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SHORT COMMUNICATION

Causal links between *Helicobacter pylori* infection and Alzheimer's disease: Insights from genome-wide summary data-based Mendelian randomization

Yuan Xin Hou[1,2], Ao Wang[1], and Ke Yi[1,2]*

[1]Key Laboratory of Obstetrics and Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China

[2]Department of Operation Management, Hubei Provincial Key Laboratory of Occurrence and Intervention of Rheumatic Diseases/Hubei Provincial Clinical Research Center for Nephrology, Minda Hospital of Hubei Minzu University, Hubei Minzu University, Enshi, Hubei, China

Abstract

Introduction: *Helicobacter pylori* infection is associated with various illnesses like Alzheimer's disease (AD).

Objective: The purpose of this work is to utilize Mendelian randomization (MR) methods to examine the possible link between AD and *H. pylori* infection.

Methods: We utilized information from the Finngen database and the UK Biobank for MR analysis. Six antibodies related to *H. pylori* were assessed for their association with AD. The MR analysis involved two-sample methods, while generalized summary data-based MR (GSMR) was employed to analyze genetic data for a robust causal inference.

Results: The two-sample MR investigation exhibited a strong link among AD and anti-*H. pylori* UREA antibodies, with an odds ratio (OR) of 1.076 (95% confidence interval [CI] = 1.010 – 1.147; p=0.024). Similarly, GSMR confirmed this relationship, showing an OR of 1.071 (95% CI = 1.004 – 1.143; p=0.038). No notable correlations were seen with other antibodies.

Conclusion: Our findings suggest that *H. pylori* infection may be related to a higher likelihood of AD development, particularly through anti-*H. pylori* UREA antibodies.

Keywords: *Helicobacter pylori*; Infection; Alzheimer's disease; Mendelian randomization; Genome-wide summary data-based Mendelian randomization

***Corresponding author:**
Ke Yi
(yike@scu.edu.cn)

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1. Introduction

The Gram-negative, spiral-shaped bacterium *Helicobacter pylori* is commonly found in the human stomach and is widely recognized as a primary pathogen responsible for chronic gastritis and peptic ulcers.[1,2] In addition, a substantial correlation exists between *H. pylori* infection and the development of stomach cancer.[3] While the bacterium's effects have traditionally been associated with the gastrointestinal system, recent studies have begun to explore its potential links to neurological disorders.[4,5]

Alzheimer's disease (AD) is a neurodegenerative illness that causes memory loss and gradual decline in cognitive abilities, severely compromising patients' day-to-day

activities and overall life quality.[6] AD's clinical importance is highlighted by its high prevalence and the substantial burden it places on affected individuals and their families.[7,8] Understanding the potential risk factors for AD becomes increasingly imperative for guiding early intervention and therapeutic strategies as the world's population ages.[9,10]

Current investigation on the correlation between AD and infection is increasingly highlighting *H. pylori*'s potential role in AD's development.[11,12] Meta-analysis findings reveal that *H. pylori* infection raises AD risk, with an OR of 1.40 in these patients, indicating a correlation between the two.[13] In addition, co-infection with periodontal pathogens further exacerbates this risk, as seen in studies where specific pathogens interact synergistically with *H. pylori* to influence AD incidence.[14] Mechanistically, *H. pylori* can cause increased β-amyloid deposition in the brain by altering the gut flora and causing chronic low-grade inflammation.[15] Through the oropharyngeal olfactory route, the bacteria's metabolites can reach the central nervous system, promoting neurodegenerative processes.[16] Moreover, the buildup of β-amyloid plaques, which are closely linked to the pathological features of AD, may be facilitated by the chronic inflammatory state linked to *H. pylori* infection.[17] However, numerous studies have predominantly employed observational designs, which are inherently constrained by potential biases and confounding variables. In addition, variations in sample selection may limit the result's generalizability, as certain populations could not fully reflect the larger population. Furthermore, reliance on specific instrumental variables (IVs) in prior analyses may undermine the validity of causal inferences. It is imperative that these methodological constraints are addressed to improve our comprehension of the intricate relationship between infection and AD.

To elucidate the correlation between them, our study employed Mendelian randomization (MR) analysis, which employs genetic variations as key variables to deduce causal relationships. A significant advantage of MR is its capacity to simulate the conditions of a randomized controlled trial, thereby addressing the constraints of observational studies.[18] Weighted median estimation, inverse variance weighting (IVW), weighted mode, and MR-Egger regression are examples of common two-sample MR techniques. These approaches are used to improve the findings' reliability as well as robustness. Generalized summary data-based MR (GSMR) presents distinct advantages over traditional MR. By taking into account linkage disequilibrium (LD) among genetic variants, GSMR improves analytical efficiency.[19] Furthermore, it employs or heterogeneity in dependent instruments (HEIDI) test to identify instrumental outliers and exclude pleiotropic single-nucleotide polymorphisms (SNPs).[20] Utilizing genetic data, MR analysis provides compelling evidence that the pathogenesis of AD may be directly influenced by *H. pylori* infection. This methodology not only enriches our comprehension of the etiological role of the infection in AD but also holds substantial promise for informing future therapeutic interventions.

2. Materials and methods

2.1. Data source

The data on *H. pylori* infection in this study is sourced from the literature by Butler-Laporte *et al.*[21] We examined six antibodies related to *H. pylori* infection: Anti-*H. pylori* CagA, Catalase, GroEL, OMP, UREA, and VacA, which correspond to genome-wide association studies (GWAS) database IDs GCST90006911 through GCST90006916. The study sample is composed of European ancestry people, with sample size details presented in Table 1. IVs for AD were extracted from the Finngen database, comprising 11,755 AD cases and 441,978 European ancestry controls. All AD cases adhered to the criteria set by the International Classification of Diseases (ICD-10).

2.2. MR analysis

To determine the correlation among *H. pylori* infection and AD, we conducted GSMR and a two-sample MR investigation. SNPs were analyzed as IVs.[22] During the whole procedure, it is crucial to validate three important hypotheses to ensure optimal outcome accuracy.[23] The first step involves confirming that the chosen IVs exhibit a direct association with the *H. pylori* infection. Second, it is essential to establish the IVs' independence from potential confounders impacting both exposure and outcome. Finally, ensuring that the IVs affect AD solely through their influence on the risk factor.

We primarily employed the IVW approach as our MR analysis strategy. To fully evaluate the possible association,

Table 1. Baseline characteristics for participants

Exposure/ Outcome	Data source	Phenotype	Sample size*
Alzheimer's disease	The FinnGen consortium	Alzheimer's disease	11,755/441,978
Antibodies against *H. pylori*	Butler-Laporte *et al.*[21]	CagA	985
		Catalase	1558
		GroEL	2716
		OMP	2640
		UREA	2251
		VacA	1571

Note: *Sample size shown as a total number for quantitative traits and cases/controls for binary traits.

we also used four more useful techniques: MR-Egger, weighted median, weighted mode, and simple mode. SNPs with genome-wide significance ($p<5 \times 10^{-6}$) were selected as IVs for both anti *H. pylori* antibodies and AD. The F-statistic for each SNP was calculated to assess the strength of the selected instruments. SNPs with an F-statistic <10 were excluded to avoid bias from weak instruments. The LD threshold was established at $r^2 < 0.001$, with a genetic distance of 10,000 kb, to guarantee SNP independence. We computed the F-statistic for the selected SNPs, applying a threshold of >10 to evaluate the strength of the IVs. To evaluate pleiotropy and heterogeneity, we used Cochran's Q statistic as well as the MR-Egger test, respectively.

2.3. GSMR analysis

GSMR is an advanced analytical method that integrates genome-wide summary data from multiple independent studies, flexibly utilizing several relatively independent IVs for MR analysis. This approach aims to analyze the causal links among various illnesses and exposure determinants, providing more reliable inference results.[19] For the genetic instruments associated with anti-*H. pylori* antibodies, we employed a clumping algorithm to identify SNPs that are genome-wide significant for each trait, applying an LD threshold of $r^2 = 0.001$ and a significance threshold of $p<5 \times 10^{-6}$. The reference for LD estimation was derived from the 1000 Genomes Project (1000G) phase 3 European samples. In the reverse analysis, we selected independent SNPs from the GWAS summary statistics for AD by establishing a LD threshold of $r^2 < 0.001$ and a significance threshold of $p<5 \times 10^{-6}$. We established a HEIDI outlier threshold of 0.01 to exclude instruments with significant putative pleiotropic effects.

2.4. Sensitivity analyses

We carried out a comprehensive set of sensitivity tests to confirm the causal impact of *H. pylori* infection on AD. Cochran's Q statistic was applied to analyze any possible heterogeneity in the data.[24] Horizontal pleiotropy was analyzed by employing the MR-Egger intercept analysis. Furthermore, by systematically excluding each SNP, a leave-one-out investigation was carried out to see whether any single SNP had a considerable influence on the results. RStudio and R (version 4.2.0) were used for all analyses, including the R packages gsmr, TwoSampleMR, and MR-PRESSO.

3. Results

3.1. Causal effect of *H. pylori* infection on AD

In our initial investigation, we utilized GSMR to examine the correlation among AD and six anti-*H. pylori* antibodies. Anti-*H. pylori* UREA was found to raise AD risk (odds ratio [OR] = 1.071; 95% confidence interval (CI) = 1.004 – 1.143; p=0.038) (Figure 1).

Anti-*H. pylori* UREA and AD were found to be similarly associated in the two-sample MR analysis, with an OR of 1.076 (95% CI = 1.010 – 1.147; p=0.024) (Figure 2). Detailed information on F-values as well as LD independent SNPs related to exposure (*H. pylori* antibodies) can be found in Tables S1-S6 (available in Supplementary File).

3.2. Reverse MR analysis

In the reverse MR study exploring the correlation among *H. pylori* and AD, both the two-sample MR and GSMR analyses failed to identify a meaningful correlation among the two. These results indicate that AD does not appear to influence *H. pylori* infection risk. Further details are presented in Tables S7 and S8 (Supplementary File).

3.3. Sensitivity analysis

The assessment of *H. pylori* infection's effect on AD revealed no substantial heterogeneity, as per the Cochran's Q test. The MR-Egger intercept test also found no proof of horizontal pleiotropy. Scatter plots demonstrated the impact of the infection on AD across five MR approaches, with a positive slope indicating a direct correlation (Figure S1 in Supplementary File). Furthermore, as indicated by leave-one-out analysis, specific SNPs are unlikely to significantly influence the causal estimates (Figure S2 in Supplementary File). Together, these findings strengthen the robustness of the observed associations.

4. Discussion

This study explored the causal link of *H. pylori* infection with AD. Employing MR techniques, a substantial positive association was found between AD and anti-*H. pylori* UREA antibodies, with an OR of 1.071 (95% CI = 1.004 – 1.143, p=0.038). This result highlights that higher levels of these antibodies may correlate with a higher chance of AD development, thereby offering new insights for clinical and public health interventions. Importantly, the notable association with anti-*H. pylori* UREA underscores its distinct function in AD pathogenesis, which may inform future therapeutic and preventive approaches to mitigate the impact of this neurodegenerative disorder.

The strong correlation between the two suggests that *H. pylori* infection is critical in the etiology of AD. Investigations indicated that *H. pylori* can induce chronic inflammation and immune responses, potentially resulting in neural damage.[25] Moreover, the infection may release neurotoxic substances that impair neuronal function and survival, thereby accelerating cognitive decline.[26] Although

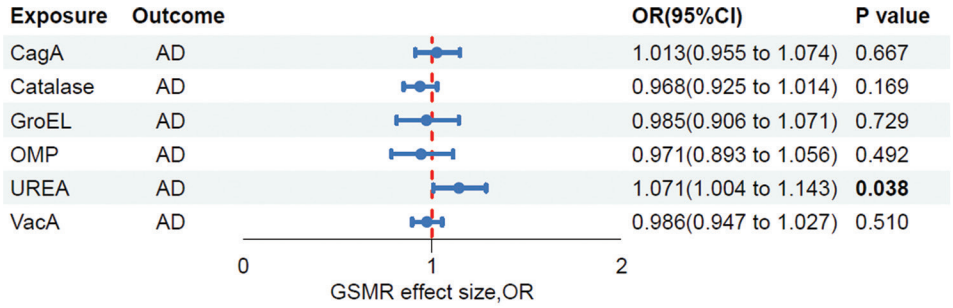

Figure 1. Forest plot for the GSMR effect of antibodies against *Helicobacter pylori* on Alzheimer's disease
Note: *p*-value in boldface indicates anti-*H. pylori* UREA was found to be significantly associated with an increased risk of AD in GSMR.
Abbreviations: AD: Alzheimer's disease; CI: Confidence interval; GSMR: Generalized summary data–based Mendelian randomization; OR: Odds ratio.

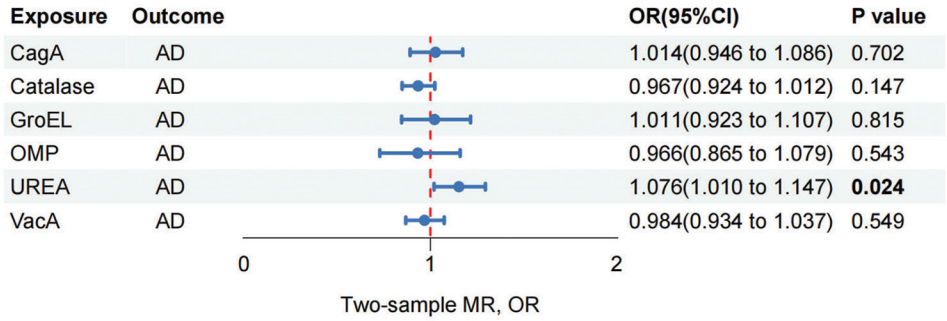

Figure 2. Forest plot for two-sample Mendelian randomization effect of antibodies against *Helicobacter pylori* on Alzheimer's disease
Note: *p*-value in boldface indicates anti-*H. pylori* UREA was found to be significantly associated with an increased risk of AD in Two-sample MR.
Abbreviations: AD: Alzheimer's disease; CI: Confidence interval; OR: Odds ratio.

our reverse MR analysis found no significant impact of AD on *H. pylori* infection, this does not diminish the potential of *H. pylori* as an intervenable risk factor for AD. Therefore, further investigation into the causal link and underlying mechanisms between AD and *H. pylori* is essential to enhance prevention and treatment strategies for AD.

In this study, we identified a strong correlation among AD and anti-*H. pylori* UREA antibodies, which aligns with prior research examining the correlation between neurodegenerative disorders and *H. pylori* infection.[27-29] Numerous studies indicate that this infection may raise AD risk by inducing chronic inflammation and immune responses that adversely affect neuronal function and viability.[30,31] However, the discrepancies in findings across various studies necessitate further examination. For example, some investigations have not demonstrated a direct correlation among AD and *H. pylori* infection,[32] potentially attributable to variations in sample selection, study design, and methodologies. In addition, differences in *H. pylori* strains may result in distinct pathogenic mechanisms, thereby influencing the strength of the association with neurodegenerative diseases. Factors such as individual genetic predispositions, environmental influences, and lifestyle choices may also contribute to these inconsistent results. Consequently, future research should account for these variables to further elucidate the precise role played by *H. pylori* infection in the etiology of neurodegenerative disorders and the inherent complexities involved.

A significant advantage of this work is the use of advanced MR techniques, specifically GSMR and two-sample MR. These methodologies utilize information from large-scale genome-wide association investigations, thereby enhancing both the statistical power and reliability of the findings. In addition, GSMR facilitates the flexible use of multiple independent IVs, resulting in more robust causal inferences. The implementation of these techniques establishes a solid theoretical foundation and analytical framework for investigating the correlation among AD and *H. pylori* infection.

Despite the strengths of this study, several limitations must be acknowledged. First, reliance on specific SNPs as IVs may restrict the generalizability of the findings.

If these SNPs do not adequately represent the genetic architecture of *H. pylori* infection, the validity of the causal inferences could be compromised. Second, the potential for residual confounding remains a significant concern, as unmeasured factors may simultaneously influence both AD and *H. pylori* infection, complicating result interpretation. In addition, despite the strengths of MR in reducing confounding, it is important to note that potential confounders, such as microbial communities and lifestyle factors, may still affect both AD and *H. pylori* infection. These factors were not included in our analysis, which could influence the explanatory power. Moreover, the fact that the population in this study is exclusively European limits the generalizability of the findings to other racial and ethnic groups. It remains unclear whether the results would hold true for populations with different genetic backgrounds or environmental exposures. To shed light on the interactions between *H. pylori* and neurodegenerative illnesses, future studies should employ bigger, more varied cohorts and longitudinal data.

5. Conclusion

This investigation indicates a strong correlation among AD and anti-*H. pylori* UREA antibodies, suggesting a potential role of *H. pylori* infection in the etiology of AD. These findings suggest *H. pylori* as a modifiable risk factor, emphasizing the necessity for additional investigations to clarify causal mechanisms and address existing limitations.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization: Ke Yi
Formal analysis: Yuan Xin Hou, Ke Yi
Methodology: Yuan Xin Hou, Ke Yi
Writing – original draft: Yuan Xin Hou, Ao Wang
Writing – review & editing: Yuan Xin Hou, Ao Wang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Original data generated and analyzed during this study are included in this published article or supplementary material. Further inquiries can be directed to the corresponding author.

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