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Posted Date: 17 March 2026

doi: 10.20944/preprints202603.1008.v1

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 doi:10.20944/preprints202603.1008.v1

Review

From Gastric Mucosa to Brain: Neurological Dimensions of *Helicobacter pylori* Infection

Maria Pina Dore [1,2,*], Giuseppe Lasaracina [1], Giovanni Mario Pes [1], Paolo Solla [1] and Elettra Merola [1]

[1] Dipartimento di Medicina, Chirurgia e Farmacia, University of Sassari, Clinica Medica, Viale San Pietro 8, 07100 Sassari, Italy

[2] Department of Medicine, Baylor College of Medicine, One Baylor Plaza Blvd, Houston, TX 77030, USA

* Correspondence: mpdore@uniss.it; Tel.: +39-079-229886

Abstract

Objective: *Helicobacter pylori* infects nearly half of the global population and has traditionally been viewed as a pathogen restricted to the gastric mucosa. Growing evidence, however, suggests that chronic infection may exert systemic effects extending to the central nervous system. This review critically examines the potential neurological implications of *H. pylori* infection within the emerging framework of the gut–brain axis. *Methods*: We performed a narrative, hypothesis-generating review of human observational and interventional studies complemented by mechanistic experimental research. The literature was evaluated with particular attention to study design, heterogeneity, and potential confounding in reported associations between *H. pylori* infection and neurological disorders. *Results*: Across multiple studies, *H. pylori* infection has been linked to a modestly increased prevalence of Parkinson's disease and dementia, although findings remain heterogeneous. In Parkinson's disease, infection may exacerbate motor fluctuations and reduce levodopa bioavailability, with partial clinical improvement reported following eradication in selected patients. Experimental studies further demonstrate that bacterial outer membrane vesicles can access the brain and promote neuroinflammatory and amyloidogenic processes, supporting biological plausibility. By contrast, several epidemiological studies report an inverse association with multiple sclerosis, suggesting potential immunomodulatory effects. Evidence relating *H. pylori* to migraine and mood disorders remains inconsistent. *Conclusions*: Current data do not support *H. pylori* as a primary cause of neurological disease. Instead, the infection may act as a context-dependent modifier within the complex inflammatory and immunometabolic networks of the gut–brain axis. Clarifying this relationship will require prospective studies integrating microbial strain profiling, biomarker-defined neurological phenotypes, and adequately powered interventional trials.

Keywords: neurological disorders; migraine; dementia; Parkinson's disease; multiple sclerosis; Alzheimer

1. Introduction

Nearly half of the world's population is chronically infected with *Helicobacter pylori*, a Gram-negative microaerophilic bacterium that colonizes the gastric mucosa [1]. While often acquired in childhood and asymptomatic, *H. pylori* can persist for life and is the principal cause of chronic active gastritis, peptic ulcer disease, and gastric adenocarcinoma [2]. Beyond these well-established gastrointestinal (GI) effects, a growing body of evidence indicates that *H. pylori* infection has systemic consequences, including associations with extragastric diseases. Among these, neurological disorders have garnered intense interest, fueled by epidemiological observations and the emerging concept of the microbiota-gut-brain axis [3,4]. The gut-brain axis refers to the bidirectional communication network linking the GI tract and the central nervous system (CNS) through neural, immune, metabolic, and endocrine pathways [5] (**Figure 1**).

 doi:10.20944/preprints202603.1008.v1

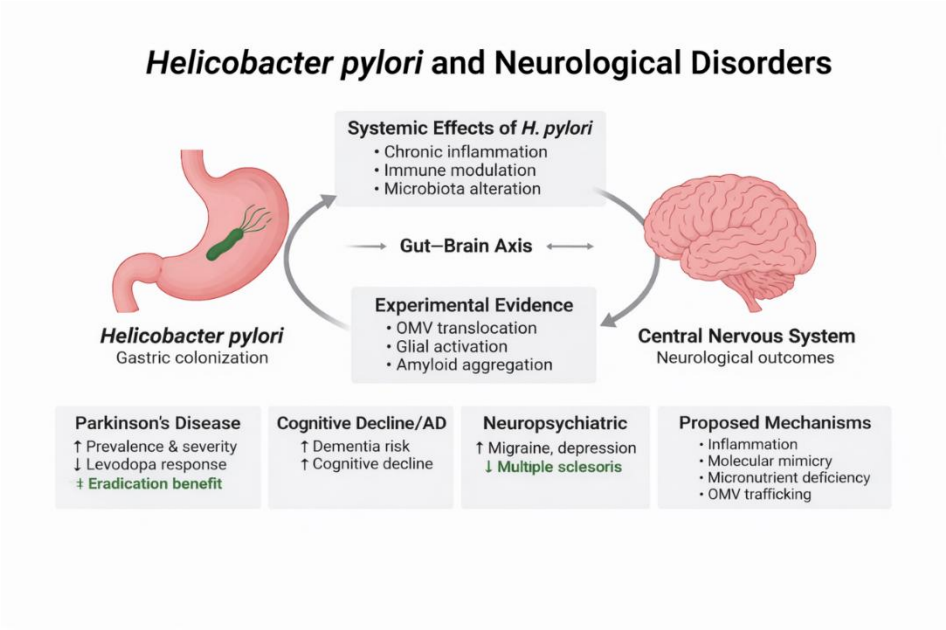

Figure 1. Conceptual pathways linking gastric colonization by *H. pylori* to neurological outcomes. Proposed systemic mediators include chronic low-grade inflammation, immune modulation, and alterations in the microbiota. Experimental reports suggest that bacterial products such as outer membrane vesicles can contribute to neuroinflammation and may exacerbate amyloid pathology in preclinical models. The figure summarizes hypothesized mechanisms and should be interpreted as hypothesis-generating.

Disruptions in gut homeostasis, for example, chronic infections or dysbiosis, can influence brain function and have been implicated in neurodegenerative and neuropsychiatric diseases [6–12]. In the case of *H. pylori*, researchers have proposed multiple mechanisms by which a gastric infection might affect the brain. First, *H. pylori* can induce persistent mucosal inflammation, with local release of cytokines (IL-1, IL-8, IL-6, TNFα) and acute-phase reactants that enter the systemic circulation [4,5,13]. Low-grade chronic inflammation can promote neuroinflammation over time, and elevated peripheral inflammatory markers are a known risk factor for cognitive decline and other CNS pathologies [13]. Second, *H. pylori* expresses numerous virulence factors, including VacA (vacuolating cytotoxin A), CagA (cytotoxin-associated gene A protein), and HP-NAP (neutrophil-activating protein), which may have neurotoxic properties [5]. Some *H. pylori* antigens share epitopes with human proteins (molecular mimicry), raising the possibility of autoimmune reactions affecting neural tissue [3,14]. Third, *H. pylori* infection alters gastric physiology (hypochlorhydria in some cases or delayed gastric emptying) and the composition of the gut microbiota. Resultant small intestinal bacterial overgrowth (SIBO) and changes in microbial metabolites (such as short-chain fatty acids and neurotransmitter precursors) could influence the enteric nervous system or vagal signaling to the brain [3,4,15]. Fourth, the physical breach of barriers. Chronic *H. pylori* infection has been reported to increase gut permeability, facilitating the passage of inflammatory monocytes or bacterial components across the blood-brain barrier (BBB) [1,16,17]. Recent experimental evidence is particularly striking, nanoscale outer membrane vesicles (OMVs) shed by *H. pylori* have been shown to enter the bloodstream, penetrate the BBB, and incite CNS inflammation and injury in animal models [18]. In mice, *H. pylori* OMVs co-localize with amyloid plaques and worsen cognitive performance, directly linking this pathogen to Alzheimer's pathology hallmark [19]. Epidemiological studies over the past two decades have linked *H. pylori* to various neurological outcomes. Initial clues came from observations that patients with *H. pylori* infection more commonly exhibited certain neurodegenerative disorders than their uninfected counterparts [20–30]. Notably, a higher prevalence of *H. pylori* was observed among Parkinson's disease (PD) patients in multiple case-control studies, and *H. pylori* eradication in PD was associated with improved motor function in early reports [27,28]. Similarly, *H. pylori* seropositivity has been linked to poorer cognition and greater risk

 doi:10.20944/preprints202603.1008.v1

of dementia in older adults [20]. There have also been intriguing findings in other conditions: for example, an inverse relationship in multiple sclerosis (MS) (fewer *H. pylori*-infected individuals among MS patients), hinting at a protective effect [31–33], and correlations between *H. pylori* and mood disorders or migraine headaches [34,35]. These associations have sparked intense research and controversy. While some meta-analyses and systematic reviews support a positive link (e.g., *H. pylori* roughly doubling the odds of PD or all-cause dementia) [36], others find no significant association or only modest effects, often with substantial heterogeneity [13]. Distinguishing correlation from causation is a major challenge: *H. pylori* infection is more common with increasing age, among individuals of lower socioeconomic status, and among patients with other comorbidities, which themselves could confound neurodegenerative risk. Reverse causation is also possible, where neurological illness or its treatments could predispose to *H. pylori* infection (for instance, via immune suppression or increased healthcare exposure).

This review endeavors to critically examine the current evidence linking *H. pylori* to neurological disorders, focusing on three main domains: (i) Parkinson's disease, where the most robust clinical data exist regarding infection effects on motor symptoms and medication pharmacokinetics; (ii) cognitive decline and Alzheimer's disease (AD), where multiple observational studies and mechanistic experiments suggest a connection; and (iii) other neuropsychiatric disorders such as migraine, MS, and mood disorders, where data are emerging or mixed. For each area, we summarize key epidemiological findings, discuss pathogenic mechanisms (with insights from animal models and molecular studies), considering clinical implications, including whether *H. pylori* screening or eradication might be part of the management. The limitations of the current research were highlighted, and directions for future investigation were outlined. By integrating findings from microbiology, neurology, and gastroenterology, we aimed to provide a comprehensive picture of how a stomach pathogen might influence brain health, an illustrative example of the interplay of bodily systems.

2. Literature Search and Study Selection

This work is a narrative, hypothesis-generating review that critically summarizes the evidence linking *H. pylori* infection to selected neurological outcomes. In line with recommended quality items for narrative reviews, we explicitly describe the sources and approach used to identify the literature. We searched PubMed and Embase from inception to December 2025. Search terms combined controlled vocabulary and free-text keywords including ("Helicobacter pylori" OR "H. pylori" OR "Hp") AND ("Parkinson" OR "Alzheimer" OR "dementia" OR "cognitive decline" OR "multiple sclerosis" OR "migraine" OR "depression" OR "anxiety" OR "neuro*" OR "central nervous system" OR "gut-brain axis" OR "microbiota" OR "outer membrane vesicles"). We also screened reference lists of relevant systematic reviews and key primary studies to identify additional records. We prioritized peer-reviewed human studies (observational and interventional designs, when available) and selected mechanistic preclinical reports when they provided plausible biological links (e.g., neuroinflammation, microbial products/vesicles, nutrient malabsorption). Exclusion criteria were: non-peer-reviewed abstracts, non-English articles (unless deemed pivotal), single-patient case reports, and studies lacking a clear definition of exposure (*H. pylori* detection method) or outcome (neurological diagnosis/phenotype). Given the narrative design, we did not perform a formal meta-analysis or a comprehensive risk-of-bias scoring; instead, we explicitly discuss study design, confounding, and heterogeneity to contextualize the strength and limits of the available evidence.

3. Results

3.1. Parkinson's Disease

The etiopathogenesis of PD remains incompletely elucidated and reflects a multifaceted interaction between genetic susceptibility and environmental influences [6]. Pathologically defined by dopaminergic neuronal loss within the substantia nigra and widespread α-synuclein aggregation

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[8,37], PD is increasingly interpreted through the lens of the gut–brain axis. Braak's staging hypothesis, together with subsequent "body-first" and "brain-first" models, proposes that in a subset of patients the pathological process may originate within the enteric nervous system and ascend via autonomic pathways to the central nervous system [3,9,38–40]. Within this conceptual framework, *H. pylori* has been proposed as a plausible environmental contributor or disease modifier.

Epidemiological data consistently report a higher prevalence of *H. pylori* infection among PD patients compared with age-matched controls [41]. Meta-analyses estimate approximately 1.5-1.6-fold increased odds of seropositivity in PD [7,30], although reported prevalence varies widely (37-59%) across geographic region, diagnostic modality, and study design [10]. Importantly, infection appears to influence not only disease occurrence but also clinical expression. Several studies have shown that *H. pylori*-positive patients exhibit more severe motor impairment, greater motor fluctuations, and diminished responsiveness to levodopa (L-DOPA) [5,12]. A recent meta-analysis confirmed poorer motor scores and reduced L-DOPA benefit among infected individuals [12].

From a pharmacokinetic perspective, chronic *H. pylori*-associated gastritis may impair L-DOPA absorption through hypochlorhydria, delayed gastric emptying, and promotion of small intestinal bacterial overgrowth [4,28,29]. Early clinical observations demonstrated lower plasma L-DOPA concentrations and delayed time-to-peak in infected patients, with partial normalization following eradication therapy [27]. Small uncontrolled studies and open-label trials suggested improvements in motor function and drug responsiveness after eradication [11,26]. However, a subsequent randomized placebo-controlled trial failed to demonstrate significant long-term differences in motor or non-motor outcomes [11], thereby tempering earlier enthusiasm and highlighting the need for larger, rigorously designed studies.

Beyond pharmacological interference, several biological mechanisms provide theoretical plausibility for a pathogenetic link. Chronic infection induces systemic low-grade inflammation, with elevated cytokines, such as IL-1β, IL-6, and TNFα, able to cross or modulate the blood–brain barrier and amplify microglial activation [4,13]. Molecular mimicry and cross-reactive antibodies targeting neural antigens have also been proposed [3,13,14,42]. Furthermore, intestinal inflammation may influence α-synuclein misfolding in enteric neurons, potentially facilitating its propagation along vagal pathways to the brain [43–45], an interpretation consistent with early gastrointestinal α-synuclein deposition and epidemiological data suggesting reduced PD risk after vagotomy [46–48]. Additional contributory pathways may include micronutrient deficiencies, particularly vitamin B12, and infection-related alterations in epithelial and vascular barrier integrity [4,49]. Notwithstanding these convergent observations, causality remains unproven. Mendelian randomization analyses have not supported a direct causal role of *H. pylori* infection in PD risk [41], suggesting instead that infection may modulate disease phenotype or therapeutic response rather than initiate neurodegeneration. Confounding, reverse causation, and exposure misclassification further complicate interpretation. Accordingly, the most defensible conclusion at present is pragmatic rather than etiological: *H. pylori* may represent a treatable modifier of motor fluctuations and L-DOPA pharmacokinetics in selected PD phenotypes [7,12,25–28]. Targeted testing and eradication may therefore be reasonable in patients with prominent GI dysfunction or erratic drug response, while claims of disease-modifying effects should be approached cautiously pending robust prospective evidence (Table 1).

Table 1. Parkinson's disease and *Helicobacter pylori* infection.

Area	Key Message	References
Disease concept	PD may start in the gut (gut-brain axis hypothesis)	[1–6]
Epidemiology	*H. pylori* more frequent in PD [1] (~1.5×)	[7–9]
Clinical impact	Worse motor symptoms and motor fluctuations	[10,11]

 doi:10.20944/preprints202603.1008.v1

Pharmacology	Impairs levodopa absorption → weaker response	[12–15]
Main mechanisms	Inflammation, molecular mimicry, α-synuclein propagation, SIBO	[2,4–6,15–19]
Eradication therapy	Improves selected patients but not disease-modifying	[20,21]
Causality	Not proven cause of PD [1]	[9]
Current interpretation	Disease modifier rather than trigger	[9,11–13,21]
Disease concept	PD [1] may start in the gut (gut-brain axis hypothesis)	[1–6]
Epidemiology	*H. pylori* more frequent in PD [1] (~1.5×)	[7–9]

[1] Parkinson's disease.

3.2. Cognitive Decline and Alzheimer's Disease

Alzheimer's disease, the most prevalent cause of dementia, is neuropathologically defined by extracellular amyloid-β (Aβ) plaque deposition and intracellular tau neurofibrillary tangles, leading to progressive cognitive decline. Its etiopathogenesis is multifactorial, encompassing age, genetic predisposition (notably APOE ε4), vascular risk factors, and environmental influences [49–51]. Within this framework, chronic infection and systemic inflammation have re-emerged as potential contributors, reviving the longstanding "infectious hypothesis" of AD [52,53]. Given its global prevalence and its capacity to induce persistent immune activation, *H. pylori* has been proposed as a candidate.

Observational studies have yielded mixed but generally suggestive findings. A 2021 meta-analysis reported a significant association between *H. pylori* infection and all-cause dementia (pooled OR ~1.5), although the association with AD specifically did not reach statistical significance [54]. A more recent meta-analysis demonstrated that infected individuals had approximately 33% higher odds of cognitive impairment and that *H. pylori* prevalence was elevated among patients with established AD (pooled OR ~1.63) [13]. However, prospective cohort data did not consistently confirm infection as a predictor of incident AD, and substantial heterogeneity ($I^2 > 70\%$) and potential publication bias temper interpretation [13]. Confounding by age, vascular burden, and socioeconomic factors remains a central limitation.

Interventional data, though limited, are provocative. A non-randomized study reported slower cognitive decline over two years among AD patients who underwent eradication therapy compared with untreated controls [55]. A subsequent small trial in individuals with mild cognitive impairment suggested improvement in memory performance following eradication [56,57]. While preliminary, these findings raise the possibility that *H. pylori* may influence disease trajectory in selected patients. Nonetheless, antibiotic effects on the broader gut microbiome and correction of micronutrient deficiencies (e.g., vitamin B12 and iron) complicate causal inference.

Biological plausibility rests on several converging mechanisms. Chronic *H. pylori* infection induces a Th1-predominant inflammatory response with elevated IL-1, IL-6, and TNFα, mediators that can cross or modulate the BBB and amplify microglial activation [3,14]. Indeed, infected AD patients have demonstrated higher systemic and cerebrospinal inflammatory markers, correlating with accelerated cognitive decline [58–60].

Preclinical evidence has further strengthened mechanistic plausibility. *H. pylori* releases nanoscale OMVs containing virulence factors such as VacA and lipopolysaccharide, which can disseminate systemically and reach the brain [18]. In murine models, OMVs induce astrocyte activation, neuronal injury, and exacerbate Aβ aggregation and cognitive deficits [19]. Lipid components within OMVs appear capable of catalyzing Aβ fibrillization, while VacA has been shown

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to promote neuronal apoptosis [60–64]. Although compelling, these findings remain preclinical and cannot yet be directly extrapolated to human disease.

Additional pathways may include molecular mimicry and autoimmunity [3,14], micronutrient deficiency secondary to chronic atrophic gastritis [65–67], and cerebrovascular mechanisms mediated by infection-driven endothelial dysfunction and atherosclerosis [68,69]. Given the well-established vascular contributions to cognitive decline, such mechanisms may be particularly relevant in mixed dementia phenotypes [54].

Yet, recent large population-based analyses underscore the need for restraint. While earlier meta-analyses suggested increased dementia risk (pooled OR ~1.71), more recent large-scale studies have reported only modest associations (OR ~1.11) or null findings after confounder adjustment, particularly when eradication therapy was used as a proxy for exposure. These data suggest that *H. pylori* may function more plausibly as a risk correlate or modifier within broader inflammatory and socioeconomic contexts than as a deterministic causal driver of AD.

In sum, *H. pylori* infection fulfills several criteria of biological plausibility and is associated with modest increases in the risk of cognitive impairment, yet definitive causality remains unestablished. It is conceivable that the infection acts as an accelerant in susceptible individuals rather than an initiating factor. From a pragmatic standpoint, evaluation and eradication may be reasonable in cognitively impaired patients with GI symptoms, anemia, or evidence of micronutrient deficiency [65], while recognizing that robust disease-modifying effects have not yet been demonstrated in adequately powered prospective trials (Table 2).

Table 2. Alzheimer's disease and *Helicobacter pylori* infection.

Area	Key Message	References
Association	*H. pylori* linked to ↑ dementia risk (OR ~1.3–1.6); causality unproven; high heterogeneity.	[17,22]
Clinical Evidence	Eradication therapy may slow cognitive decline (small, non-definitive trials).	[23,24]
Mechanisms	Chronic inflammation + OMVs [1]/VacA → neuroinflammation, ↑ Aβ deposition, neuronal injury.	[1,18,25–30]
Indirect Pathways	B12 deficiency + vascular damage may mediate cognitive effects.	[22,23,31–34]
Conclusion	Biologically plausible risk modifier; evidence is associative, not causal.	[17,22]

[1] Outer membrane vesicles.

3.3. Neuropsychiatric Disorders: Migraine, Multiple Sclerosis, and Mood Disorders

Beyond classical neurodegenerative diseases, *H. pylori* has been investigated in a range of neuropsychiatric conditions characterized by immune dysregulation and neurochemical imbalance. Among these, migraine, MS, and depression/anxiety provide illustrative, albeit methodologically heterogeneous, examples of how chronic infection might intersect with brain function (Table 3).

Table 3. Neuropsychiatric Disorders and *Helicobacter pylori* Infection.

Area	Key Message	References

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Association	*H. pylori* linked to depression, anxiety, panic disorder; higher prevalence in dyspeptic infected patients.	[35–37]
Hormonal Pathways	↓ Ghrelin and altered leptin signaling may contribute to anxiety/depressive-like behavior; human causality unproven.	[38–41]
Inflammatory Mechanisms	↑ IL-1β, IL-6, TNF-α may affect monoamines via BBB signaling; limited direct human evidence.	[42–44]
Eradication Effects	Some studies suggest mood improvement after eradication; evidence heterogeneous.	[45]
Clinical Perspective	Likely contributor, not primary cause; relevant in refractory mood disorders with GI symptoms.	[36,45]

[1] Outer membrane vesicles

3.3.1. Migraine

Migraine is a complex neurovascular disorder involving trigeminovascular activation, neurogenic inflammation, and dysregulation of mediators such as serotonin and calcitonin gene-related peptide (CGRP). The frequent coexistence of dyspeptic symptoms has long suggested a gut-brain interface. Given that *H. pylori* is a major cause of chronic gastritis and dyspepsia, its potential role as a migraine trigger has been widely explored.

Early meta-analytic data reported a higher prevalence of *H. pylori* among migraineurs (OR ~1.9), though with substantial heterogeneity ($I^2 \approx 77\%$) and regional variability [70]. More recent PRISMA-based analyses encompassing larger populations have suggested stronger pooled associations (OR ~2.8), yet again with very high heterogeneity and methodological inconsistency. Importantly, subgroup analyses indicate that the association may be more pronounced in migraine with aura and in regions of high *H. pylori* endemicity [70]. Interventional studies, though largely uncontrolled, have reported reductions in headache frequency and severity following eradication therapy in selected patients [71,72]. However, variability in trial design and outcome assessment precludes firm conclusions. Proposed mechanisms include infection-induced release of pro-inflammatory cytokines (IL-8, TNFα), increased nitric oxide production via inducible nitric oxide synthase, and potential molecular mimicry affecting trigeminal or meningeal pathways [73–78].

Overall, current evidence supports a contributory or modulatory role in a subset of patients, particularly those with concomitant GI symptoms, rather than a universal etiologic effect.

3.3.2. Multiple Sclerosis

In contrast to the generally positive associations observed in Parkinson's disease and dementia, MS has frequently demonstrated an inverse relationship with *H. pylori*. Several case-control studies reported lower seroprevalence among MS patients compared with controls, with pooled estimates suggesting reduced odds of infection (OR ~0.69) [79–82]. These findings have been interpreted within the "hygiene hypothesis" framework, whereby early-life infections may promote regulatory immune pathways that mitigate autoimmune risk [32,33].

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Mechanistically, *H. pylori* induces robust regulatory T-cell responses and the production of anti-inflammatory cytokines such as IL-10, potentially dampening autoreactive processes [31]. Experimental autoimmune encephalomyelitis models have demonstrated reduced demyelination following *H. pylori* exposure, lending preclinical plausibility to an immunomodulatory effect [31].

Yet, the literature is far from consistent. More recent meta-analyses incorporating broader datasets have reported no statistically significant overall association (OR ~0.79, confidence intervals crossing unity), with assay type (serology versus histology) contributing materially to heterogeneity. Regional differences, strain variability (e.g., CagA status), timing of infection, and host genetics are likely to modulate the observed effects.

Accordingly, the most defensible conclusion is not that *H. pylori* is protective or harmful in MS, but that its association is uncertain, method-sensitive, and highly vulnerable to selection bias and exposure misclassification. The MS data underscore the broader principle that chronic infection may recalibrate immune balance, though its net clinical impact remains unresolved.

3.3.3. Depression and Anxiety

Chronic inflammatory states are increasingly implicated in mood disorders, and *H. pylori* infection has been associated with depression and anxiety in several observational studies [83–85]. Meta-analytic data suggest a significant association with anxiety disorders (OR ~2.5), whereas pooled analyses for depression have been less consistent, with cohort-based designs yielding higher estimates than cross-sectional studies. Such heterogeneity likely reflects confounding by dyspeptic symptom burden, healthcare utilization patterns, and socioeconomic factors.

Biological plausibility derives from multiple pathways. Altered ghrelin and leptin signaling secondary to gastric inflammation may further modulate mood-related circuits [86–89]. Moreover, infection-related cytokines (IL-1β, IL-6, TNF-α) can influence monoaminergic neurotransmission via peripheral-to-central immune signaling [90–92]. However, direct causal pathways remain speculative, and longitudinal interventional evidence is sparse.

Eradication therapy has been reported to improve both dyspeptic and mood symptoms in some patients with functional dyspepsia [93], yet disentangling psychobiological effects from symptomatic relief remains challenging. Thus, while *H. pylori* cannot be considered a primary cause of mood disorders, it may represent a modifiable contributor within a broader biopsychosocial framework.

3.4. Other Neurological Associations

Isolated reports have linked *H. pylori* to Guillain–Barré syndrome, stroke, seizure disorders, and peripheral neuropathy [94–96], largely through mechanisms of molecular mimicry, prothrombotic inflammation, or vitamin B12 deficiency. At present, these associations remain preliminary and require systematic validation.

4. Discussion

Despite a growing body of literature linking *H. pylori* infection to neurological disorders, the overall evidence remains suggestive rather than definitive. Most available data derive from observational studies, primarily case-control and cross-sectional designs, which are inherently susceptible to residual confounding, selection bias, and reverse causation. Infection prevalence varies substantially by age, geographic region, socioeconomic status, and comorbidity burden, all of which independently influence neurological risk. Disentangling the specific contribution of *H. pylori* from these overlapping determinants remains methodologically complex.

Substantial between-study heterogeneity further complicates interpretation. Variability in population characteristics, infection ascertainment (serology, urea breath test, stool antigen, histology), bacterial strain differences (including CagA status), and definitions of neurological outcome (all-cause dementia versus AD; clinically defined versus biomarker-supported diagnoses) contribute to inconsistent findings. Exposure misclassification is a particular concern, especially in

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MS and neuropsychiatric research, where diagnostic methods differ widely. Meta-analyses frequently report high heterogeneity (I^2 often >70%) [13]. Publication bias and selective reporting cannot be excluded, particularly in fields dominated by small single-center cohorts.

Effect sizes across studies are modest and inconsistent. For example, a meta-analysis reported an association between *H. pylori* and all-cause dementia but not specifically AD [54], suggesting that some signals may reflect vascular or mixed cognitive phenotypes rather than primary AD pathology. Mendelian randomization analyses have not demonstrated a causal effect of *H. pylori* on PD risk [41], underscoring the possibility that observational associations may not reflect direct biological causation.

Randomized interventional evidence remains limited. In PD, a placebo-controlled eradication trial failed to show significant motor improvement [41], despite earlier uncontrolled studies suggesting benefit. In AD, available data derive from small open-label studies [5], lacking adequate power and long-term follow-up. Moreover, antibiotics themselves may exert independent neurobiological effects through anti-inflammatory properties or microbiome modulation, complicating attribution of benefit specifically to *H. pylori* eradication.

Mechanistic pathways are biologically plausible, including systemic inflammation, cytokine-mediated neuroimmune activation, molecular mimicry, micronutrient deficiency, vascular injury, and bacterial OMVs trafficking [19,97]. However, most mechanistic evidence is derived from animal or in vitro studies. Direct demonstration of these processes in human neurological disease remains incomplete, and the relative importance of individual mechanisms may vary across conditions, for example, impaired drug absorption in PD versus vascular-inflammatory pathways in dementia.

Geographic variability introduces additional complexity. Much of the positive association data originates from regions with high *H. pylori* prevalence. In low-prevalence populations, associations may be attenuated or absent, whereas in settings with near-universal exposure, differential risk becomes difficult to detect statistically. Strain differences, including CagA-positive variants, may further modulate neurological impact, yet strain genotyping has rarely been incorporated into clinical studies.

Diagnostic imprecision also persists in the specific literature. Several cognitive investigations relied on screening tools or broad “all-cause dementia” classifications without biomarker confirmation [54]. Misclassification may dilute disease-specific signals. As biomarker-supported phenotyping (e.g., amyloid and tau imaging) becomes standard, future studies may better delineate whether associations are preferentially driven by Alzheimer’s pathology, vascular cognitive impairment, or mixed etiologies.

Confounding by healthcare utilization and medication exposure must also be considered. Patients with neurological disease may undergo more frequent medical evaluations, increasing the likelihood of detecting infection. Proton-pump inhibitor use, common among older adults, may influence both *H. pylori* biology and cognitive outcomes, adding another layer of complexity.

Taken together, the current literature is best regarded as hypothesis-generating rather than conclusive. Definitive clarification will require large prospective cohorts with rigorous confounder adjustment, standardized infection diagnostics, strain-specific analyses, biomarker-supported neurological phenotyping, integration of host immunogenetic profiling, and adequately powered randomized eradication trials in carefully defined high-risk populations.

4.1. Limitations of This Review

Several limitations of the present work warrant acknowledgment. First, this is a narrative review rather than a formal systematic review. Although search strategies and databases were described, study selection and synthesis remain qualitative, and pooled effect sizes were not recalculated independently. Consequently, interpretation relies partly on previously published systematic reviews and meta-analyses. Second, the underlying evidence base is uneven across neurological domains. Parkinson’s disease and dementia are supported by meta-analytic data, whereas migraine and mood disorders rely more heavily on smaller observational cohorts. This imbalance may

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influence interpretive emphasis. Third, most human evidence remains observational, with unavoidable residual confounding related to age, comorbidities, socioeconomic determinants, healthcare access, and medication exposure. Reverse causation remains a plausible explanation in some contexts. Fourth, exposure ascertainment varies considerably. Seropositivity does not necessarily reflect active infection, whereas histology-based studies may preferentially include symptomatic individuals, introducing selection bias. Such variability likely contributes to the heterogeneity observed across studies.

Finally, mechanistic studies, particularly those examining bacterial OMVs and neuroinflammatory pathways [19,97], provide compelling biological plausibility but remain largely preclinical. These findings should not be interpreted as direct proof of causality in humans. Accordingly, this review should be interpreted as a critical synthesis aimed at contextualizing existing evidence, identifying methodological gaps, and generating testable hypotheses for future translational and clinical research.

5. Conclusion

The evolving literature challenges the traditional perception of *H. pylori* as a pathogen confined to the gastric mucosa. Chronic infection has been associated with increased PD severity, modestly elevated risk of dementia, and selected neuropsychiatric conditions, while potentially exerting immunomodulatory effects in MS. These patterns suggest systemic immune and inflammatory influences extending beyond the GI tract.

However, causality has not been established. *H. pylori* is unlikely to be either necessary or sufficient to cause neurodegeneration. Rather, it may function as a disease modifier within a multifactorial framework shaped by genetic susceptibility, vascular risk, environmental exposures, and aging. Observational associations, often modest in magnitude and heterogeneous, should therefore be interpreted with appropriate caution. Although eradication therapy is unlikely to cure neurodegenerative disease, targeted testing may be reasonable in selected contexts, particularly in PD with erratic L-DOPA response or in cognitively impaired patients with GI symptoms or anemia. Such an approach reflects pragmatic clinical judgment rather than a claim of disease modification.

Ultimately, the *H. pylori*-brain connection exemplifies the expanding understanding of the gut-brain axis. What was once considered a localized infection now appears capable of influencing systemic and neural physiology through inflammatory, vascular, immunological, and microbial pathways. Whether these influences prove pathogenic, protective, or context-dependent will depend on the rigor of future translational and clinical investigation. The stomach and the brain are not isolated organs but components of an integrated biological network. *H. pylori* may represent one of the clearest illustrations of this dialogue, subtle, multifactorial, and still incompletely understood.

Author Contributions: Conceptualization, M.P.D. and E.M.; methodology, G.M.P.; software, G,M,P.; validation, M.P.D., G.M.P. and E.M..; formal analysis, G.M.P.; investigation, G.L.; resources, M.P.D.; data curation, G.L. and G.M.P.; writing—original draft preparation, M.P.D. and G.M.P.; writing—review and editing, M.P.D., G.L., G.M.P., P.S. and E.M.; visualization, M.P.D.; supervision, M.P.D.; project administration, M.P.D.; funding acquisition, M.P.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data are available within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202603.1008.v1

Abbreviations

The following abbreviations are used in this manuscript:

BBB	Blood-Brain Barrier
CGRP	Calcitonin gene-related peptide
CNS	Central Nervous System
GI	Gastrointestinal
HP-NAP	Neutrophil-activating protein
MS	Multiple Sclerosis
OMVs	Outer membrane vesicles
OR	Odds Ratio
PD	Parkinson's disease
SIBO	Small intestinal bacterial overgrowth

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