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ORIGINAL RESEARCH

No Causal Relationship Between Helicobacter Pylori Infection and Rosacea: A 2-Sample Mendelian Randomization Study

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Background: Previous studies have shown that patients with rosacea have a higher prevalence of Helicobacter pylori (H. pylori) infection. However, whether H. pylori infection contributes to the development of rosacea remains unclear, and no genetic association studies between the two have been conducted to date. Genome-wide association studies (GWAS) database is a public resource that stores and shares data that aims to identify genetic links to complex diseases, physiological traits, or drug responses. Mendelian randomization (MR) is an epidemiological approach to investigate the effect of the exposure on a specific outcome. Due to the random assortment of single nucleotide polymorphisms (SNPs), they are less likely to be influenced by confounding factors. The MR design can mitigate residual confounding and reverse causation, strengthening the causal inference of the exposure's association with the outcome.

Methods: We use GWAS database and MR design to assess the causal relationship between H. pylori infection and rosacea. Inverse variance weighted (IVW) was the main method in this study, along with MR Egger, simple mode, weighted median, and weighted mode. GWAS data for H. pylori infection and rosacea were retrieved from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) Open GWAS, GWAS catalog and FinnGen database.

Results: We used H. pylori infection as exposure data and rosacea as outcome data, and all p-values in MR analysis were all greater than 0.05. These conclusions were confirmed by sensitivity analysis.

Conclusion: Our MR analysis provides no evidence of a causal relationship between H. pylori infection and rosacea. This indicates that patients with rosacea may not need routine testing for H. pylori infection and routine eradication of H. pylori may not benefit rosacea patients.

Keywords: Helicobacter pylori infection, rosacea, Mendelian randomization study

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Introduction

Helicobacter pylori (H. pylori)[1] is a bacterium known for colonizing the stomach lining and causing gastrointestinal conditions such as chronic gastritis, peptic ulcers, and gastric cancer, has also been investigated for its potential role in extra-gastric diseases,[2] including rosacea.[3] While the exact relationship between H. pylori and rosacea remains under investigation, the evidence suggests that H. pylori may play a role in the pathogenesis or exacerbation of rosacea in certain individuals.[4] Further research is needed to clarify the mechanisms and establish whether H. pylori eradication should be considered as part of the treatment strategy for rosacea patients with concurrent H. pylori infection.

Previous studies have shown that patients with H. pylori infection may have an increased risk of rosacea,[5] and the cure of H. pylori led to partial regression of the skin symptoms in rosacea patients.[3,6] However, whether there is a potential link between rosacea and H. pylori infection remains uncertain, and no genetic association studies between the two have been conducted up to now.

GWAS database is a public resource that stores and shares data. By analyzing associations between genomic variants and specific traits or diseases across large populations, GWAS aims to identify genetic links to complex diseases,

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physiological traits, or drug responses. Mendelian randomization (MR) is an epidemiological approach that employs genetic variants as instrumental variables to proxy for the exposure of interest, thereby investigating the effect of the exposure on a specific outcome.[7,8] Due to the random assortment of single nucleotide polymorphisms (SNPs), they are less likely to be influenced by confounding factors. The MR design can mitigate residual confounding and reverse causation, strengthening the causal inference of the exposure's association with the outcome. In this study, we conducted a two-sample MR analysis to assess the causal relationship between H. pylori infection and rosacea.

Materials and Methods

Data Sources

We retrieved GWAS data for H. pylori infection from MRC-IEU Open GWAS (https://gwas.mrcieu.ac.uk) and GWAS catalog (https://www.ebi.ac.uk/gwas/), and the GWASID were "ieu-b-4905" and "ebi-a-GCST90006910", and we call them H. pylori infection (ieu) and H. pylori infection (ebi) separately in this study. Data for rosacea were retrieved from FinnGen database (https://r12.finngen.fi/), and the GWASID were "finngen_R12_L12_ROSACEANAS". The study population consisted exclusively of individuals with European ancestry, potentially limiting the generalizability of our findings.

Instrumental Variants (IVs) Selection

We use Linkage-disequilibrium pruning to remove the influence of highly correlated single nucleotide polymorphisms (SNPs). These SNPs were clumped based on the linkage disequilibrium (LD) structure of European ancestry ($r2 < 0.001$, 10000 kb). We selected SNPs with $P < 5\times10^{-8}$ and found that the H. pylori dataset contained fewer than 3 SNPs in the MR analysis. Therefore, we adjusted the SNPs screening threshold to $P < 5\times10^{-6}$. Additionally, the F-statistics was calculated using the formula $F = [(n-k-1)/k] \times [R^2/(1-R^2)]$, where an F-value > 10 indicated sufficient strength of the instrumental variables. For datasets missing the effect allele frequency (eaf), the formula $F = \beta^2/SE^2$ was applied for calculation. Conceptual framework diagram was shown in Figure 1.

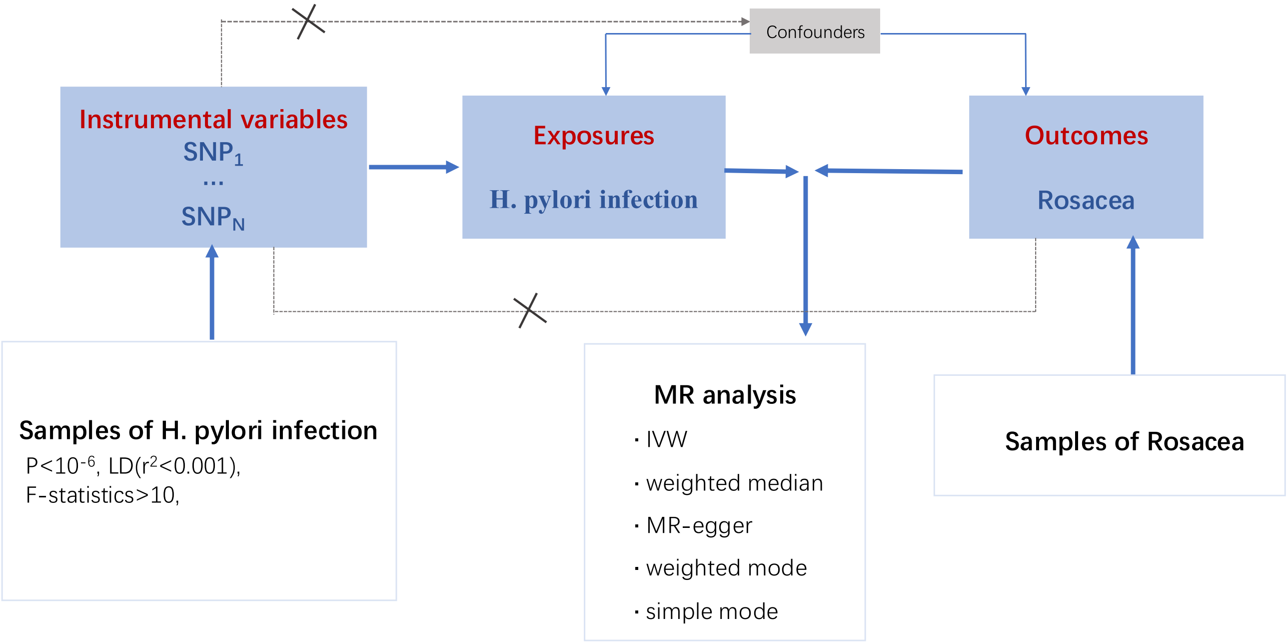


Figure 1 The frame chart of the MR analysis.

Finally, 12 SNPs associated with “H. pylori infection (ieu)” and 11 SNPs related to “H. pylori infection (ebi)” were retrieved from GWAS. After removing SNPs for being unavailable or being palindromic with intermediate allele frequencies (rs7281117), there were 12 SNPs left as IVs for “H. pylori infection (ieu)” and 10 for “H. pylori infection (ebi)”.

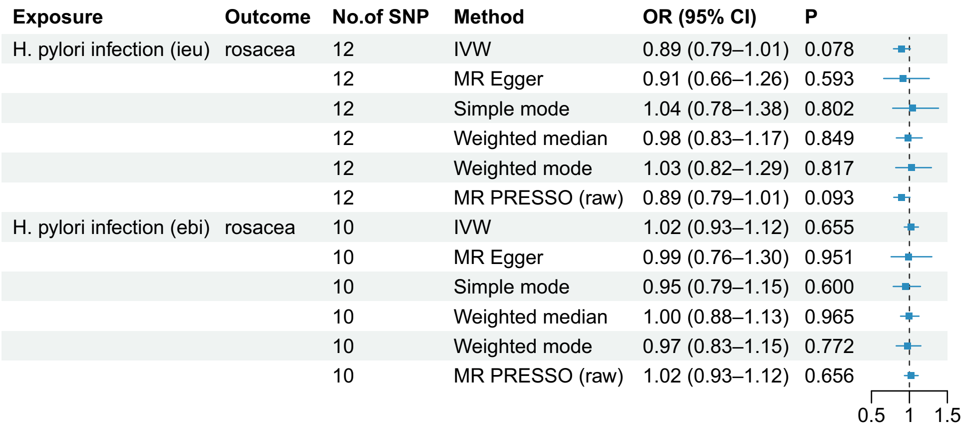
Statistical Analysis

Inverse-variance weighted (IVW) method was the main method we used in this study. To make the results more accurate, MR Egger, simple mode, weighted median, and weighted mode were also performed by using the “TwoSampleMR” package in R (version 4.2.3). We used MR-PRESSO test to eliminate outliers and the heterogeneity was also carried out by Cochran’s Q test. And the reliability of the results is also proved by the method of leave-one-out.

Results

We conducted an MR analysis between H. pylori infection and rosacea. In the H. pylori infection (ieu) group, we identified 12 SNPs. All instrumental variables showed sufficient strength (F > 10), comfortably exceeding the weak instrument threshold. The IVW results indicated no genetic association between H. pylori infection and rosacea (OR = 0.894, 95% CI 0.70–1.013, P = 0.078). In the H. pylori infection (ebi) group, we obtained 10 SNPs. Similarly, the IVW analysis showed no significant genetic association (OR = 1.021, 95% CI 0.932–1.119, P = 0.655). Results were similar in the analysis based on the weighted median method: H. pylori infection (ieu) (OR = 0.98, 95% CI 0.83–1.17, P = 0.849), H. pylori infection (ebi) (OR = 1.0, 95% CI 0.88–1.13, P = 0.965). Meanwhile, results based on the simple mode: H. pylori infection (ieu) (OR = 1.04, 95% CI 0.78–1.38, P = 0.802), H. pylori infection (ebi) (OR = 0.95, 95% CI 0.79–1.15, P = 0.600), and results based on the weighted mode: H. pylori infection (ieu) (OR = 1.03, 95% CI 0.82–1.29, P = 0.817), and H. pylori infection (ebi) (OR = 0.97, 95% CI 0.83–1.15, P = 0.772). They all contribute to enhancing the credibility of this causal inference. The main results of this study are shown in Figure 2. And two scatters are shown in Figures 3 and 4.

Additionally, the results of heterogeneity and pleiotropy are presented in Table 1. As for heterogeneity, no statistically significant findings were observed in either the H. pylori infection (ieu) group (p = 0.4840) or the H. pylori infection (ebi) group (p = 0.5188). As for the MR-Egger pleiotropy test, no statistically significant results were detected in either the H. pylori infection (ieu) group (p = 0.3908) or the H. pylori infection (ebi) group (p = 0.4308), indicating the reliability of the findings. Furthermore, MR-PRESSO did not identify any outliers, confirming the stability and robustness of the results.



Exposure	Outcome	No.of SNP	Method	OR (95% CI)	P
H. pylori infection (ieu)	rosacea	12	IVW	0.89 (0.79–1.01)	0.078
		12	MR Egger	0.91 (0.66–1.26)	0.593
		12	Simple mode	1.04 (0.78–1.38)	0.802
		12	Weighted median	0.98 (0.83–1.17)	0.849
		12	Weighted mode	1.03 (0.82–1.29)	0.817
		12	MR PRESSO (raw)	0.89 (0.79–1.01)	0.093
H. pylori infection (ebi)	rosacea	10	IVW	1.02 (0.93–1.12)	0.655
		10	MR Egger	0.99 (0.76–1.30)	0.951
		10	Simple mode	0.95 (0.79–1.15)	0.600
		10	Weighted median	1.00 (0.88–1.13)	0.965
		10	Weighted mode	0.97 (0.83–1.15)	0.772
		10	MR PRESSO (raw)	1.02 (0.93–1.12)	0.656

Figure 2 Forest plot of MR results.

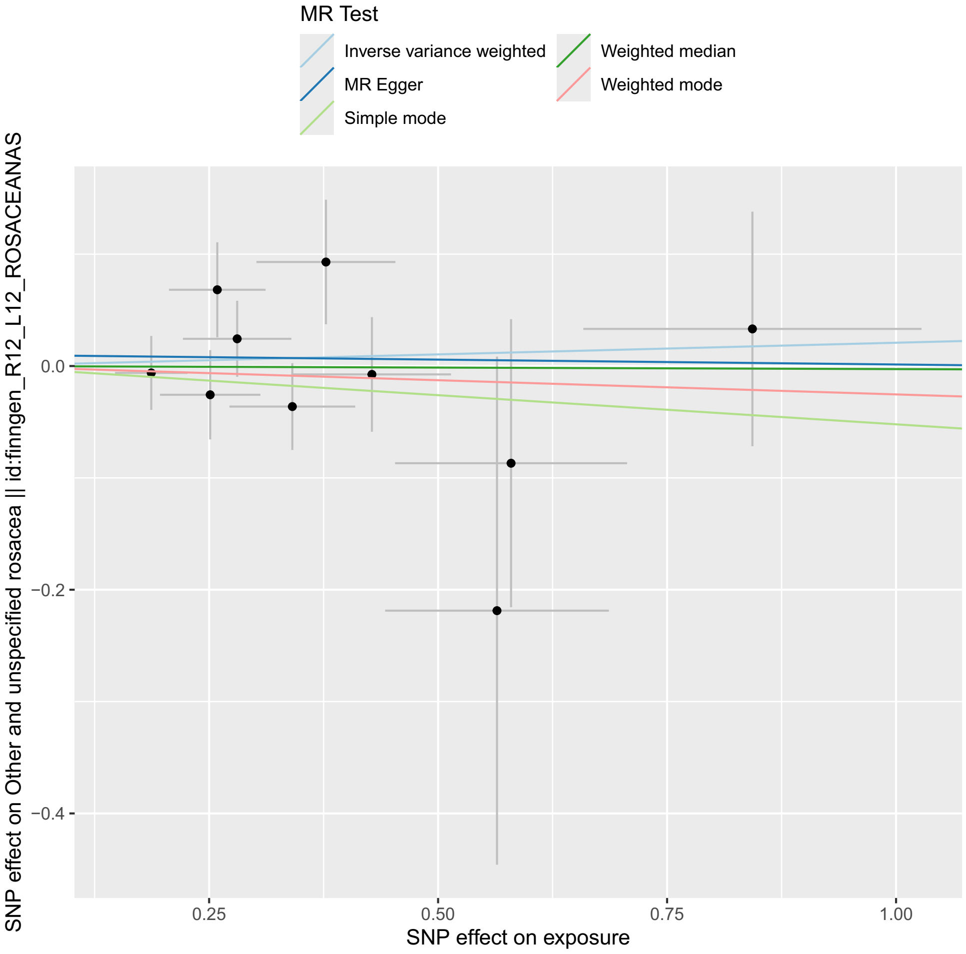


Figure 3 Scatterplot of SNP potential effects of H. pylori infection ebi-a-GCST90006910 to rosacea.

Discussion

Rosacea is a common, sometimes hereditary, chronic inflammatory facial skin condition that primarily affects adults, mostly in women.[9,10] Although the underlying causes of rosacea are not fully understood, several studies have suggested there is an association with H. pylori infection.[11,12] Some studies have also observed that symptoms in rosacea patients can improve following the eradication of H. pylori.[3,6,13] It has been reported that H. pylori can stimulate the immune system to produce a large number of inflammatory mediators, resulting in the occurrence and aggravation of rosacea inflammation.[14,15] H. pylori increases the synthesis of oxygen metabolites,[15,16] such as superoxide and pro-inflammatory cytokines, which can affect skin physiology, including vasodilation, inflammation and immune regulation.[14,17] And TLR2 and TLR4 can activate Toll-like receptors, leading to NF-κB pathway activation, along with nonspecific release of chemokines such as IL-8. Additionally, H. pylori infection may alter neuropeptide levels, impairing the Nrf2 antioxidant pathway and amplifying local inflammatory responses.[18,19] These mechanisms could potentially exacerbate rosacea. However, these shared pathways only indicate correlation and cannot establish a causal relationship.

In our study, we found that all methods used in this study suggested no association between H. pylori infection and rosacea, align with a previously published meta-analysis[20] concluded that there was weak correlation association between rosacea and H. pylori infection and that no significant improvement in rosacea skin symptoms was observed after H. pylori treatment. It seems like H. pylori is an aggravating factor rather than a cause. Moreover, we postulated that the lifestyle of H. pylori-infected individuals might potentially exert an influence on the outcomes of previous studies. We employed MR methodology, which effectively mitigated the influence of confounding factors through the utilization of genetic variants as instrumental variables.

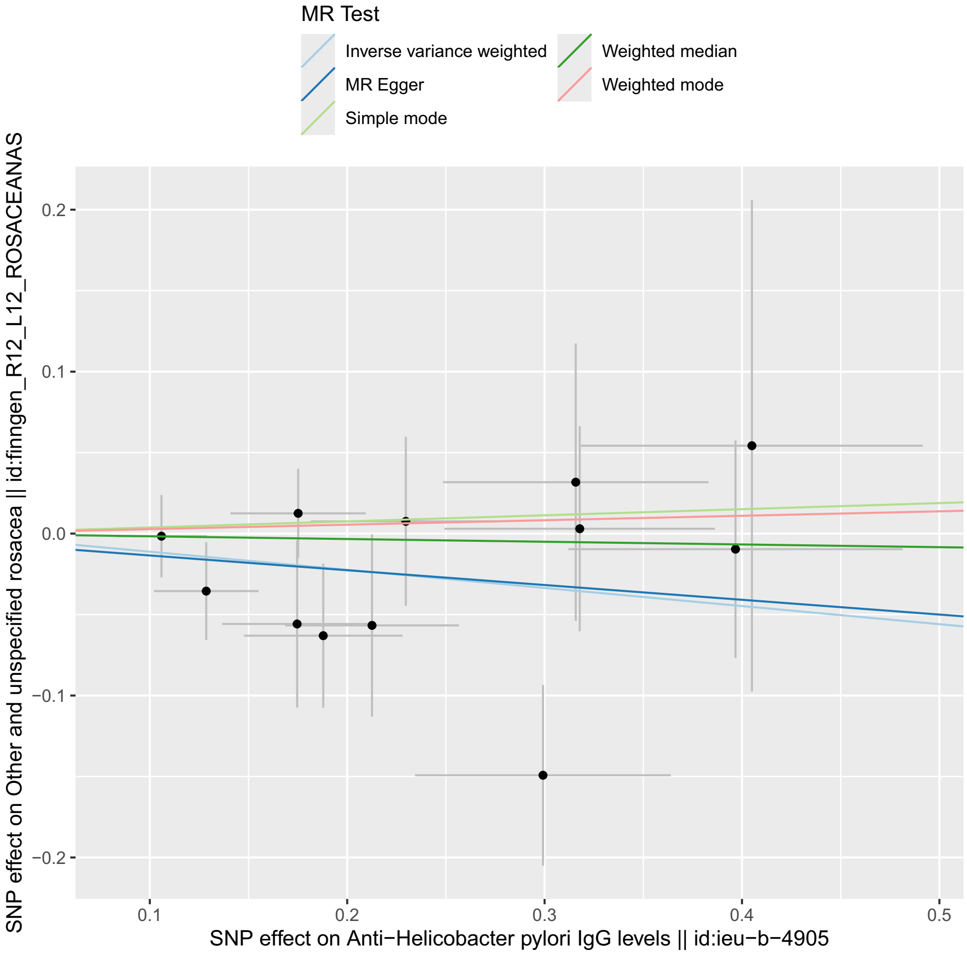


Figure 4 Scatterplot of SNP potential effects of H. pylori infection ieu-b-4905 to rosacea.

We identified multiple H. pylori-related datasets in the GWAS database, among which only the Anti-H. pylori IgG dataset contained a sufficient number of SNPs, thus justifying our selection of these two specific datasets for this study. Additionally, our analysis was confined to northern European populations to ensure genetic homogeneity, as genetic variations across different ethnic groups could potentially confound the results. While this approach enhances the reliability of our findings within this specific population, it may introduce a degree of bias, limiting the generalizability of our conclusions. Future research should aim to include diverse racial and ethnic groups to explore the association between rosacea and H. pylori infection. Rosacea comprises multiple clinical subtypes.[21] However, since current rosacea GWAS databases lack subtype classification and do not provide specific case numbers or proportions for each subtype, we were unable to conduct MR analyses between H. pylori infection and distinct rosacea subtypes—a significant limitation of this study. Nevertheless, our null findings do not preclude potential associations in specific subtypes, as substantial literature reports elevated H. pylori infection rates in papulopustular rosacea patients. Current studies on the

Table 1 Sensitivity Analyses of MR

Exposure	Outcome	SNPS	Heterogeneity Test		MR Egger Pleiotropy Test		MR-PRESSO Global Outlier Test
			Q	p-value	Intercept	p-value	
H. pylori infection (ieu)	Rosacea	12	8.5063	0.4840	8.4499	0.3908	None
H. pylori infection (ebi)	Rosacea	10	10.1293	0.5188	10.1107	0.4308	None

association between H. pylori infection and rosacea have covered a wide range of regions, including Egyptian, Chinese, Russian, and German patients. Studies suggesting no significant association between H. pylori and rosacea[5,22] may also be influenced by factors such as: sample size limitations, heterogeneous composition of rosacea subtypes, geographical variations and sensitivity of detection methods. Future research should prioritize the following directions to address current limitations: 1. Precision subtype stratification of rosacea; 2. broader geographical representation; 3. standardized high-sensitivity detection protocols; 4. expand the sample size.

Conclusion

Our MR analysis provides no evidence of a causal relationship between H. pylori infection and rosacea. This indicates that patients with rosacea may not need routine testing for H. pylori infection and routine eradication of H. pylori may not benefit rosacea patients.

Ethics Approval and Consent to Participate

According to item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects adopted by the National Science and Technology Ethics Committee of the People's Republic of China dated February 18, 2023, since the data used in this study will not cause any harm to humans, does not involve any sensitive personal information or commercial interests, and the selected database is open and legal, approval from the ethics review committee is not required.

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Disclosure

The authors declare that there is no conflict of interest.

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