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Association between inflammatory bowel disease and all-cause dementia: A two-sample Mendelian randomization study

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Abstract

BACKGROUND

Numerous observational studies have documented a correlation between inflammatory bowel disease (IBD) and an increased risk of dementia. However, the causality of their associations remains elusive.

AIM

To assess the causal relationship between IBD and the occurrence of all-cause dementia using the two-sample Mendelian randomization (MR) method.

METHODS

Genetic variants extracted from the large genome-wide association study (GWAS) for IBD (the International IBD Genetics Consortium, n = 34652) were used to identify the causal link between IBD and dementia (FinnGen, n = 306102). The results of the study were validated *via* another IBD GWAS (United Kingdom Biobank, n = 463372). Moreover, MR egger intercept, MR pleiotropy residual sum and outlier, and Cochran's Q test were employed to evaluate pleiotropy and heterogeneity. Finally, multiple MR methods were performed to estimate the effects of genetically predicted IBD on dementia, with the inverse variance weighted approach adopted as the primary analysis.

RESULTS

The results of the pleiotropy and heterogeneity tests revealed an absence of significant pleiotropic effects or heterogeneity across all genetic variants in outcome GWAS. No evidence of a causal effect between IBD and the risk of dementia was identified in the inverse variance weighted [odds ratio (OR) = 0.980, 95%CI : 0.942-1.020, P value = 0.325], weighted median (OR = 0.964, 95%CI : 0.914-

1.017, *P* value = 0.180), and MR-Egger (OR = 0.963, 95%CI : 0.867-1.070, *P* value = 0.492) approaches. Consistent results were observed in validation analyses. Reverse MR analysis also showed no effect of dementia on the development of IBD. Furthermore, MR analysis suggested that IBD and its subtypes did not causally affect all-cause dementia and its four subtypes, including dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere, and unspecified dementia.

CONCLUSION

Taken together, our MR study signaled that IBD and its subentities were not genetically associated with all-cause dementia or its subtypes. Further large prospective studies are warranted to elucidate the impact of intestinal inflammation on the development of dementia.

Key Words: Inflammatory bowel disease; All-cause dementia; Mendelian randomization; Causal effect; Risk factor

Core Tip: Dementia is a major disease burden for public health and healthcare systems worldwide. This study used two-sample Mendelian randomization (MR) to assess the causal relationship between inflammatory bowel disease (IBD) and all-cause dementia. Multiple MR methods have failed to find that IBD increases the risk of developing all-cause dementia and its four subtypes. The present study suggests that genetically predicted IBD is not associated with risk of all-cause dementia and that dementia prevention interventions for patients with IBD can be similar to those for the healthy population.

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INTRODUCTION

Dementia is a syndrome arising from brain disorders, usually of a chronic or progressive nature, characterized by acquired behavioral and cognitive deficits, including domains such as memory, communication and language abilities, concentration and attention span, reasoning and judgment, and visual perception[1]. It is a global health concern and has emerged as a pandemic in the aging population. Over 1315 million people are predicted to be affected by the mid-21st century[2]. Mounting evidence suggests that intestinal homeostasis is involved in psychiatric and neurologic disorders through the bidirectional microbiome-gut-brain axis. Besides conventional brain-gut disorders (*e.g.*, functional gastrointestinal disorders), recent studies point toward a potential role of the interaction between the gut and central nervous system in depression, anxiety, Parkinson's disease, autism spectrum disorders, and other related disorders[3].

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), refers to a chronic intestinal disorder featured by a relapsing and remitting course. Its cause remains to be elucidated, but its pathogenesis may involve environmental factors triggering an aberrant immune response between the gut microbiota and the intestinal immune system in genetically susceptible hosts, thereby eliciting intestinal mucosal inflammation[4]. The genome-wide association study (GWAS) identified gene loci associated with IBD susceptibility, influencing not only gut microbial recognition and clearance but also the maintenance of intestinal immune homeostasis[5].

Several studies have reported that IBD patients are at increased risk of neurodegenerative diseases such as Parkinson's disease, multiple sclerosis, and dementia[6-8]. A Taiwanese population-based cohort study determined a significantly increased risk of developing dementia among IBD patients, whereas a Danish study concluded that IBD patients had a marginally increased risk of all-cause dementia[9,10]. Contrastingly, a longitudinal cohort study found no association between IBD and dementia[8]. To date, the causal relationship between IBD and dementia remains underexplored. Furthermore, the aforementioned observational studies might be susceptible to various measurement errors, underlying biases, and confounding factors, which could have compromised the results or even reverse causality.

Mendelian randomization (MR) is conceptually similar to randomized controlled trials (RCTs), using genetic variants as instrumental variables (IVs) to infer causality between an exposure and an outcome based on the principle of random assortment of alleles during gamete formation and conception[11,12]. The former utilizes genetic data, such as single nucleotide polymorphisms (SNPs) associated with an exposure (in this study, IBD), as IVs to examine the causal effect of the exposure on the target outcome (in this study, dementia)[13]. The intrinsic nature of the random assortment of genetic variants at conception dictates that their effects on outcomes remain unaffected by postnatal environmental, behavioral, and economic confounders. Besides, they are not susceptible to reverse causality bias[14]. Given that these confounding factors are inherently balanced across subgroups at conception, MR closely mimics the randomization process in RCTs.

A large number of MR studies have been undertaken to investigate the causal effect of IBD on neurodegenerative diseases, encompassing Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis[15-17]. While Li and Wen[15] did not identify a correlation between IBD and AD, Guo *et al*[17] found that IBD exerted a genetically

protective effect against AD. There are currently no MR studies or RCTs focusing on the effect of IBD on the risk of dementia subtypes other than AD. Based on the publicly available GWAS data from a large population, a two-sample MR analysis was adopted to identify the effect of IBD on all-cause dementia and its subtypes, which holds clinical implications for the formulation of interventions to delay cognitive decline and mitigate the burden of dementia in the IBD population. Our results may provide novel insights into the bidirectional interactions in the gut-brain axis.

MATERIALS AND METHODS

Study design

A two-sample MR method was conducted to evaluate the causal relationship between IBD and all-cause dementia. MR follows three key assumptions (Figure 1): (1) The IVs are strongly associated with the exposure (IBD); (2) the IVs are unrelated to confounder factors linked to the selected exposure and outcome, and (3) the IVs exclusively influence the outcome (dementia and its six subtypes) *via* IBD. Considering that this study used publicly available datasets from participant studies conducted in compliance with ethical standards, the requirement for ethical approval was waived.

IBD GWAS and genetic instrumental variants

The GWAS summary data for IBD were extracted from the International IBD Genetics Consortium (IIBDGC)[18] that is composed of 15 cohorts of European ancestry (enrolled cohorts are listed in Supplementary Table 1) and contained data on IBD as a whole (12882 cases; 21770 controls) and also on CD (5956 cases; 14927 controls) and UC (6968 cases; 20464 controls). All cases were confirmed using standard clinical, endoscopic, and histopathological criteria. The validation analysis incorporated summary statistics acquired from a United Kingdom Biobank GWAS involving European participants (7045 self-reported cases and 456327 controls) wherein IBD cases were identified using the International Classification of Diseases 10th Revision (ICD-10) codes F50 and F51[19]. Information about the GWAS of exposure is summarized in Table 1.

Independent genetic IVs were extracted from the respective exposure based on several criteria. To begin, SNPs strongly associated with the exposure were selected (P-value < 5 × 10^{-8}). Following this, to ensure the inclusion of IVs without linkage disequilibrium (LD), the clumping procedure (R^2 < 0.001, window size = 10000 kb) was executed utilizing European samples to calculate the LD. Thirdly, SNPs associated with other potential risk factors at genome-wide significance, which may act as confounders and interfere with the effect of IBD (including UC and CD) on dementia, were excluded using PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/). Known risk factors for dementia include diabetes, hypertension, atrial fibrillation or flutter, obesity, chronic obstructive pulmonary disease, cerebrovascular disease, smoking, and hypothyroidism[8-10]. SNPs associated with dementia due to other diseases identified by the ICD-10 code F02 were also excluded in this analysis. The strength of the relationship between IVs and exposure was estimated using the F statistic (F statistics < 10 indicating a weak IV bias)[20]. For each IV, the F statistic was calculated using the following formula: F= [R^2 × (N-2)/(1 -R^2), where N denotes the sample size, R^2 represents the variance of exposure explained by the IVs (R^2 = 2 × beta^2 × eaf × (1-eaf)/[2 × beta^2 × eaf × (1-eaf) + 2 × se × N × eaf × (1-eaf)], eaf stands for the effect allele frequency, se represents standard error, and beta is the estimated effect of the SNP) [21-23].

Extraction of IVs from dementia GWAS

All-cause dementia was defined as ICD-10 codes F00 (dementia in AD), F01 [vascular dementia [VaD)], F02 (dementia in other diseases classified elsewhere) and F03 (unspecified dementia)[24]. The GWAS summary statistics for dementia were utilized as a whole and its subtypes from the FinnGen study[25]. The sample of all-cause dementia consisted of 11602 cases (ICD-10 F00-F03, ICD-9 290 | 3310 | 4378A, ICD-8 290) and 294500 controls; the sample of dementia in AD consisted of 3540 cases (ICD-10 F00, ICD-8 29010) and 294500 controls; the sample of VaD consisted of 1602 cases (ICD-10 F01, ICD-9 4378) and 297552 controls; the sample of dementia in other diseases classified elsewhere consisted of 882 cases (ICD-10 F02) and 294500 controls; and the sample of unspecified dementia consisted of 2729 cases (ICD-10 F03, ICD 290 | 2941, ICD-8 2900 | 29019) and 294500 controls. Details on the outcome of GWAS are listed in Table 1.

IVs were sequentially extracted from the outcome GWASs as described above, while outcome-related SNPs were eliminated. Subsequently, ambiguous SNPs with incompatible alleles (*e.g.*, A/G *vs*. A/C) and palindromic SNPs (*e.g.*, A/T or G/C) were excluded when harmonizing exposure and outcome datasets[26]. SNPs absent in the outcome data were substituted by proxy SNPs obtained from the online platform LDlink (https://Ldlink.nih.gov/) based on high LD from European data. Proxies were required to have a minimum R^2 value of 0.8, and palindromic SNP strands were aligned using a minor allele frequency of up to 0.3[27]. The summary characteristics of all genetic IVs are illustrated in Supplementary Tables 2-4. The correlations between IBD (including UC and CD) genetic IVs and the GWAS datasets for dementia and its subtypes are displayed in Supplementary Tables 5-7. Additionally, a comprehensive summary of IVs associated with the validation analysis is presented in Supplementary Tables 8 and 9.

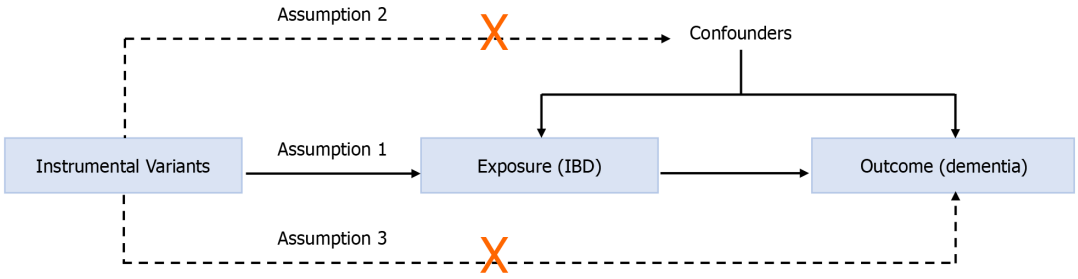
Pleiotropy and heterogeneity assessments

MR egger intercept and MR pleiotropy residual sum and outlier (MR-PRESSO) tests are typically used to assess horizontal pleiotropy[28]. If the selected IVs are not pleiotropic, the MR Egger intercept term tends to approach zero with an increase in sample size[29]. MR-PRESSO can correct horizontal pleiotropy by eliminating underlying outliers prior to each MR analysis[28]. The harmonized SNPs underwent the MR-PRESSO test (NbDistribution=10000). A P > 0.05 in the MR-PRESSO global test indicates no significant pleiotropy of all IBD-associated IVs in the dementia GWAS dataset. In the

Table 1 Details of the genome-wide association studies included in the Mendelian randomization

Phenotype	Consortium	Year	Ncase	Ncontrol	Population
IBD	IIBDGC	2015	12882	21770	European
UC	IIBDGC	2015	6968	20464	European
CD	IIBDGC	2015	5956	14927	European
IBD (val)	United Kingdom Biobank	2021	7045	449282	United Kingdom
All-cause dementia	FinnGen	2022	11602	294500	Finnish
Dementia in AD	FinnGen	2022	3540	294500	Finnish
VaD	FinnGen	2022	1602	297552	Finnish
Dementia in other diseases classified elsewhere	FinnGen	2022	882	294500	Finnish
Unspecified dementia	FinnGen	2022	2729	294500	Finnish

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; AD: Alzheimer's disease; VaD: Vascular dementia; IIBDGC: International Inflammatory Bowel Disease Genetics Consortium.



Assumption 1: The instrumental variants are strongly associated with exposure;

Assumption 2: The instrumental variants are not associated with confounders;

Assumption 3: The instrumental variants influence the outcome only through the exposure.

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Figure 1 Diagram of the two-sample Mendelian randomization study for the associations of inflammatory bowel disease with dementia.
IBD: Inflammatory bowel disease.

MR-PRESSO outlier test, outliers with a *P*-value less than 0.05 should be removed. The Cochran's *Q* statistic was employed to evaluate heterogeneity, which is extensively employed in MR Egger and inverse variance weighted (IVW) analyses[30,31]. A $P > 0.05$ indicates the absence of significant heterogeneity. The summarized results of the pleiotropy and heterogeneity tests are shown in Supplementary Table 10.

MR analysis

Three different MR methods (IVW, weighted median, and MR Egger) were performed to estimate the effect of the exposure on outcome susceptibility. IVW was selected as the primary method, with the remaining MR methods assessing the sensitivity of our findings with robust estimates. IVW represents the weighted average of Wald ratio estimates of the causal impact for each variant and provides the most accurate estimate when all IVs are valid[32]. The weighted median yields consistent estimates even if up to 50% of selected SNPs are not valid[28,29]. MR Egger accounts for pleiotropy among all IVs but requires that the associations between genetic variants and exposure remain independent of the effects of genetic variants on the outcome[33]. Additionally, a "leave one out" analysis was carried out to systematically exclude each SNP individually to examine the influence of SNPs on the MR estimate[34].

All analyses in this MR study were performed using the Package "TwoSampleMR version 0.5.6" in R version 4.2.2. The significance threshold was set at $P < 0.05/X/Y = 0.05/3/5 = 0.003$, corrected by the Bonferroni method (X: the number of exposures, Y: the number of outcomes). An overview of our study's process is presented in Figure 2.

Reverse MR analysis

Genetic IVs were selected from the dementia GWAS summary data based on several criteria: (1) *P*-value (genome-wide significance threshold $< 5 \times 10^{-8}$); (2) an LD R^2 of < 0.001, and < 10000 kb from the index variant; and (3) no effects on potential risk factors, including inflammation, immune response, and gut microbiota. Then, IVs were extracted from the IBD GWAS. The IBD GWAS and dementia GWAS were sourced from the IIBDGC and FinnGen, respectively (Table 1).

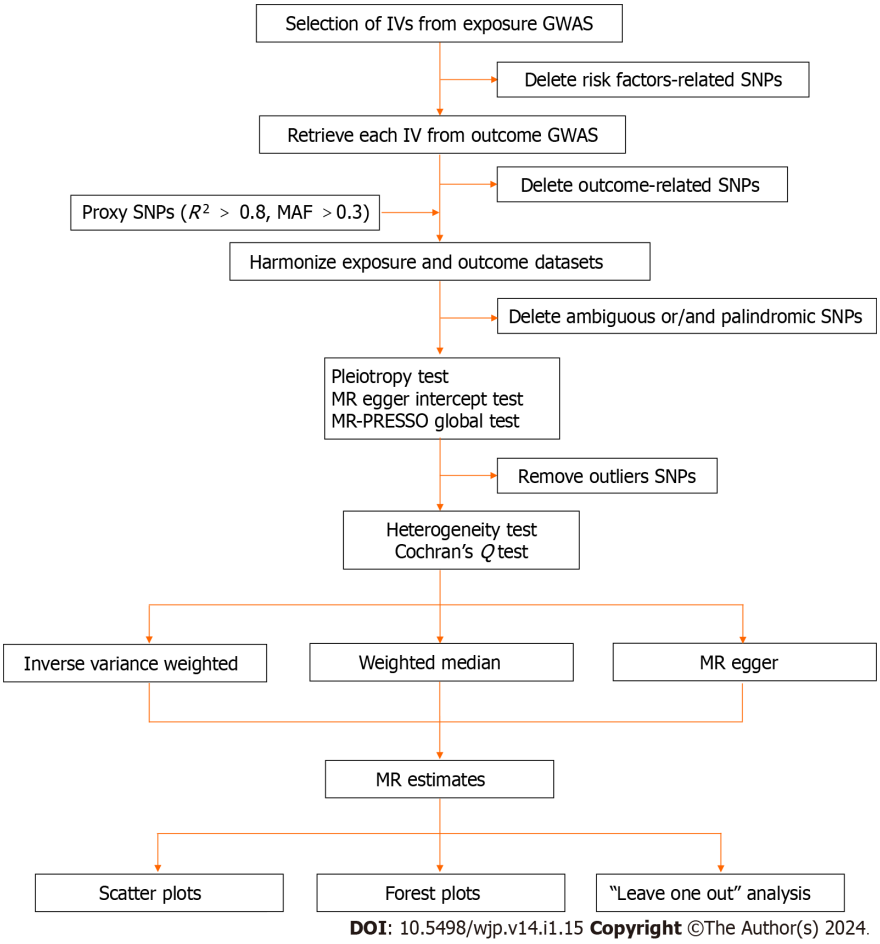

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Figure 2 Flow chart of this Mendelian randomization study. MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms; GWAS: Genome-wide association study; IV: Instrumental variables.

The summary characteristics of dementia IVs and their association with IBD GWAS are depicted in Supplementary Table 11 and 12.

The MR Egger intercept and PRESSO methods were applied to determine the pleiotropy of dementia-associated IVs in IBD GWAS, whilst MR Egger and IVW in Cochran's *Q* statistic were employed to determine the heterogeneity of dementia-associated IVs in IBD GWAS (Supplementary Table 10). The methods of reverse MR analysis were consistent with those described above.

RESULTS

Genetic instrumental variants

In the primary analysis investigating the causal impact of IBD on dementia, 65 SNPs were screened as potential genetic IVs, of which 19 SNPs related to other potential risk factors were excluded, nine SNPs could not be extracted from the outcome GWASs, and five SNPs were ambiguous or/and palindromic (Supplementary Table 2). In the analysis concerning the impact of UC on dementia, 39 SNPs were screened as potential genetic IVs, of which 13 SNPs related to other potential risk factors were excluded, four SNPs could not be extracted from the outcome GWASs, and three SNPs were ambiguous or/and palindromic (Supplementary Table 3). In the analysis of the impact of CD on dementia, 53 SNPs were initially identified as potential genetic IVs, among which 19 SNPs related to other potential risk factors were excluded, two SNPs could not be extracted from the outcome GWASs, and five SNPs were ambiguous or/and palindromic (Supplementary Table 4). Besides, 19 SNPs were identified as IVs in the validation analyses (Supplementary 8). The selected IVs could explain 6.75%, 4.36%, and 9.06% variance of IBD, UC, and CD, respectively. Additionally, the accounted variance by IVs was 0.19% in the validation analyses. The *F*-statistic of all selected IVs was > 10, demonstrating a marginal possibility of a weak instrument bias (Supplementary Table 2-4 and 8).

MR egger intercept and MR-PRESSO global tests both exposed the absence of significant pleiotropy (Supplementary Table 10). Furthermore, no statistical heterogeneity was detected in the MR egger and IVW in Cochran's *Q* tests (Supplementary Table 10). Thus, all selected genetic SNPs were regarded as effective IVs in this MR study.

Causal effects of IBD on the risk of all-cause dementia

In the primary analysis, the IVW method determined that IBD was not causally related to all-cause dementia [odds ratio (OR) = 0.980, 95%CI : 0.942-1.020, *P* value = 0.325] (Figure 3). Subsequently, the causal relationship between IBD and the four subtypes of dementia was examined. Subgroup analyses did not support a significant association between IBD and dementia in AD (OR = 0.957, 95%CI : 0.899-1.018, *P* value = 0.165), VaD (OR = 0.944, 95%CI : 0.866-1.030, *P* value = 0.195), dementia in other diseases classified elsewhere (OR = 1.089, 95%CI : 0.952-1.246, *P* value = 0.214), and unspecified dementia (OR = 1.011, 95%CI : 0.936-1.092, *P* value = 0.776) (Figure 3). Similarly, the weighted median and MR Egger methods provided no evidence of a genetic causal relationship between IBD and all-cause dementia and its subtypes (Supplementary Table 13). As anticipated, these results were corroborated by the validation sample (Figure 4; Supplementary Table 13). The scatter plots and forest plots of the single SNP effect and combined effects are displayed in Supplementary Figure 1-4. The "leave one out" sensitivity analysis indicated that no individual SNP influenced the MR estimates (Supplementary Figures 5 and 6).

Furthermore, the causal effects of UC and CD on all-cause dementia and its four subtypes were assessed in a similar approach. The IVW method revealed that UC and CD were not causally related to all-cause dementia and its four subtypes, including dementia in AD, VaD, dementia in other diseases classified elsewhere, and unspecified dementia (Figure 3). The results of the weighted median and MR Egger are presented in Supplementary Table 13. All scatter plots, forest plots, and "leave one out" analysis plots for MR analyses of UC and CD on dementia are shown in Supplementary Figures 7-12.

Causal effect of dementia on IBD

To explore reverse causality, 12 SNPs were selected from dementia GWAS summary statistics as potential IVs, of which three SNPs associated with potential risk factors were excluded, whilst another SNP was excluded due to palindrome after harmonization of dementia GWAS and IBD GWAS (Supplementary Tables 11 and 12). The intercept term from the MR Egger regression and MR-PRESSO global test demonstrated no significant pleiotropy among the eight independent dementia-associated IVs in IBD GWAS. Importantly, Cochran's *Q* test did not identify significant heterogeneity among the effects of dementia-associated SNPs on IBD (Supplementary Table 10). Therefore, all eight dementia-associated SNPs could be regarded as valid genetic IVs for the ensuing MR analysis. In the reverse MR analysis, the results of IVW, weighted median, and MR Egger uncovered no genetically causal effect of dementia on IBD (Supplementary Table 14). The scatter plot, forest plot, and "leave one out" analysis plot for reverse MR analysis are shown in Supplementary Figure 13.

DISCUSSION

Herein, a two-sample MR approach was employed to comprehensively evaluate the causal relationship between genetically predicted IBD (including UC and CD) and the risk of all-cause dementia and its subtypes, namely, AD, VaD, dementia in other diseases classified elsewhere and unspecified dementia. The results of several methods of MR analyses did not indicate that IBD played a genetic role in the development of dementia (Supplementary Table 13). The findings were further confirmed by conducting a validation analysis in another summary statistics of IBD GWAS (Supplementary Table 13). Likewise, the reverse MR analysis did not support a causal role of all-cause dementia in the risk of IBD (Supplementary Table 14).

IBD is etiologically related to gut microbiota dysbiosis, which induces proinflammatory activity in the gut that is transmitted to the nervous system *via* the microbiome-gut-brain axis, eventually resulting in neuroinflammation[35,36]. Recently, compelling evidence from population-based observational studies has insinuated an association between IBD and an increased risk of dementia. For instance, a longitudinal cohort study including 1742 patients with IBD and 17420 controls from the Taiwanese population demonstrated an increased risk of all-cause dementia following the diagnosis of IBD [hazard ratio (HR) = 2.54, 95%CI : 1.91-3.37], especially at younger ages, compared to controls[9]. Two other retrospective cohort studies from Germany and Denmark reported significant but less pronounced effects of IBD on the risk of dementia[10,37]. A recent systematic review and meta-analysis based on six studies including 2334472 subjects suggested an increased risk for developing dementia in IBD patients (HR = 1.27, 95%CI : 1.10-1.47)[38]. Notably, this result was in line with the findings of other systematic reviews and meta-analyses[39,40]. Furthermore, a large case-control study established systemic inflammation as a potential risk factor for AD, while the latest meta-analysis concluded that chronic elevation in the level of the inflammatory biomarker C-reactive protein was directly correlated with the lifetime risk of developing dementia[41,42]. Interestingly, drugs for the treatment of IBD, such as tumor necrosis factor blocking agents, might be associated with a lower risk of developing AD[41,43]. In a mouse model of IBD induced by sodium dextran sulfate, Kaneko *et al*[44] observed that neutrophils infiltrated the brain parenchyma of AD mice and accelerated amyloid plaque accumulation during acute colitis. Meanwhile, He *et al*[45] found that intestinal inflammation disrupted glymphatic clearance and triggered neuroinflammation, resulting in increased amyloid-β deposition and, ultimately, cognitive impairment.

However, the results of observational studies are largely inconsistent. A longitudinal cohort study of 497775 participants recruited from 2006 to 2010 in the UK Biobank highlighted an HR of 1.14 for incident dementia among IBD patients, but the differences were not significant (95%CI : 0.94-1.39, *P* value = 0.182). Besides, there was no statistically significant difference in the anatomical and tissue-specific volumes of their brains on magnetic resonance images[8]. Furthermore, a recent meta-analysis including seven observational studies (six cohort studies and one case-control study) and 20174 cases did not identify a significant association between UC [relative risks (RR) = 1.16, 95%CI : 0.96-1.41) or CD

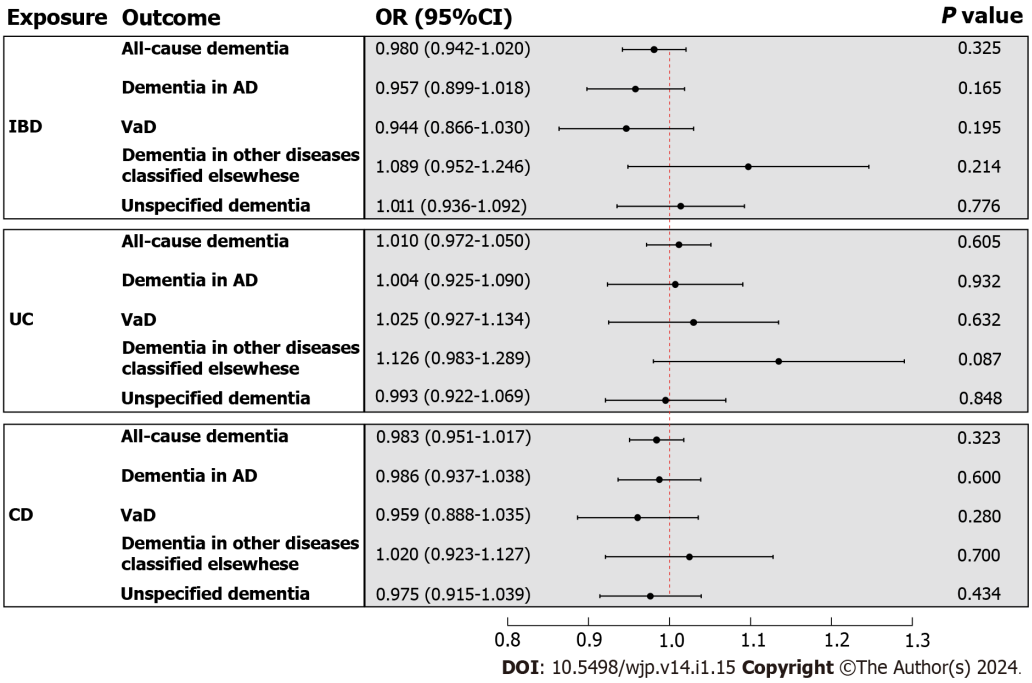

Figure 3 The inverse variance weighted estimates of inflammatory bowel disease on dementia. The exposure is inflammatory bowel disease and subentities including ulcerative colitis and Crohn's disease, and the outcome is all-cause dementia and its subtypes including dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere, and unspecified dementia. The inverse variance weighted estimates, presented as odds ratios (OR) and 95% confidence intervals, are the summed ORs calculated from the individual instrumental variables. IBD: Inflammatory bowel disease; AD: Alzheimer's disease; VaD: Vascular dementia; UC: Comprising ulcerative colitis; CD: Crohn's disease.

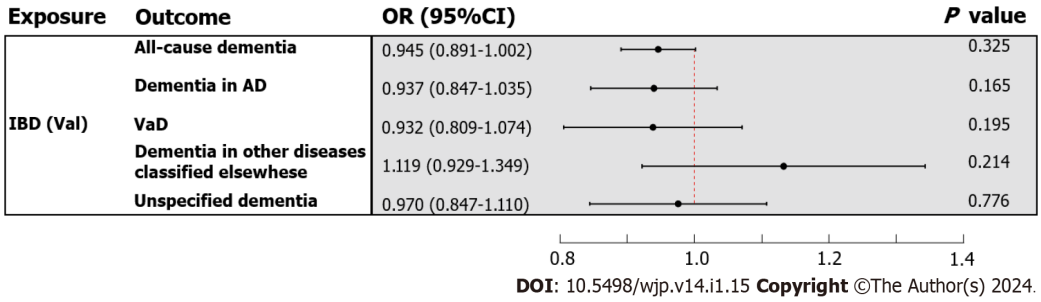

Figure 4 The inverse variance weighted estimates of inflammatory bowel disease (validation) on dementia. The exposure is inflammatory bowel disease (validation), and the outcome is all-cause dementia and its four subtypes. The inverse variance weighted estimates, presented as odds ratios (OR) and 95% confidence intervals, are the summed ORs calculated from the individual instrumental variables. IBD: Inflammatory bowel disease; AD: Alzheimer's disease; VaD: Vascular dementia.

(RR = 1.17, 95%CI : 0.84-1.62] and the risk of AD[43]. Another meta-analysis encompassing nine studies, including seven cohort studies, one cross-sectional study, and one case-control study, described that a previous diagnosis of IBD did not influence the risk of subsequent all-cause dementia (RR = 1.32, 95%CI : 0.98-1.77) and AD (RR = 1.62, 95%CI : 0.96-2.76) [46]. Of note, subgroup analysis based on the study of the above meta-analysis implied that IBD increased the risk of all-cause dementia but not AD in the cohort study, UC increased the risk of subsequent all-cause dementia and AD, and CD only increased the risk of all-cause dementia[46]. So far, the causal relationship between IBD and dementia has not been established.

In the present MR study, no causal relationship was discovered between genetically predicted IBD and subentities and all-cause dementia and its four subtypes, which contradicts the results of the above-mentioned studies implicating an association between IBD and dementia (Supplementary Table 13). What's more, our finding is not in agreement with that of Guo *et al*[17]. It is worthwhile emphasizing that their MR study had some limitations, including sample selection bias in the selected AD dataset that included older clinically diagnosed patients but excluded patients with shortened life expectancy due to IBD-related comorbidities, thus reducing or even reversing the MR estimated effect. In addition, Guo *et al*[17] used univariable MR to estimate the causal roles of UC and CD in AD, which might have led to horizontal pleiotropy due to IV overlapping. Excitingly, a recent study published in Neurology with a large sample size carried out an observational analysis combined with MR analysis corroborated our findings. The observational analysis using data from the United Kingdom Clinical Practice Research Datalink described that the overall incidence of AD was higher in

patients with IBD (HR = 1.17, 95%CI : 1.15-1.19, *P* value = 2.1 × 10^{-4}). Nonetheless, their MR analysis yielded no association between IBD and AD, suggesting that confounding factors may compromised the observed association[47]. Observational studies are susceptible to inherent methodological shortcomings, such as bias and confounding variables. For instance, the recruitment of the majority of participants from Medicare databases or inpatient registries could have increased the risk of selection bias. Surveillance bias also may increase the likelihood of a positive correlation. The gut microbiota, obesity, and other factors have been established as risk factors for both IBD and dementia in previous studies [5,48-50]. On the other side, the use of medications such as proton pump inhibitors and tumor necrosis factor blocking agents might interfere with the results when assessing the association between IBD and dementia[51,52]. At the same time, shared genetic components, such as PPARG and NOS2, could also increase genetic susceptibility to both diseases [53]. Furthermore, meta-analyses typically exhibit statistical heterogeneity arising from differences in study populations, study designs, and inclusion criteria. Finally, two large-scale GWAS comprehensively evaluated the genetic overlap between cognitive traits or AD and gastrointestinal disorders, with neither detecting significant genetic overlap and correlation with IBD[54,55].

A major strength of our study is that the causal effects between IBD and the risk of all-cause dementia and its six subtypes were assessed by utilizing a two-sample MR design, which mitigates limitations inherent noted in observational studies, including measurement error, residual confounding, and reverse causation bias. This MR study incorporated independent and robust genetic variants as IVs, not only to limit the effect of LD and weak instrument bias but also to circumvent the time-consuming and labor-intensive challenges generally encountered in observational studies (Supplementary Tables 2-9). Furthermore, our methodology utilized an iterative approach that is conservative and resilient against the influence of outliers (Supplementary Table 10). A series of pleiotropy and heterogeneity tests were also conducted to ensure the consistency of causal estimates and to confirm the robustness of the present findings (Supplementary Table 10). Finally, our findings were validated through a second, largely independent GWAS that yielded concordant results (Supplementary Table 13). Nevertheless, our study has several limitations. Despite the strength of all selected IVs, they collectively accounted for only 6.75% of the variance in the IBD sample (Supplementary Table 2). In addition, the datasets used in this study were based on subjects of European ancestry (Table 1), thereby restricting the generalizability of our observations to other ethnicities.

CONCLUSION

Herein, no association was identified between the risk of all-cause dementia and genetically predicted IBD. While there is no clear genetic evidence to support IBD as a risk factor for dementia, the possibility of a potential association between the two diseases cannot be ruled out. Further research is necessitated to identify factors that exert a causal effect on the development of dementia.

ARTICLE HIGHLIGHTS

Research background

Evidence from observational studies has not been able to establish a causal link between inflammatory bowel disease (IBD) and dementia.

Research motivation

Gut homeostasis is implicated in many psychiatric and neurological disorders through the bidirectional microbiome-gut-brain axis.

Research objectives

The aim was to find out whether IBD was causally related to all-cause dementia.

Research methods

Based on the publicly available genome-wide association study data from large population, multiple methods of Mendelian randomization (MR) were performed to estimate the effects of genetically predicted IBD on dementia, and inverse variance weighted was considered as the primary analysis. MR egger intercept, MR pleiotropy residual sum and outlier, and Cochran's *Q* test were used to test pleiotropy and heterogeneity.

Research results

No evidence for a causal effect of IBD on dementia risk was found in three MR methods of MR, which was consistent with validation analyses. Furthermore, MR analysis suggested that IBD and subentities did not causally affect all-cause dementia and its four subtypes.

Research conclusions

Our MR study found no association between the risk of all-cause dementia and genetically predicted IBD.

Research perspectives

Genetically predicted IBD is not associated with all-cause dementia risk, and dementia prevention interventions for patients with IBD can be similar to those in healthy populations.

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FOOTNOTES

Co-corresponding authors: Qin Du and Guo-Chun Lou.

Author contributions: Liao OL designed the study, acquired and analyzed data, and wrote the manuscript; Xie SY contributed to conceptualization and methodology; Ye J contributed to writing review and editing; Du Q and Lou GC designed, refined the study protocol, and supervised this study. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Du Q and Lou GC contributed equally to this work as co-corresponding authors. Firstly, both researchers were co-principal investigators of this study and have made equally significant contributions throughout the study process. Designating them as co-corresponding authors accurately reflects the allocation of responsibilities related to completing the study. Secondly, both researchers shared responsibility for ensuring the authenticity of the manuscript's content and credibility of its conclusions, as well as handling communication and consultation work. Therefore, we believe that designating Du Q and Lou GC as co-corresponding authors is appropriate, reflecting the collaborative spirit and equal contributions of our team.

Institutional review board statement: No institutional review board statement is required since this study was based on public databases.

Clinical trial registration statement: The data was from large sample size GWAS, and no Clinical Trial Registration Statement is required.

Informed consent statement: The data was from large sample size genome-wide association study, and no informed consent statement is required.

Conflict-of-interest statement: The authors have no conflict of interest to report.

Data sharing statement: The summary statistics of IBD, UC, and CD GWAS (IIBDGC) is available at https://gwas.mrcieu.ac.uk/datasets/ieu-a-31, https://gwas.mrcieu.ac.uk/datasets/ieu-a-32, and https://gwas.mrcieu.ac.uk/datasets/ieu-a-30, respectively. The summary data for the second IBD GWAS (UK Biobank) is provided at https://cnsgenomics.com/data/wu_et_al_2021_nc/5_IBD_summary. The summary statistics of all-cause dementia, dementia in AD, VaD, dementia in other diseases classified elsewhere, and unspecified dementia GWAS (FinnGen) is available at https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_DEMENTIA.gz, https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_ALZHDEMENT.gz, https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_VASCDEM.gz, https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_DEMINOTH.gz, and https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_DEMNAS.gz, respectively. All datasets were downloaded on 2023-7-11.

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