) and B celiac disease and Stroke. Primary analysis (IVW) and sensitivity analysis (IVW-MRE, weighted median, MR-Egger, and RAPS) were utilized. Data are displayed as odds ratio (OR) and 95% confidence interval (CI) per log-odds increment in SE/Stroke risk. (C, D) Scatterplot of potential effects of the targeted SNPs on C CeD vs SE and D CeD vs Stroke. The slope of each line corresponds to the estimated MR effect for each method used. Positive slope indicates a positive correlation, and negative slope indicates a negative correlation.

The WM method produced an OR of 0.9834 with a Cl of 0.9601 to 1.0072, which also indicates a lack of a significant causal relationship. Similarly, the MR-Egger method resulted in an OR of 0.9841 (95% CI=0.9570~1.0120, p=0.2671), and the RAPS method produced an OR of 0.9908 (95% CI=0.9705~1.0116, p=0.3832), both implying no effect of importance of CeD on dementia.

Overall, the results across all MR methods suggest that CeD does not have a significant causal impact on the risk of developing Dementia. The odds ratios are close to 1, and the CIs consistently include 1, while the p-values are way above the threshold for statistical significance. This indicates that there is no strong evidence to support a causal relationship between CeD and dementia based on the genetic data analyzed in this study.

CeD on Alzheimer's disease

This two-way MR analysis between CeD and AD utilized a total of 23 SNPs that were selected after excluding those with confounding effects from the initial pool. The outcomes of these methods are illustrated in Fig. 4B, while the scatterplots of SNP effect sizes for CeD and AD are depicted in Fig. 4D. The results showed the following: The IVW method produced an OR of 0.9688 (95% CI=0.9431~0.9952, p=0.0206). This result suggests a statistically significant inverse relationship between CeD and AD, indicating that CeD might slightly reduce the risk of developing AD. The IVW(MRE) method provided identical results (OR=0.9688, 95% CI=0.9431~0.9952, p=0.0206), reinforcing the findings of the IVW method. The WM method showed an OR of 0.9600 (95%

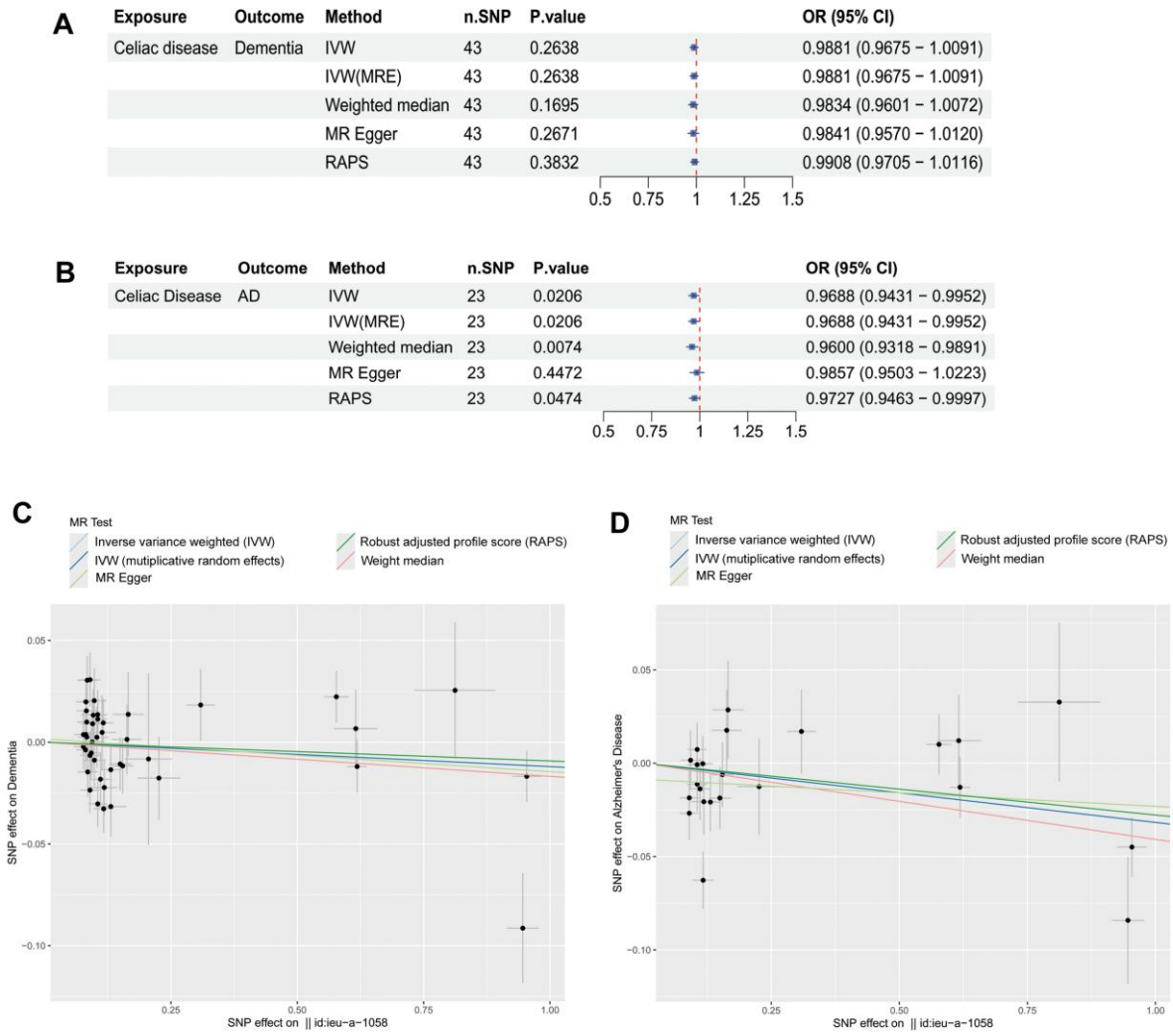

Fig. 4. (A, B) Mendelian randomization (MR) estimates between A celiac disease (CeD) and dementia Alzheimer's disease (AD) and B celiac disease (CeD) and Alzheimer's disease (AD). Primary analysis (IVW) and sensitivity analysis (IVW-MRE, weighted median, MR-Egger, and RAPS) were utilized. Data are displayed as odds ratio (OR) and 95% confidence interval (CI) per log-odds increment in dementia/AD risk. (C, D) Scatterplot of potential effects of the targeted SNPs on C CeD vs dementia and D CeD vs AD. The slope of each line corresponds to the estimated MR effect for each method used. Positive slope indicates a positive correlation, and negative slope indicates a negative correlation.

CI=0.9318~0.9891, p=0.0074). This method also indicates a significant protective effect of CeD against AD, as the CI does not cross 1 and the p-value is well below 0.05, supporting the conclusion of the IVW method. Similarly, the RAPS method, with an OR of 0.9727 (95% CI=0.9463~0.9997, p=0.0474), suggests a borderline significant inverse relationship between CeD and AD, aligning with the trends observed in the IVW and WM methods.

On the other hand, the MR Egger method yielded an OR of 0.9857 (95% CI=0.9503~1.0223, p=0.4472). This result differs from the other methods, as the CI crosses 1 and the p-value is not statistically significant, indicating no strong evidence for a causal effect. Although the MR Egger method is valuable for detecting potential violations of the assumptions underlying instrumental variables, it can produce biased causal estimates and elevated Type 1 error rates under certain conditions [22]. Specifically, the method may be compromised by violating the assumption that the variance of the association between the IV and the exposure is small enough to be negligible [23]. Presence of outlier variants can also distort the results.

All in all, while the MR Egger method shows less significance and recommends caution in terms of interpretation, the consistent results from the IVW, IVW-MRE, WM, and RAPS methods point toward a weak but statistically significant inverse association between CeD and AD. These findings suggest that CeD might

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slightly lower the risk of AD, with the general trend across most methods indicating a potentially meaningful protective effect. Despite the limitations of the MR Egger method, the general results remain significant, supporting the hypothesis that CeD may have a modest protective role against AD.

Gluten free diet and Alzheimer's disease

The relationship between CeD and AD suggests a potential link between gluten ingestion and AD, including cases of non-celiac gluten sensitivity (NCGS). This underscores the need to investigate how gluten consumption—whether related to CeD or not—might influence the risk of developing AD, highlighting the importance of exploring gluten's impact on cognitive health.

Research indicates that a gluten-free diet (GFD) significantly reduces inflammation markers in both the gut and brain of CeD patients, leading to decreased systemic inflammation and potentially offering protection against neurodegenerative diseases like AD [5]. Elevated interleukin-6 (IL-6), a pro-inflammatory cytokine, is notably high in untreated CeD patients consuming gluten, but levels decrease after a year on a GFD [24]. Studies show that adherence to a GFD not only lowers pro-inflammatory cytokines but also improves cognitive function in CeD patients, suggesting effective gluten management may safeguard against neurodegenerative diseases [25].

Beyond CeD, it is crucial to examine gluten's effects on cognitive health in individuals without CeD, particularly those with NCGS. NCGS involves adverse reactions to gluten without CeD or wheat allergy and can manifest as various extra-intestinal symptoms, including neurological issues [26]. Conditions like cerebellar ataxia and peripheral neuropathy have been linked to NCGS, indicating that gluten-related inflammation can affect the nervous system even in those without CeD [27, 28]. This aligns with evidence suggesting gluten sensitivity may lead to systemic inflammation impacting brain health [29].

In individuals with NCGS, gluten ingestion has been associated with neurological symptoms, and systemic inflammation may disrupt brain function [30]. Mechanisms may include a compromised blood-brain barrier (BBB) and heightened neuroinflammatory responses [31]. Increasing evidence suggests gluten may exacerbate neuroinflammation, potentially accelerating cognitive decline [32]. Moreover, gluten-related neuropathies can negatively affect quality of life and contribute to cognitive decline. However, a recent study found no significant association between long-term gluten intake and cognitive decline among U.S. women, indicating that gluten's impact on cognitive health might be influenced by overall diet and individual health conditions [33].

In light of these findings, we conducted MR analyses to explore the impact of a GFD on AD (GWAS ID: ukb-b-11189; cases: 1,376, controls: 63,573) (Fig. 5). Our results indicate that a GFD does not significantly affect AD risk, emphasizing the need for further research to clarify this relationship. This suggests that connections between gluten ingestion and AD may be influenced more by environmental factors than the genetically mediated risk seen in CeD. Understanding these mechanisms is vital for developing targeted dietary strategies to manage cognitive health across diverse populations.

DISCUSSION

CeD and MS

The findings from various Mendelian randomization (MR) methods, including IVW, IVW(MRE), WM, and RAPS, indicate a positive association between celiac disease (CeD) and an increased risk of multiple sclerosis (MS). This suggests that individuals with CeD may have a heightened risk of developing MS, implying that immune dysregulation in CeD could contribute to MS susceptibility and offering insights into shared mechanisms underlying these autoimmune disorders.

To understand the connection between CeD and MS, it's essential to explore the immunopathogenic mechanisms linking these conditions. In CeD, the immune response is triggered by gluten ingestion, while MS involves an autoimmune attack against the myelin sheath, leading to demyelination and neurological dysfunction [34]. Although the primary targets differ, both conditions can induce widespread inflammation affecting various systems. CeD primarily impacts the gastrointestinal tract, whereas MS targets the CNS. The systemic inflammation characteristic of CeD may extend its effects to the CNS, potentially contributing to MS pathogenesis [35]. Gluten ingestion leads to pro-inflammatory cytokine production, activating microglia—resident immune cells in the CNS—which is central to neuroinflammation in MS [36].

Epidemiological studies suggest that individuals with CeD may be at higher risk for MS. The coexistence of both conditions highlights shared pathogenic mechanisms, such as chronic inflammation and immune dysregulation [37]. Population-based studies report a higher prevalence of CeD among MS patients compared to the general population, implying that autoimmune processes triggered by CeD might increase MS susceptibility [35, 38]. A meta-analysis also found a significantly higher incidence of CeD among MS patients, reinforcing the notion that CeD may predispose individuals to MS through shared immunological pathways or genetic factors [39].

However, the relationship between CeD and MS remains debated, with conflicting results in some studies. These discrepancies

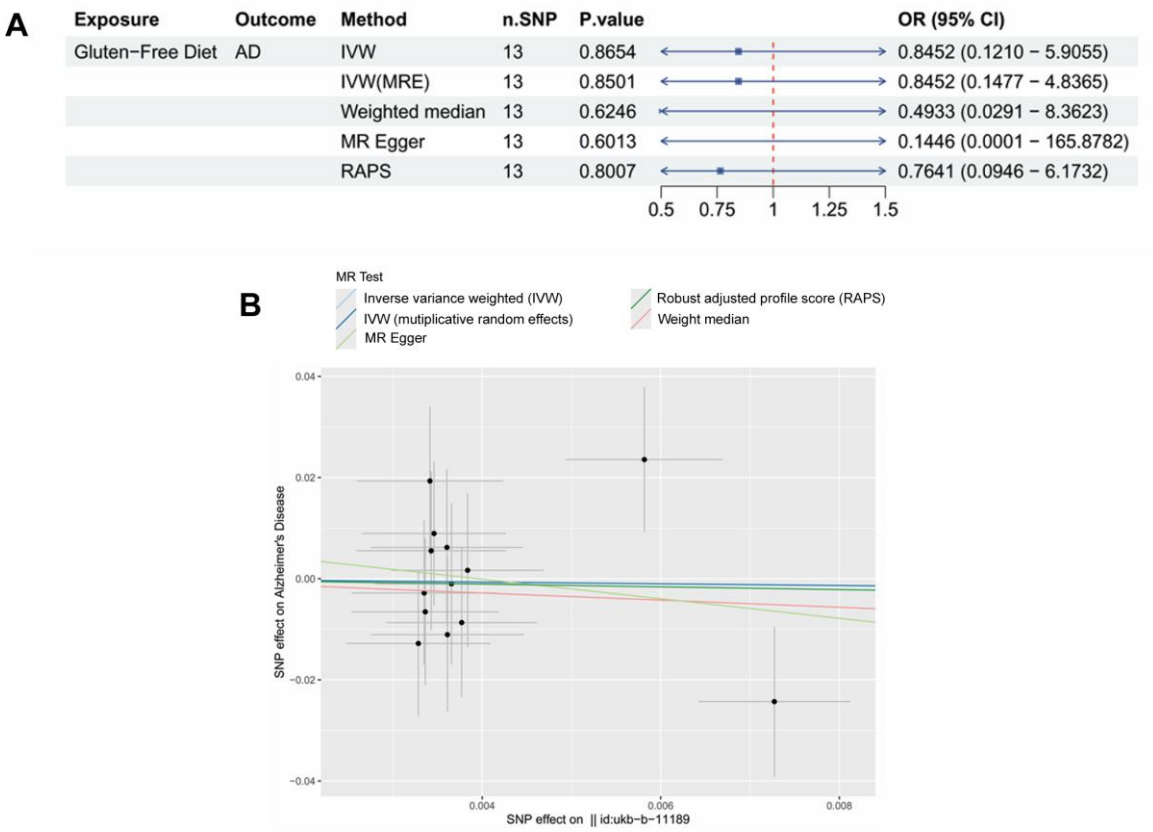

Fig. 5. (A) Mendelian randomization (MR) estimates between Gluten-free diet and Alzheimer's disease (AD). Primary analysis (IVW) and sensitivity analysis (IVW-MRE, weighted median, MR-Egger, and RAPS) were utilized. Data are displayed as odds ratio (OR) and 95% confidence interval (CI) per log-odds increment in AD risk. (B) Scatterplot of potential effects of the targeted SNPs on gluten-free diet vs AD. The slope of each line corresponds to the estimated MR effect for each method used. Positive slope indicates a positive correlation, and negative slope indicates a negative correlation.

may be attributed to several factors. Firstly, variability in cohort sizes can significantly influence the ability to detect significant associations. Larger cohorts provide more reliable estimates, while smaller studies may lack the power to identify associations. Secondly, genetic diversity among study populations can contribute to differences in findings. Variations in genetic predispositions related to CeD and MS across populations could influence observed associations. Next, inconsistencies in diagnostic criteria for CeD and MS can lead to variability in study outcomes. Differences in definitions and diagnostic practices may affect case and control identification. Also, differences in environmental exposures, dietary habits, and healthcare access can impact the prevalence and manifestation of CeD and MS, contributing to inconsistent results across studies. Finally, variations in study design, such as prospective versus retrospective approaches, and differences in data collection methods can result in divergent findings.

An important limitation of this study is its reliance on data predominantly derived from European populations, where CeD is more prevalent. This focus means that the findings may be particularly relevant to European populations but might not be directly applicable to populations with lower CeD prevalence or different genetic and environmental backgrounds. Genetic predispositions related to CeD and MS could vary significantly in non-European populations, potentially influencing the observed associations. Furthermore, environmental factors, such as dietary habits and healthcare access, which vary widely globally, might contribute to differences in disease prevalence and manifestation. Future research should aim to include diverse population groups to enhance the generalizability of the findings and explore potential population-specific effects.

In this study, we investigated the association between CeD and MS using MR analysis with data from a large-scale genomic database. Considering the gut-brain axis, we hypothesized that circulating proteins are likely mediators of the causal relationship between CeD and MS. Consequently, we focused on inflammatory circulating proteins as potential mediators. Fortunately, GWAS data from a genome-wide protein quantitative trait locus (pQTL) study of 91 plasma proteins were available, enabling us to

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identify CCL19 as a potential mediator [19]. Moreover, Krumbholz and collegues reported that CCL19 is constitutively expressed in the central nervous system and is significantly elevated in both active and inactive multiple sclerosis lesions [40]. CCR7 ligands, CCL19 and CCL21, are known to act as chemotactic and retentive signals in lymphoid organs. However, it has recently been reported that ectopic CCL19 and CCL21 are increased in the inflamed intestine in Crohn's disease [41, 42]. Although studies on the expression of CCL19 in the intestinal epithelium in celiac disease are insufficient, there is a report that gliadin fragments increase the migration of dendritic cells [43]. Additionally, there is a report that CCR7, a chemokine receptor of CCL19, expressed in some T cells of celiac disease patients [44]. For this reason, it is presumed that CCL19 is involved in the immune response to gluten in celiac disease. However, the precise mechanisms by which CCL19 might link CeD and MS remain unclear. The potential role of CCL19 in mediating immune responses and its involvement in both gut and CNS inflammation suggest avenues for further investigation.

CeD and Alzheimer's disease

The findings from various MR methods, including IVW, IVW(MRE), WM, and RAPS, suggest a modest inverse relationship between CeD and AD, indicating that individuals with CeD may have a slightly reduced risk of developing AD. Although the MR Egger method did not show significant protective effects, the overall trend supports the hypothesis that CeD may be associated with decreased AD risk.

The gut-brain axis facilitates communication between the brain's immune system and the peripheral immune system, allowing increased peripheral immune function to upregulate microglial activity in the brain [45]. Activated microglia release pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which can exacerbate neuronal damage and contribute to neurodegenerative conditions[46]. The inverse relationship between CeD and AD suggests that these inflammatory responses may not necessarily lead to increased AD risk, indicating potential compensatory mechanisms that mitigate the effects of systemic inflammation and microglial activation on neurodegeneration.

Elevated inflammatory markers, like interleukin-6 (IL-6), are characteristic of CeD and linked to systemic inflammation [47]. Despite elevated IL-6 levels—crucial for stimulating acute phase responses—the inverse relationship between CeD and AD risk suggests that systemic inflammation may not directly translate into increased susceptibility to AD, highlighting the complexity of these interactions.

Drawing from the relationships between CeD, AD, and MS, a compelling hypothesis emerges: CeD may inversely influence the risk of these neurodegenerative diseases. Specifically, while CeD might reduce the risk of AD, it appears to increase susceptibility to MS. This differential impact highlights the complexity of autoimmune responses triggered by gluten.

The observed inverse relationship parallels phenomena seen in allergies and parasitic infections, where immune responses to one condition can provide protection against another [48]. In the case of AD, CeD may not directly influence risk through previously assumed mechanisms, but the autoimmune processes regulated by a GFD could promote neuroprotective pathways or alter the brain's immune environment. This suggests that while CeD might not directly impact AD risk, GFD-regulated processes could still enhance neuroprotection. Conversely, in MS, the same autoimmune mechanisms driven by CeD could exacerbate the disease. Systemic inflammation resulting from CeD might worsen the autoimmune attack on the myelin sheath, leading to accelerated demyelination. Research indicates that disruptions in the intestinal barrier—a hallmark of CeD—can contribute to systemic inflammation and may influence the progression of autoimmune conditions like MS.

In response to the inquiry about why a GFD does not appear to be associated with the prevention of AD, it is important to recognize that our current understanding of the relationship between diet, CeD, and neurodegenerative diseases like AD is still evolving. At present, there is no clear evidence that a GFD has a protective effect against the development of AD. This may be due to several factors. Firstly, the pathophysiological mechanisms that link CeD and AD are complex and not yet fully elucidated. While CeD is associated with systemic inflammation and immune responses, how these processes intersect with the pathways leading to AD is not well understood. Additionally, while a GFD is effective in managing CeD by preventing immune reactions triggered by gluten, its impact on other unrelated neurodegenerative processes may be limited. The development of AD involves a myriad of factors including genetics, environmental influences, and lifestyle choices, which may not be directly influenced by dietary gluten intake.

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AUTHOR CONTRIBUTIONS

S. Lim contributed to conception, design, data acquisition and analysis, and drafted manuscript; J. Wu contributed to design, analysis, and drafted manuscript; Y.Y. Kim. & S.W. Lim contributed to design, analysis, and drafted manuscript; J. Shin, & H.J. Shin. & S.R. Kim. contributed to conception, design, interpretation, and critically revised manuscript; D.W. Kim contributed to conception, design, interpretation, and critically revised manuscript. All authors have their final approval and agree to be accountable for all aspects of work.

CONFLICT OF INTEREST

We declare no competing interests/conflicts.

CONSENT STATEMENT

This study utilized data from the GWAS and Finngen databases, where informed consent was obtained from all human subjects involved in the research. Therefore, consent was confirmed for the use of this genetic data in the analysis.

DATA SHARING

All bona fide researchers can apply for and access the public datasets from the UK Biobank, FinnGen project, and MEGASTROKE consortium. The MRC-IEU and FinnGen websites provide download links for all the data used in this study.

REFERENCES

1. Catassi C, Verdu EF, Bai JC, Lionetti E (2022) Coeliac disease. Lancet 399:2413-2426.
2. Patel SC, Shreya D, Zamora DI, Patel GS, Grossmann I, Rodriguez K, Soni M, Joshi PK, Sange I (2021) Celiac disease, beyond the bowel: a review of its neurological manifestations. Cureus 13:e20112.
3. Appleton J (2018) The gut-brain axis: influence of microbiota on mood and mental health. Integr Med (Encinitas) 17:28-32.
4. Giuffrè M, Gazzin S, Zoratti C, Llido JP, Lanza G, Tiribelli C, Moretti R (2022) Celiac disease and neurological manifestations: from gluten to neuroinflammation. Int J Mol Sci 23:15564.
5. Gala D, Scharf S, Kudlak M, Green C, Khowaja F, Shah M, Kumar V, Ullal G (2022) A comprehensive review of the neurological manifestations of celiac disease and its treatment. Diseases 10:111.
6. Kociszewska D, Vlajkovic SM (2022) The association of inflammatory gut diseases with neuroinflammatory and auditory disorders. Front Biosci (Elite Ed) 14:8.
7. Gagnon E, Daghlas I, Zagkos L, Sargurupremraj M, Georgakis MK, Anderson CD, Cronje HT, Burgess S, Arsenault BJ, Gill D (2024) Mendelian randomization applied to neurology: promises and challenges. Neurology 102:e209128.
8. Sekula P, Del Greco M F, Pattaro C, Köttgen A (2016) Mendelian randomization as an approach to assess causality using observational data. J Am Soc Nephrol 27:3253-3265.
9. Bowden J, Holmes MV (2019) Meta-analysis and Mendelian randomization: a review. Res Synth Methods 10:486-496.
10. Trynka G, Hunt KA, Bockett NA, Romanos J, Mistry V, Szperl A, Bakker SF, Bardella MT, Bhaw-Rosun L, Castillejo G, de la Concha EG, de Almeida RC, Dias KR, van Diemen CC, Dubois PC, Duerr RH, Edkins S, Franke L, Fransen K, Gutierrez J, Heap GA, Hrdlickova B, Hunt S, Plaza Izurieta L, Izzo V, Joosten LA, Langford C, Mazzilli MC, Mein CA, Midah V, Mitrovic M, Mora B, Morelli M, Nutland S, Núñez C, Onengut-Gumuscu S, Pearce K, Platteel M, Polanco I, Potter S, Ribes-Koninckx C, Ricaño-Ponce I, Rich SS, Rybak A, Santiago JL, Senapati S, Sood A, Szajewska H, Troncone R, Varadé J, Wallace C, Wolters VM, Zhernakova A; Spanish Consortium on the Genetics of Coeliac Disease (CEGEC); PreventCD Study Group; Wellcome Trust Case Control Consortium (WTCCC); Thelma BK, Cukrowska B, Urcelay E, Bilbao JR, Mearin ML, Barisani D, Barrett JC, Plagnol V, Deloukas P, Wijmenga C, van Heel DA (2011) Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nat Genet 43:1193-1201.
11. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, Butterworth AS, Staley JR (2019) PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 35:4851-4853.
12. Fadista J, Manning AK, Florez JC, Groop L (2016) The (in) famous GWAS P-value threshold revisited and updated for low-frequency variants. Eur J Hum Genet 24:1202-1205.
13. Lin Z, Deng Y, Pan W (2021) Combining the strengths of inverse-variance weighting and Egger regression in Mendelian randomization using a mixture of regressions model. PLoS Genet 17:e1009922.

14. Pierce BL, Burgess S (2013) Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol 178:1177-1184.
15. Bowden J, Davey Smith G, Haycock PC, Burgess S (2016) Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 40:304-314.
16. Bowden J, Davey Smith G, Burgess S (2015) Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 44:512-525.
17. Hartwig FP, Davey Smith G, Bowden J (2017) Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. Int J Epidemiol 46:1985-1998.
18. Richmond RC, Davey Smith G (2022) Mendelian randomization: concepts and scope. Cold Spring Harb Perspect Med 12:a040501.
19. Zhao JH, Stacey D, Eriksson N, Macdonald-Dunlop E, Hedman ÅK, Kalnapenkis A, Enroth S, Cozzetto D, Digby-Bell J, Marten J, Folkersen L, Herder C, Jonsson L, Bergen SE, Gieger C, Needham EJ, Surendran P; Estonian Biobank Research Team; Paul DS, Polasek O, Thorand B, Grallert H, Roden M, Võsa U, Esko T, Hayward C, Johansson Å, Gyllensten U, Powell N, Hansson O, Mattsson-Carlgren N, Joshi PK, Danesh J, Padyukov L, Klareskog L, Landén M, Wilson JF, Siegbahn A, Wallentin L, Mälarstig A, Butterworth AS, Peters JE (2023) Genetics of circulating inflammatory proteins identifies drivers of immune-mediated disease risk and therapeutic targets. Nat Immunol 24:1540-1551.
20. Carter AR, Sanderson E, Hammerton G, Richmond RC, Davey Smith G, Heron J, Taylor AE, Davies NM, Howe LD (2021) Mendelian randomisation for mediation analysis: current methods and challenges for implementation. Eur J Epidemiol 36:465-478.
21. Rijnhart JJM, Valente MJ, MacKinnon DP, Twisk JWR, Heymans MW (2021) The use of traditional and causal estimators for mediation models with a binary outcome and exposure-mediator interaction. Struct Equ Modeling 28:345-355.
22. Burgess S, Thompson SG (2017) Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 32:377-389.
23. Lin Z, Pan I, Pan W (2022) A practical problem with Egger regression in Mendelian randomization. PLoS Genet 18:e1010166.
24. Barartabar Z, Nikzamir A, Sirati-Sabet M, Aghamohammadi E, Chaleshi V, Rostami Nejad M, Asadzadeh-Aghdaei H, Reza Zali M (2018) The relationship between 174 G/C and -572 G/C of IL-6 gene polymorphisms and susceptibility of celiac disease in the Iranian population. Prz Gastroenterol 13:293-298.
25. Makhlouf S, Messelmani M, Zaouali J, Mrissa R (2018) Cognitive impairment in celiac disease and non-celiac gluten sensitivity: review of literature on the main cognitive impairments, the imaging and the effect of gluten free diet. Acta Neurol Belg 118:21-27.
26. Losurdo G, Principi M, Iannone A, Amoruso A, Ierardi E, Di Leo A, Barone M (2018) Extra-intestinal manifestations of non-celiac gluten sensitivity: an expanding paradigm. World J Gastroenterol 24:1521-1530.
27. Hadjivassiliou M, Grünewald RA, Kandler RH, Chattopadhyay AK, Jarratt JA, Sanders DS, Sharrack B, Wharton SB, Davies-Jones GA (2006) Neuropathy associated with gluten sensitivity. J Neurol Neurosurg Psychiatry 77:1262-1266.
28. Hadjivassiliou M, Sanders DS, Woodroofe N, Williamson C, Grünewald RA (2008) Gluten ataxia. Cerebellum 7:494-498.
29. Hadjivassiliou M, Sanders DS, Grünewald RA, Woodroofe N, Boscolo S, Aeschlimann D (2010) Gluten sensitivity: from gut to brain. Lancet Neurol 9:318-330.
30. Lerner A, Shoenfeld Y, Matthias T (2017) Adverse effects of gluten ingestion and advantages of gluten withdrawal in non-celiac autoimmune disease. Nutr Rev 75:1046-1058.
31. Rouvroye MD, Zis P, Van Dam AM, Rozemuller AJM, Bouma G, Hadjivassiliou M (2020) The neuropathology of gluten-related neurological disorders: a systematic review. Nutrients 12:822.
32. Jacob S, Zarei M, Kenton A, Allroggen H (2005) Gluten sensitivity and neuromyelitis optica: two case reports. J Neurol Neurosurg Psychiatry 76:1028-1030.
33. Wang Y, Lebwohl B, Mehta R, Cao Y, Green PHR, Grodstein F, Jovani M, Lochhead P, Okereke OI, Sampson L, Willett WC, Sun Q, Chan AT (2021) Long-term intake of gluten and cognitive function among US women. JAMA Netw Open 4:e2113020.
34. Yamout BI, Alroughani R (2018) Multiple sclerosis. Semin Neurol 38:212-225.
35. Rodrigo L, Hernández-Lahoz C, Fuentes D, Alvarez N, López-Vázquez A, González S (2011) Prevalence of celiac disease in multiple sclerosis. BMC Neurol 11:31.
36. Zhang X, Chen F, Sun M, Wu N, Liu B, Yi X, Ge R, Fan X (2023) Microglia in the context of multiple sclerosis. Front Neurol 14:1157287.
37. Batur-Caglayan HZ, Irkec C, Yildirim-Capraz I, Atalay-Akyurek N, Dumlu S (2013) A case of multiple sclerosis and celiac

disease. Case Rep Neurol Med 2013:576921.
38. Shaygannejad V, Ghasemi M, Mirmohamadsadeghi M (2013) Multiple sclerosis or neurological manifestations of celiac disease. Adv Biomed Res 2:38.
39. Olfati H, Ghoshouni H, Ebrahimi N, Mohammadi A, Ghajarzadeh M (2022) Is celiac disease (CD) prevalent in patients with multiple sclerosis (MS): a systematic review and meta-analysis. Mult Scler Int 2022:7091140.
40. Krumbholz M, Theil D, Steinmeyer F, Cepok S, Hemmer B, Hofbauer M, Farina C, Derfuss T, Junker A, Arzberger T, Sinicina I, Hartle C, Newcombe J, Hohlfeld R, Meinl E (2007) CCL19 is constitutively expressed in the CNS, up-regulated in neuroinflammation, active and also inactive multiple sclerosis lesions. J Neuroimmunol 190:72-79.
41. McNamee EN, Masterson JC, Jedlicka P, Collins CB, Williams IR, Rivera-Nieves J (2013) Ectopic lymphoid tissue alters the chemokine gradient, increases lymphocyte retention and exacerbates murine ileitis. Gut 62:53-62.
42. Middel P, Raddatz D, Gunawan B, Haller F, Radzun HJ (2006) Increased number of mature dendritic cells in Crohn's disease: evidence for a chemokine mediated retention mechanism. Gut 55:220-227.
43. Chladkova B, Kamanova J, Palova-Jelinkova L, Cinova J, Sebo P, Tuckova L (2011) Gliadin fragments promote migration of dendritic cells. J Cell Mol Med 15:938-948.
44. Han A, Newell EW, Glanville J, Fernandez-Becker N, Khosla C, Chien YH, Davis MM (2013) Dietary gluten triggers concomitant activation of CD4+ and CD8+ αβ T cells and γδ T cells in celiac disease. Proc Natl Acad Sci U S A 110:13073-13078.
45. Vasefi M, Hudson M, Ghaboolian-Zare E (2019) Diet associated with inflammation and Alzheimer's disease. J Alzheimers Dis Rep 3:299-309.
46. Wang WY, Tan MS, Yu JT, Tan L (2015) Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med 3:136.
47. Nasserinejad M, Shojaee S, Ghobakhlou M, Lak E, Eslami P, Pourhoseingholi MA (2019) The effects of IL-8, IL- 6, and IL-1 on the risk of celiac disease: a Bayesian regression analysis. Gastroenterol Hepatol Bed Bench 12:S117-S122.
48. McSorley HJ, Chayé MAM, Smits HH (2019) Worms: pernicious parasites or allies against allergies? Parasite Immunol 41:e12574.