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Can helicobacter pylori infection reduce the risk of Multiple sclerosis? A systematic review and meta-analysis

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Abstract

Background: Several studies propose the protective effect of Helicobacter pylori (HP) in reducing the risk of Multiple sclerosis (MS) whereas the others reported high HP seropositivity in the MS population. Hence, we aimed to perform a comprehensive systematic review and meta-analysis to investigate the association between the risk of MS and HP infection.

Methods: A systematic literature search was performed using three databases including PubMed, Scopus, and Web of Science in June 2022. We selected observational studies (cross-sectional, case-control, and cohort) that assessed the association between MS and HP.

Results: A total of 14 articles with 2307 patients with MS and 2024 controls were included in our systematic review and meta-analysis. The pooled odds ratio (OR) estimates for HP was 0.70 (CI 95%: 0.53-0.93) which indicates HP might reduce the risk of MS. The OR for HP in developed countries was 0.71 (CI 95%: 0.57-0.87) while it was 0.72 (CI 95%: 0.43-1.21) in developing countries. Furthermore, the pooled prevalence of HP in patients with MS was 45% (CI 95%: 35%-56%). The overall prevalence estimated for HP in MS patients in developed countries was 32% (CI 95%: 22%-41%). The prevalence of HP in MS patients from developing countries was 56% (CI 95%: 43%-69%) which was higher than in developed countries.

Conclusion: In conclusion, this systematic review and meta-analysis showed a lower rate of HP infection in patients with MS, suggesting that HP may reduce the risk of MS occurrence. However, further investigation with a large sample size while adjusting for the effect of other leading factors should be conducted to confirm our results.

Keywords: Multiple sclerosis, Helicobacter pylori, infection, Meta-analysis

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Introduction

Multiple sclerosis (MS) is a multifactorial inflammatory autoimmune disorder with a chronic neurodegenerative process of the central nervous system (CNS). Approximately, 400,000 Americans who are mostly young, experience this disorder (1, 2). The unknown pathogenesis of MS is seemed to be a complex combination of host and environmental factors such as viruses, bacteria, or chemicals (3). Among many risk factors, infection plays a pivotal role in the acquisition of MS susceptibility or resistance (4-6).

Helicobacter pylori (HP) is a gram-negative widespread organism, that has the potential to infect more than 50% of individuals around the world (7). The prevalence of HP infection is associated with demographical factors such as geographic area, age, nationality, and socio-economic status so

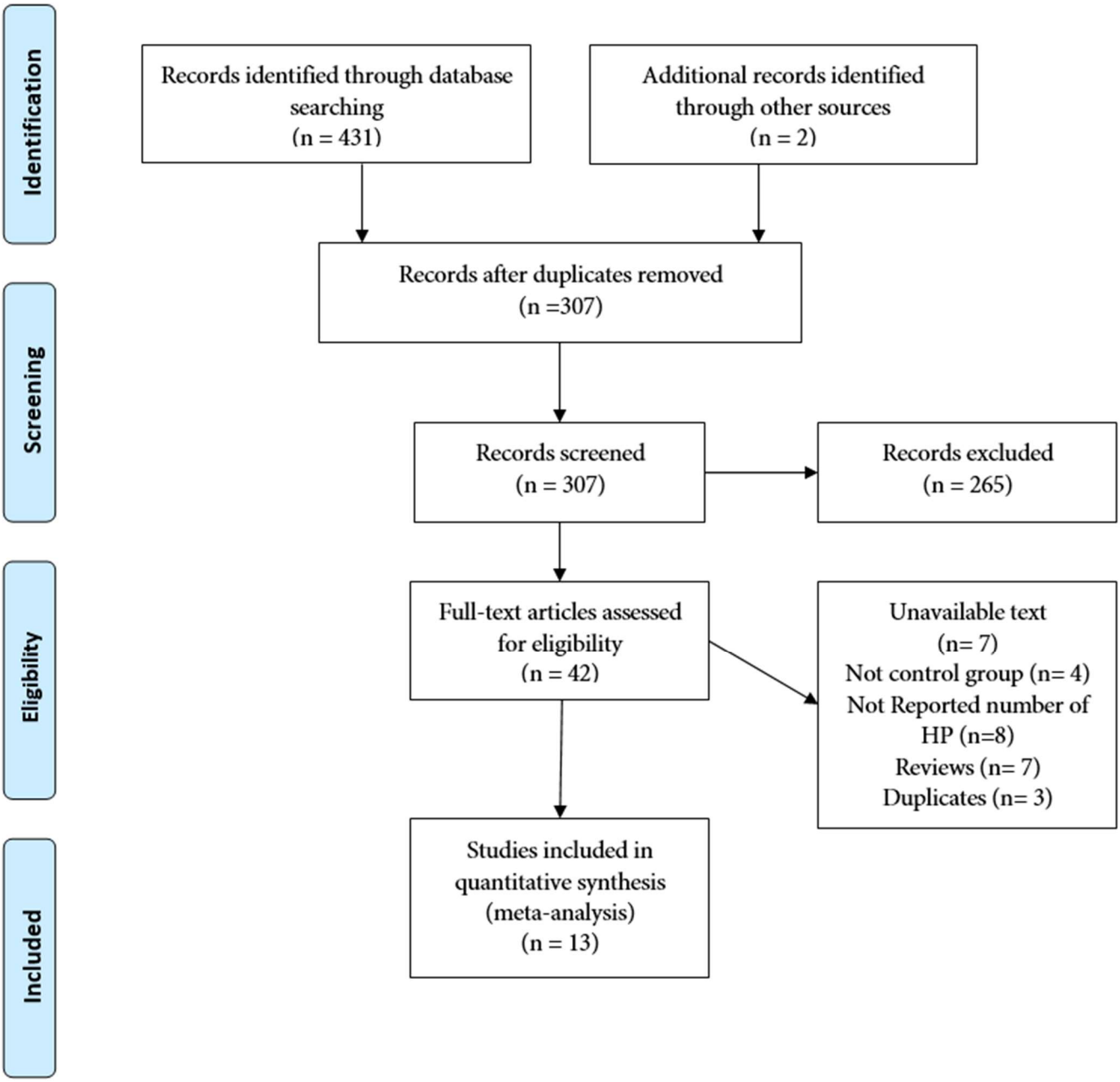

Figure 1. PRISMA diagram of the selection process. PRISMA=Preferred Reported Items for Systematic Reviews and Meta-Analyses.

numerous incidence occurs in developing countries, especially with poor socioeconomic and low sanitary conditions (8, 9). Clinically, most of the HP positive patients have no symptoms; however, it can be presented as gastrointestinal tract diseases including a wide spectrum of chronic gastritis, peptic ulcer disease low-grade gastric mucosa-associated lymphoid tissue lymphoma, adenocarcinoma, and extra gut manifestations such as liver dysfunction, pancreatic carcinoma, cardiovascular disease, central nervous system (CNS) pathogenesis and autoimmune diseases (4, 7). Patients are commonly infected by HP in age under 2 years owing to the immaturity of parietal cells that do not secret gastric acid to inhibit pathogens; so once infected is equivalent to lifelong contamination (9).

According to a large number of studies, a steady rise in autoimmune disease in developed societies has been accompanied by a decrease in infectious diseases and the prevalence of MS has no exception to this hypothesis (10). HP infection in developed countries decreases over the past years whereas MS has substantially increased and it corresponds with the hygiene hypothesis, which suggested that the prevalence of allergic and autoimmune disorders such as MS increases as the incidence of infections decreases (7, 9). Due to this hypothesis, it is indicated that frequent infection in childhood reduces the MS occurrence, later in life (11). On the other hand, regarding recent studies, recurrent HP infection could display as a chronic antigen stimulus that triggers inflammatory response and autoimmunity leading to demyelination disorders like MS (5, 12). Based on shreds of evidence, some bacteria could be beneficial for hosts but some others could be a drawback (13). Several studies propose the protective effect of HP in reducing the risk of MS whereas others reported high HP seropositivity in the MS population (4, 7, 14).

The existence or absence of a correlation between HP infection and MS has not been clearly determined and their association is still a subject of controversy (8, 10, 14). A previous

Table1. Demographic and clinical characteristic of included studies

Author	Year	Continent	Region	study design	Diagnosis of MS	EDSS score, mean SD	Number of MS	Number of females in MS	Mean age of MS group, years	HP diagnosis technique	Number of controls	Number of females in control	Mean age of control group, years	NOS
Li et al. 2006	2006	Asia	Japan	Case-control	McDonald criteria 2001	4.3±2.6	105	81	46.9	ELISA	85	64	43.5	7
Li et al. 2009	2009	Asia	Japan	Case-control	McDonald criteria 2001	3.5 (median)	162	121	39.7 (median)	ELISA	85	64	42 (median)	7
Ramroodi et al. 2012	2012	Asia	Iran	Case-control	McDonald criteria 2010	NR	78		NR	Real-time polymerase chain reaction (PCR) was employed in the detection of H. pylori genome.	123	NR	NR	6
Long et al. 2012	2012	Asia	China	Case-control	McDonald criteria 2010	2.31±1.57	42	21	33.86	Indirect immunofluorescence	27	16	31.96	8
Yoshimura et al. 2013	2013	Asia	Japan	Cross-sectional	McDonald criteria 2005	3.03±2.28	127	94	31.43±12.92	ELISA	177	NR	NR	7
Ram et al. 2013	2013	Latin America	Multicenter	Cross-sectional	McDonald criteria 2010	NR	98	NR	NR	ELISA	140	NR	NR	6
Mohebi et al. 2013	2013	Asia	Iran	Case-control	McDonald criteria 2010	2.3±1.5	163	76	32	ELISA	150	68	30	8
Malli et al. 2015	2015	Asia	India	Cohort	McDonald criteria 2010	NR	139	92	36.56	ELISA	278	184	36.69	8
Cook et al. 2015	2015	Europe	United Kingdom	Cross-sectional	McDonald criteria 2010	NR	71	51	53	ELISA	42	27	50	7
Pedrini et al. 2015	2015	Australia	Australia	Cross-sectional	McDonald criteria 2010	NR	550	412	47.7	ELISA	299	218	43.7	8
Efthymiou et al. 2017	2017	Europe	Greece	Cross-sectional	McDonald criteria 2010	3.5±2.2	139	98	43.2	ELISA	68	40	47.4	7
Ranjbar et al. 2019	2019	Asia	Iran	Case-control	McDonald criteria 2017	2.6 ± 1.4	387	200	31	ELISA	420	218	32	8
Mirmosayyeb et al. 2020	2020	Asia	Iran	Cross-sectional	McDonald criteria 2017	RRMS:0.0, SPMS:4.0 (median)	154	117	CIS:36.07, RRMS:36.45, SPMS:39.82	ELISA	39	30	36.84	8
Kiani et al. 2020	2020	Asia	Iran	Case-control	McDonald criteria 2017	NR	92	81	36.88	ELISA	91	79	38.55	7

NR, Not Reported; EDSS, Expanded Disability Status Scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; NOS, Newcastle-Ottawa Scale

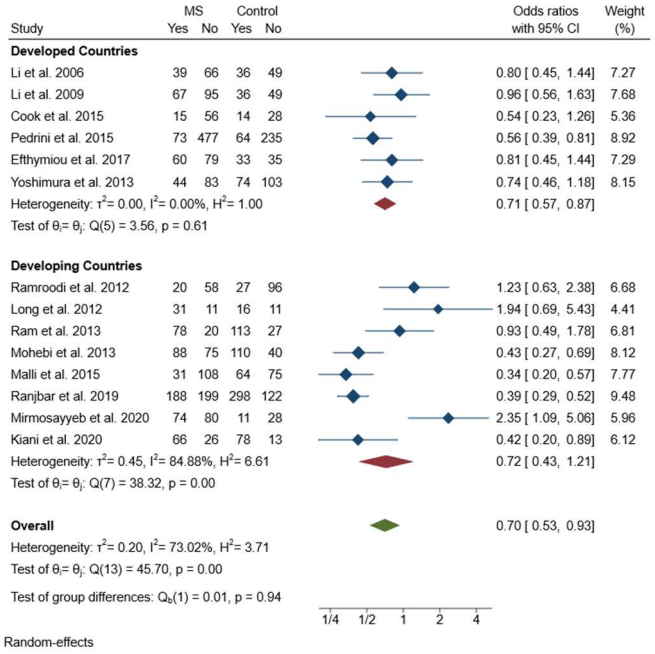

Figure2. Forest plot of HP in patients with MS versus controls

between HP and MS, but we believed that a new study with a better methodology is required (15). Hence, we aimed to perform a comprehensive systematic review and meta-analysis to investigate the association between the risk of MS and HP infection.

Methods

The Current systematic review and meta-analysis were conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement guidelines (16).

Search strategy

A systematic literature search was performed using three databases including PubMed, Scopus, and Web of Science in June 2022. The following terms were used in our search strategy: (Helicobacter pylori) or (H. pylori) or (Campylobacter pylori) and (Multiple sclerosis). Potential studies were identified via hand-searching the reference list of review articles.

Eligibility criteria

We selected peer-reviewed observational studies (cross-sectional, case-control, and cohort) that assessed the association between MS and HP. The included studies had to provide information on MS diagnosis and a control group (healthy individuals) as a reference group. We excluded review articles, case reports, conference abstracts, case series, and studies with patients on HP eradication.

Study selection

Two reviewers (N.R, M.V) independently screened the studies in a two-step process. First, the title and abstract were reviewed and irrelevant articles were excluded. Then the full text of remained studies was carefully screened and final eligible papers were selected. Any disagreements were resolved by consulting with a third investigator (F.N).

Data extraction

The following variables were obtained from selected studies by the same reviewers (N.R, M.V): Author, year of publication, country, study design, diagnosis criteria for MS, number of patients with MS, mean EDSS score, the mean age of patients with MS, number of females in patients with MS, the definition of the control group, number of the control group, the mean age of control group, number of females in the control group, HP diagnosis method, number of cases with HP in MS group, number of cases with HP in the control group.

Quality assessments

The Newcastle–Ottawa scale (NOS) was used to measure the quality of included studies in aspects including the selection of the participants, comparability of study groups, and outcome assessment with a score ranging from 0 to 8 (17).

Statistical analysis

We used Stata 11.0 (College Station, TX) was used to perform statistical analyses. The odds ratio (OR) using the random-effect model with a 95% confidence interval (CI) for the association measures among included studies. I-squared (I2) and Q tests were used to assess the heterogeneity. Sub-group analysis was performed based on the country of origin (developed or developing) obtained from the UN (www.un.org).

Results

The initial search and manual adding yielded 307 studies after duplicate removal (Figure 1). After title and abstract screening, 265 studies were excluded. Finally, 14 articles were included in our systematic review and meta-analysis (18-31). Overall, 2307 patients with MS and 2024 controls entered our study (Table 1). Moreover, seven studies were case-control, five were cross-sectional, and one was a cohort. The mean NOS score was 7.28 which is quietly acceptable.

Meta-analysis

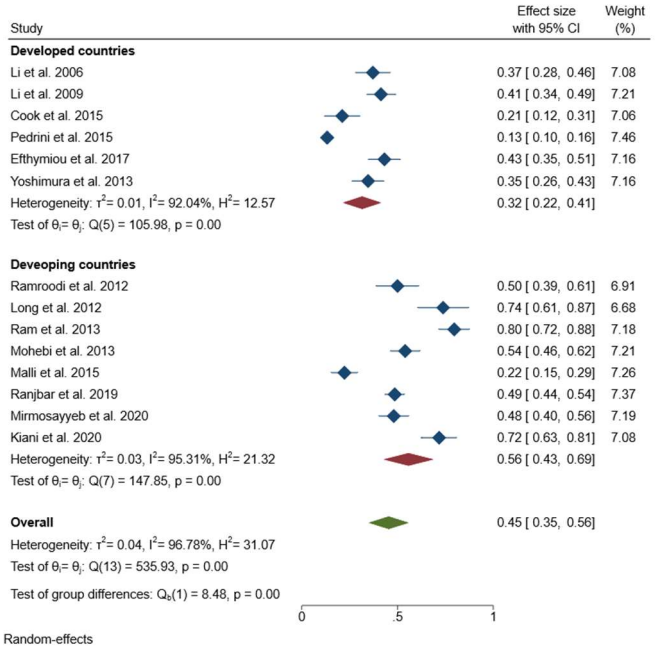

Figure3. Forest plot of prevalence of HP in patients with MS

The pooled OR estimates for HP were 0.70 (CI 95%: 0.53-0.93, Q: 45.70, I2: 73.02%, p< 0.001) which indicates HP might reduce the risk of MS (Figure 2). The OR for HP in developed countries was 0.71 (CI 95%: 0.57-0.87, Q: 3.56, I2: 0%, p:0.61) while it was 0.72 (CI 95%: 0.43-1.21, Q: 38.32, I2: 84.88%, p< 0.001) in developing countries.

Furthermore, the pooled prevalence of HP in patients with MS was 45% (CI 95%: 35%-56%, Q: 535.93, I2: 96.78%, p< 0.001) (Figure 3). The overall prevalence estimated for HP in MS patients in developed countries was 32% (CI 95%: 22%-41%, Q: 105.98, I2: 92.04%, p< 0.001). The prevalence of HP in MS patients from developing countries was 56% (CI 95%: 43%-69%, Q: 151.10, I2: 95.42%, p< 0.001) which was higher than in developed countries. Furthermore, the prevalence of HP in our controls was 49% (CI 95%: 37%-60%, Q: 611.50, I2: 97.05%, p< 0.001)(Figure 4). The sub-group analysis for HP among controls showed a prevalence of 38% (CI 95%: 29%-46%, Q: 41.88, I2: 81.77%, p< 0.001) in developed countries and 57% (CI 95%: 39%-74%, Q: 405.87, I2: 98.06%, p< 0.001) in developing countries.

Discussion

This meta-analysis aimed to assess the association between H. pylori infection and the occurrence of MS. The results showed that the risks of H. pylori infection are lower among MS patients with pooled OR of 0.70, suggesting a protective effect against MS. Also, the prevalence of H. pylori was 46% among MS patients, demonstrating less percentage than the normal population (32).

H. pylori can affect the human body in multiple ways. It has extra-gastric side effects such as cardiovascular, hepatobiliary, dermatologic, neurological, etc.; Neurological disorders like Alzheimer's disease (AD), Parkinson's disease (PD), Guillain-Barré syndrome (GBS), and MS are companies with H. pylori (33). Multiple pathways induce protective effects by H. pylori for MS (34). The first one is the hygiene hypothesis which indicates that lower exposure to pathogens results in immune-mediated diseases in later life (35). Inhibition of Th1 and Th17 responses that increase IL-10 and decrease IFN-γ, TNF-α, IL-6, and IL-17 is one of the reasons for these protective effects (8, 34). Elevated Foxp3+ regulatory T cells, T cell apoptosis, and decreased Myelin oligodendrocyte glycoprotein (MOG) are other reasons to conserve MS (25). Heat shock proteins (HSPs), especially HSP60 and HSP70, are overexpressed in MS patients' brains (34, 36). Positive anti-aquaporin 4 (AQP4) antibodies have higher HP seropositivity, which can be another protective mechanism (5, 37). Therefore, these effects suggest that the gut-brain axis interferes with the function of the blood-brain barrier (BBB), which causes changes in the immune system and inflammatory cytokines response to HP (38, 39). Accessing the brain via an oral-nasal-olfactory pathway can be another HP mechanism to affect the brain (40). So, the main mechanism that affects HP on MS changes in the autoimmunity of the disease.

Although the exact cause of MS is unknown yet, the multifactorial model is widely believed which demonstrates that environmental factors such as infections can trigger the immune response and cause MS in genetically susceptible persons (41). Previous studies indicated the role of Epstein–Barr virus (EBV) infection in MS initiation and there was a strong association between the level of antibodies against EBV and MS (42). Moreover, a previous investigation indicated that about 10% of MS patients produced antibodies against Clostridium perfingens epsilon toxin (43). Also, in the COVID-19 pandemic, several cases of triggered MS and other autoimmune diseases were introduced (1, 44).

Our findings demonstrated that HP can reduce the risk of MS consistent with the results of previous systematic reviews and meta-analyses that investigated the association between HP infection and MS. However, a low number of studies and lack

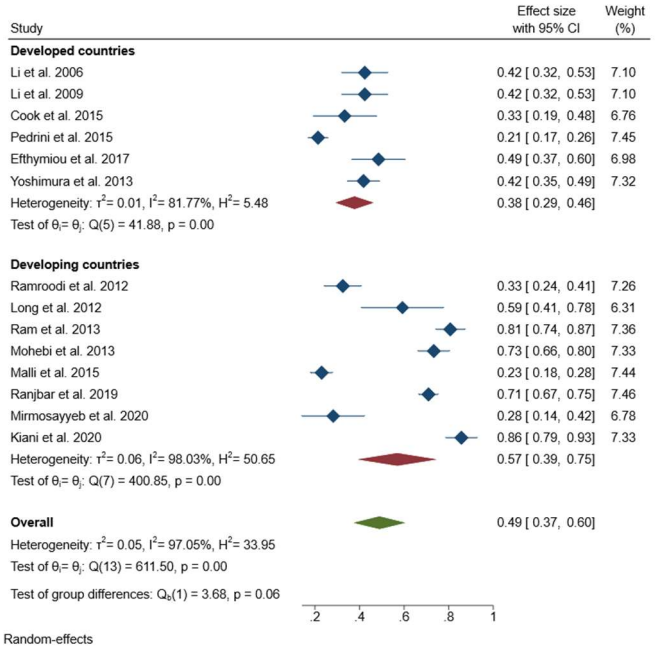

Figure4. Forest plot of prevalence of HP in patients with controls

of subgroup analysis were limitations of the previous investigation (14). Our study probed the association between MS and HP infection separately in developing and developed counties and found that the association between MS and HP and also, the prevalence of HP among MS patients was higher in developing countries. Income, educational and economic situation, and environmental health factors are differences between developing and developed countries (45).

A previous systematic review and meta-analysis by Arjmandi et al. investigated the association between HP and MS recently (15). They found that there was no protective effect for HP against MS which depends on diagnostic tests also. However, there are several differences between the current study and Arjmandi et al. investigation. First, they included not peer-reviewed papers in the analysis. Second, their results were mainly derived from two studies by an author which suspects having similar participants with significantly different OR from the other included articles which might be due to the use of histology for HP diagnosis and also shared similar participants (46, 47). Third, the two articles were missed in their study which was included in the current investigation (18, 22). The mentioned differences can suggest that there is no certain conclusion regarding the protective effect of HP against MS and further studies are required to confirm these results.

This study had several strengths. First, this study updates previous studies and has a bigger sample size by searching in more databases. Second, studies were chosen in different countries, so we performed a sub-group analysis based on whether the study was conducted in a developed or developing country. However, there were some limitations. First, this study had high heterogeneity due to different study designs, sub-types of MS, and diagnostic methods for detecting HP infection (Western Blot, immunofluorescence, and ELISA). Second, there was no history of eradication in patients with HP infection, which affects the presence of HP. Third, some of the included studies had a small number of subjects, reducing the analysis's power.

In conclusion, this systematic review and meta-analysis showed a lower rate of HP infection in patients with MS, suggesting that HP may reduce the risk of MS occurrence. However, further investigation with a large sample size while adjusting for the effect of other leading factors should be conducted to confirm our results.

Deceleration

Funding

We do not have any financial support for this study.

Conflict of interest

The author declares no conflict of interest regarding the publication of this paper.

Ethical approval

Not applicable

Availability of data and material

The datasets analyzed during the current study are available upon request with no restriction.

Consent for publication

This manuscript has been approved for publication by all authors.

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