BPR MCS | Bulletin of Pioneering Researches of Medical and Clinical Science

Bulletin of Pioneering Researches of Medical and Clinical Science

Available online: https://bprmcs.com
2023 | Volume 2 | Issue 1 | Page: 58-72

Exploring the Link Between Helicobacter and Idiopathic Parkinsonism: A Systematic Review of Neuropsychiatric Implications

Amyleigh Watts[1], Emma Pitchforth[2], Victoria Easton[3], Stephen Abbott[2*]

[1] Host Microbiome Interaction, Clinical Pharmacology and Therapeutics, Institute of Pharmaceutical Science, King's College London, London SE1 9NH, UK.
[2] South London and Maudsley NHS Foundation Trust, London SE5 8AB, UK.
[3] Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK.

Abstract

The potential role of Helicobacter species in the development of neuropsychiatric disorders has been a subject of interest, particularly in idiopathic parkinsonism (IP), where core motor symptoms can be objectively quantified. This systematic review, based on an EMBASE search, evaluated evidence addressing the association between Helicobacter infection and IP, the impact of bacterial eradication, and the outcomes of untreated infection, following Oxford Centre for Evidence-Based Medicine guidelines. Applying PRISMA criteria, 21 of 204 identified articles were included. Findings indicate that improvements following Helicobacter eradication are not solely due to enhanced levodopa absorption. A strong relationship exists between Helicobacter infection and IP, with H. pylori virulence factors—linked to autoimmune and immune tolerance mechanisms—affecting disease susceptibility, progression, and severity. The usual age-related pattern of virulence marker antibodies seen in healthy controls is absent in IP patients, supporting a causal role. Successful eradication in IP patients, including those naive to anti-parkinsonian therapy, appears to modify disease course but does not prevent onset. Motor symptoms such as hypokinesia improve, and overall motor impairment decreases. Nonetheless, eradication may alter gut microbiota in ways that potentially contribute to subsequent rigidity. Persistent H. pylori, even at molecular levels, or failed eradication, worsens hypokinesia. Short follow-up durations limit the assessment of long-term consequences of untreated infection. Overall, evidence supports Helicobacter as a significant pathophysiological contributor to IP.

Keywords: Helicobacter pylori, Virulence factors, Non-H. pylori helicobacters, Eradication therapy, Parkinson's disease, Pathophysiology, Bradykinesia, Hypokinesia, Rigidity

Corresponding author: Stephen Abbott
E-mail: Abbott.stephen1961@yahoo.com

How to Cite This Article: Watts A, Pitchforth E, Easton V, Stephen Abbott S. Exploring the Link Between Helicobacter and Idiopathic Parkinsonism: A Systematic Review of Neuropsychiatric Implications. Bull Pioneer Res Med Clin Sci. 2023;2(1):58-72. https://doi.org/10.51847/WCdqoKF4vq

Introduction

Helicobacter pylori is among the most prevalent human pathogens, infecting an estimated 4.4 billion individuals worldwide, with 45–80% remaining asymptomatic [1, 2]. Its primary colonization site is the gastric mucosa, where the bacterium is protected from acidic conditions by mucus and the production of ammonia via urease activity [3]. Warren and Marshall first isolated these spiral-shaped bacteria in patients with chronic gastritis (1983) and peptic ulcers (1984) [4, 5]. H. pylori is now recognized as the principal cause of chronic gastritis, peptic ulcer disease, non-cardia gastric cancer, and gastric mucosa-associated

lymphoid tissue (MALT) lymphoma, with eradication significantly reducing the incidence of gastric carcinoma [6, 7]. Colonization has also been reported in extra-gastric sites, including the oral cavity and liver [8–10], and evidence continues to mount for systemic effects beyond the stomach [11–20]. Certain conditions, such as iron and vitamin B12 deficiencies, result directly from gastric infection and atrophy, while others, including idiopathic thrombocytopenic purpura, respond positively to eradication therapy [16]. Associations have also been suggested with Sjögren's syndrome, atherosclerosis, migraine, and rosacea, though these remain largely correlative [17, 18, 21].

Interestingly, H. pylori infection—particularly CagA-positive strains—appears inversely related to Barrett's esophagus [22] and may help maintain immune homeostasis, potentially lowering the risk of chronic immune-mediated conditions like asthma, rheumatoid arthritis, and inflammatory bowel disease [23, 24]. Conversely, eradication may increase susceptibility to autoimmune or inflammatory bowel conditions, as suggested by registry data from Taiwan [24].

Evidence linking Helicobacter to neuropsychiatric disorders has emerged, particularly for idiopathic parkinsonism (IP). Prior observations noted a higher prevalence of peptic ulcers in IP patients as early as the 1960s [25, 26], and it was later hypothesized that an infectious agent might underlie both conditions [27, 28]. Dopaminergic therapy can prevent duodenal ulcer recurrence [29], though the mechanism—possibly via Helicobacter modulation—remains uncertain. Epidemiological data support the association: H. pylori infection is ubiquitous, often lifelong, shows familial aggregation, and is linked to environmental exposure, rosacea, and migraine [17, 18, 30–33]. Transmission typically occurs within close household environments, from parent or sibling to infant, and infection persists. Notably, Charlett *et al.* demonstrated that both IP patients and their siblings were more likely than controls to test seropositive for H. pylori antibodies, and siblings exhibited measurable early IP signs [34]. The current review systematically examines evidence defining Helicobacter's role in IP.

Methods

Search strategy

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [35] and applied a PICO framework: population (individuals with or without IP), intervention (anti-Helicobacter therapy), comparison (pre- vs. post-eradication IP severity, or by Helicobacter status), and outcomes (clinical severity, manifestations, or prevalence).

A comprehensive literature search was conducted in the Ovid EMBASE database, limited to studies published between 2000 and 2019 in peer-reviewed journals, in English or with available translations. Keywords combined terms for Helicobacter infection (Helicobacter, Helicobacter pylori) with IP-related terms (Parkinson's disease, idiopathic parkinsonism). Eligible studies included randomized or open-label Helicobacter eradication trials, as well as cross-sectional observational designs (cohort or case–control). Case reports, reviews, and meta-analyses were excluded from the systematic review but were considered for contextual background.

Assessment of IP outcomes

Clinical outcomes in IP included global motor severity (e.g., UPDRS Part III [36], Webster scale [37]), disability measures (PDQ-39 [38]), functional staging (Hoehn and Yahr [39]), independence in activities of daily living (Schwab and England [40]), and changes in symptomatic treatment requirements. Preference was given to objective assessment of individual cardinal motor signs on continuous scales—for example, mean stride length at free walking speed as a measure of hypokinesia [41]. Immune manifestations and levodopa-related motor complications (UPDRS-IV) [36] were also included to account for potential effects of Helicobacter eradication on drug bioavailability.

Microbial outcomes included current infection status (biopsy, urea breath test, stool antigen) and historical or serological evidence of exposure. When available, antibody titers or virulence marker profiles were extracted.

Study selection

Figure 1 illustrates the study selection process. Two reviewers (R.M.T. and A.D.A.) independently screened titles and abstracts for relevance, followed by full-text review of potentially eligible studies. Discrepancies were resolved through consensus, with a third reviewer (R.J.D.) adjudicating any remaining uncertainties.

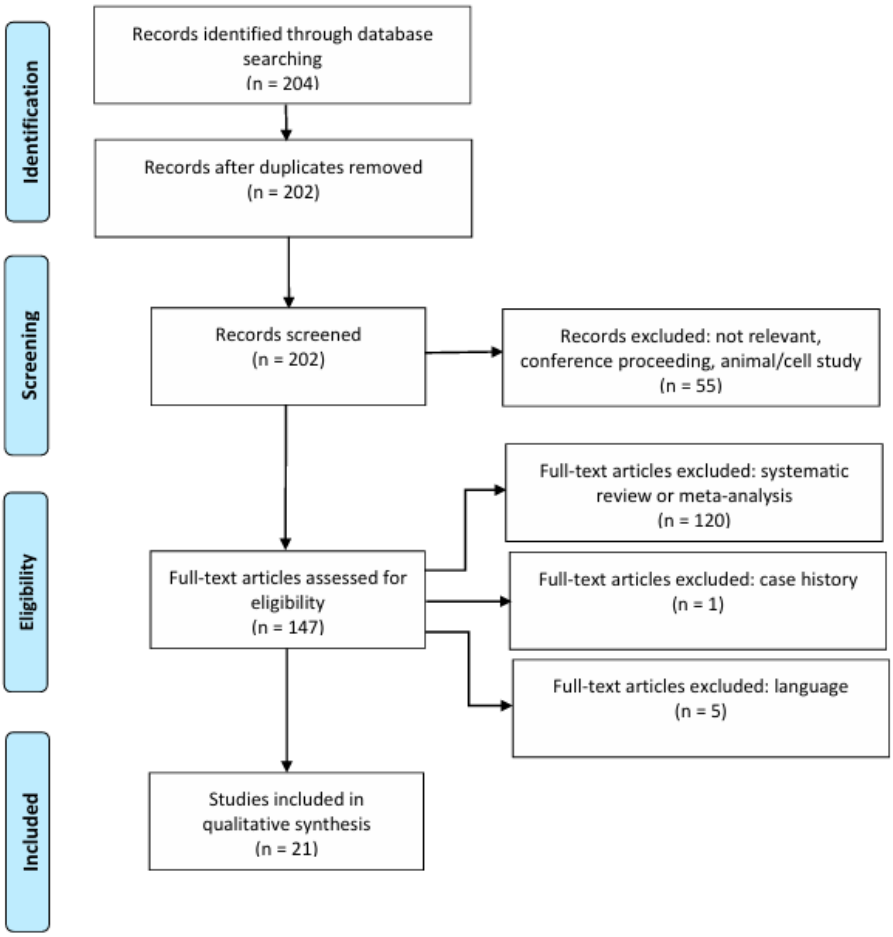

Figure 1. Preferred reporting for systematic review and meta-analysis (PRISMA) flow chart

Data extraction and key questions

From each included study, the following data were systematically extracted **(Tables 1–5)**: (i) bibliographic citation; (ii) study design—classified as randomized or open-label eradication trials, or cross-sectional observational studies with retrospective or prospective data; (iii) cohort size; (iv) methods for determining Helicobacter infection and confirmation of eradication; (v) clinical outcomes; and (vi) the country where the study was conducted.

The review addressed key questions following the Oxford Centre for Evidence-Based Medicine (OCEBM) framework [42]: (i) Does Helicobacter eradication confer a therapeutic benefit? (ii) What are the likely outcomes if eradication therapy is not undertaken? (iii) How prevalent is Helicobacter infection among people with IP?

Risk of bias

Two reviewers (R.M.T. and A.D.A.) independently assessed methodological quality, followed by a consensus discussion and review with a senior investigator (R.J.D.). Randomized controlled trials were evaluated using the Cochrane risk-of-bias tool [43].

Results and Discussion

Search results

The initial database search yielded 204 records **(Figure 1)**. After removing duplicates (n=2), irrelevant studies (n=18), conference abstracts (n=33), animal studies (n=4), reviews or meta-analyses (n=120), a case report (n=1), and non-English articles (n=5), 21 original studies met the inclusion criteria. Among these, one study was published as an interim report [45] with a subsequent final report [46]. Included studies were geographically distributed: Europe (11/20), East Asia (4/20), Southeast Asia (3/20), and the Middle East (2/20).

Study characteristics

Tables 1 and 2 summarize the trials evaluating Helicobacter eradication and its impact on IP severity or cardinal motor signs.

Randomized Controlled Trials (RCTs): Two RCTs [44–46] used a 7-day triple therapy regimen consisting of two antimicrobials and a proton pump inhibitor, with infection confirmed by endoscopic biopsy. The first study [44, 45] tailored antimicrobials according to in vitro sensitivities and applied molecular methods to detect low-

level infections, whereas the second study [46] employed a fixed drug regimen. Control arms differed: the first trial used placebo tablets matching the active regimen, while the second employed allopurinol (antioxidant) with a placebo balance to equalize tablet count between groups. In the first trial, participants on short half-life levodopa were excluded to prevent confounding from drug-induced motor fluctuations, while the second trial included patients exhibiting levodopa-related motor fluctuations. Recruitment in the first trial was halted when hypokinesia worsened among participants with failed eradication. Despite this, the one-year intention-to-treat effect size exceeded initial power calculations by 1.5-fold. The final report [45] extended follow-up to two years, incorporating participants who crossed over to open active eradication after placebo. In the second trial [46], sample size exceeded the first RCT but lacked a pre-specified effect size, with a follow-up of three months. Both trials compared outcomes between successful and failed eradication.

Non-Randomized Trials: Table 2 details four non-randomized studies. One used a fixed-order crossover from placebo to active therapy with two-week follow-up per phase [47]. Three were open-label trials with follow-up periods of three months [48, 49] or one year [50]. Infection was assessed using isotope-labelled urea breath tests (UBT) [48–50] or serology. Motor fluctuations due to levodopa were an inclusion criterion in two trials [47, 48], and all participants received levodopa in a third [50] and partially in a fourth [50].

Cross-Sectional Observational Studies: Table 3 summarizes two eradication trials [48, 51] plus six additional observational studies [51–56] evaluating the association between Helicobacter status and IP severity or cardinal signs. Infection was determined by UBT [48, 49, 54], stool antigen [52], or serology. Seven studies included participants on levodopa therapy [48, 49, 51–55], with motor fluctuations as an inclusion criterion in two [2, 55].

Other Outcome Studies: Table 4 lists studies examining Helicobacter's influence on outcomes beyond global motor severity [57–60]. **Table 5** presents studies assessing Helicobacter prevalence by IP status, or vice versa, including analyses of national registry data [51, 53, 55, 56, 59–64]. Some studies evaluated the obliteration of birth cohort effects in IP [51, 61], while others compared the frequency of H. pylori or non-H. pylori Helicobacter (NHPH) infections in IP patients and controls [59, 63]. Limitations include potential household transmission confounding in studies using spousal controls [59] and lack of IP-status data in large control cohorts [63].

Table 1. Randomised controlled trials of e*ffe*ct of *H. pylori* eradication on severity of, and hypokinesia in, idiopathic parkinsonism

Study	Helicobacter Positivity Assessment	Interventions	Number of Participants (Levodopa Status)	Primary Relevant Outcome Measure	Duration of Blinded Phase (Eradication Confirmation)	Findings
Bjarnason *et al.*; Dobbs *et al.* [44, 45]	Urea breath test (UBT), endoscopic biopsy (histopathology, culture, sensitivities, PCR)	1-week triple therapy based on in vitro sensitivities/suspected intolerance or matched placebo (tablets/capsules without active drug)	30: 14 active, 16 placebo (no levodopa)	Mean stride length at free walking speed	De-blinded at 54 weeks (UBT for all at 1 year, repeat biopsy for active group)	Intention-to-treat: Effect size 1.02 times between-subject SD (study designed for 0.75 SD with n=56). Protocol analysis (excluding two eradication failures in active group): Stride length improved by 7.3 cm/year in active group vs. placebo. Effect consistent in patients on stable long-half-life anti-parkinsonian drugs or treatment-naïve.
Pierantozzi *et al.* [46]	Serology (ELISA), stool antigen, endoscopic biopsy (rapid urease test, histopathology, culture)	1-week fixed triple therapy or allopurinol 100 mg twice daily for 15 days (balanced with placebo to match pill count and duration)	36: 19 active, 17 allopurinol (all with levodopa-induced motor fluctuations)	Sum of serial UPDRS-III scores post-levodopa dose (4 h, including two additional	De-blinded at 3 months (repeat biopsy for all at 3 months)	Triple therapy group (excluding two eradication failures) showed improved UPDRS-III scores; allopurinol group showed no significant change or worsening.

					doses over 11 h)	

* Interim analysis when recruitment stopped because of marked deterioration with failed eradication. At this stage, 31 participants had been randomised, including one drop-out with no data after blinded treatment, and 20 had reached de-blinding. ** Final analysis includes all 30 with post-treatment assessment and follow-up to 3 years after blinded-active treatment or to 2 years after open-active (following blinded-placebo). † Isotope-labelled urea breath test. †† Proton pump inhibitor plus two antimicrobials. # Standard deviation. ¶ Sample size calculation.

‡ Unified Parkinson's Disease Rating Scale Part III-motor section.

Table 2. Non-randomised trials of e*ff*ect *Helicobacter* eradication on severity of, and hypokinesia in, idiopathic parkinsonism

Study	Helicobacter Positivity Assessment	Interventions	Number Helicobacter-Positive (Levodopa Status)	Primary Relevant Outcome Measures	Duration of Follow-Up (Eradication Confirmation)	Findings
Pierantozzi *et al.* [47]	Anti-urease-IgG serology (ELISA)	1-week placebo followed by 1-week fixed triple therapy	6 (all with levodopa-associated wearing-off phenomenon)	UPDRS-III	2 weeks after each intervention (no confirmation)	UPDRS-III score lower after triple therapy compared to placebo at 2 hours post-levodopa test-dose, but not at 1 hour.
Lee *et al.* [48]	Urea breath test (UBT)	1-week fixed triple therapy	35 (all with levodopa-induced motor fluctuations)	UPDRS-III	3 months (UBT at 9 weeks)	Numerical, but not statistically significant, reduction in UPDRS-III score after eradication (excluding one eradication failure).
Hashim *et al.* [49]	Urea breath test (UBT)	1-week fixed triple therapy	21 (on levodopa therapy for ≥1 month)	UPDRS-III, PDQ-39	12 weeks (UBT at 12 weeks)	Significant improvements in UPDRS-III (by 13 points) and PDQ-39 (by 19 points, including mobility) after eradication.
Liu *et al.* [50]	Urea breath test (UBT)	2-week fixed triple therapy	24 (half untreated, levodopa used but not an inclusion criterion)	UPDRS-III	1 year (UBT at 1 year)	Improvement in UPDRS-III score, particularly in bradykinesia/hypokinesia subscores, in triple therapy group compared to untreated group (excluding two eradication failures).

* After excluding six drop-outs. † Parkinson's Disease Questionnaire (disability).

Table 3. Cross-sectional observational studies of relationship of *Helicobacter*-status to motor severity and hypokinesia within idiopathic parkinsonism

Study	Helicobacter Positivity Assessment	Number of IP Participants (Levodopa Status)	Primary Relevant Outcome Measures	Findings
Weller *et al.* [51]	Serum immunoblot antibody profile	124 with immunoblot profile (81% on levodopa, evenly spaced to minimize fluctuations)	Stride length, deterioration over 4 years, Webster Rating Scale	Clinically relevant associations between discriminant index for IP status (based on immunoblot) and shorter stride length, greater deterioration over 4 years, and worse Webster rating.
Lee *et al.* [48]	Urea breath test (UBT)	30 Helicobacter-negative, 35 positive (all on levodopa)	UPDRS-III	No difference in UPDRS-III scores between Helicobacter-positive and -negative groups.
Hashim *et al.* [49]	Urea breath test (UBT)	53 Helicobacter-negative, 21 positive (all on levodopa for ≥1 month)	UPDRS-II, UPDRS-III, PDQ-39	Helicobacter-positive group had worse UPDRS-II, UPDRS-III, and PDQ-39 scores compared to Helicobacter-negative group.
Narozanska *et al.* [52]	Stool antigen	48 Helicobacter-negative, 25 positive (all with levodopa-induced motor fluctuations)	UPDRS-III	No difference in UPDRS-III scores between Helicobacter-positive and -negative groups.
Bu *et al.* [53]	Anti-urease-IgG serology (ELISA)	131 with antibody status against six pathogens (including H. pylori), compared with 141 without IP (unspecified number on levodopa)	Schwab and England Stage	Infection burden (based on seropositivity for six pathogens) associated with having IP and worse Schwab and England Stage.

Tan *et al.* [54]	Urea breath test (UBT)	69 Helicobacter-negative, 33 positive (unspecified number on levodopa)	UPDRS-III, Timed walking test, Purdue Pegboard test	Helicobacter-positive group had worse UPDRS-III scores, longer timed walking test, and inserted fewer pegs in the Purdue Pegboard test compared to Helicobacter-negative group.
Esmael *et al.* [55]	Anti-urease-IgG serology (ELISA)	27 Helicobacter-negative, 23 positive (all with levodopa-induced motor fluctuations)	Total UPDRS (six parts), PDQ-39	Helicobacter-positive group had worse total UPDRS and PDQ-39 scores compared to Helicobacter-negative group.
Roshan *et al.* [56]	Anti-urease-IgG serology (ELISA)	66 Helicobacter-negative, 33 positive (no information on levodopa receipt)	UPDRS-II, UPDRS-III	No difference in UPDRS-II and UPDRS-III scores between Helicobacter-positive and -negative groups.

* idiopathic parkinsonism. † Hoehn & Yahr Stage also performed but no di*ff*erence found in Stage according to *Helicobacter*-status.

Table 4. Cross-sectional observational studies of relationship of *Helicobacter*-status to other outcomes in idiopathic parkinsonism

Study	Helicobacter Positivity Assessment	Number of Participants (Levodopa Status)	Primary Relevant Outcome Measure	Findings
Dobbs *et al.* [57]	Serum immunoblot antibody profile	124 with IP, 194 without IP (81% on levodopa, evenly spaced to minimize fluctuations)	Body mass index	Presence of anti-VacA antibodies tripled the odds of being underweight, regardless of IP status.
Suwarnalata *et al.* [58]	Serology (ELISA), anti-CagA, anti-H. pylori whole cell	60 with IP, 30 seropositive (unspecified number on levodopa)	Autoantibody screen	13 autoantibodies against proteins essential for normal neurological functions distinguished Helicobacter-positive from Helicobacter-negative participants.
Fasano *et al.* [59]	Urea breath test (UBT)	33 with IP, 11 UBT-positive, 18 hydrogen breath test positive for SIBO (all with levodopa-induced motor fluctuations)	Levodopa-induced motor complications	Unpredictable motor fluctuations were significantly more frequent with both SIBO and Helicobacter positivity, and tended to be more frequent with SIBO alone, compared to absence of both conditions.
Rahne *et al.* [60]	Urea breath test (UBT)	40 with IP, 20 UBT-positive (all taking levodopa)	Levodopa-induced motor complications	Helicobacter-positive participants had worse UPDRS-IV scores compared to Helicobacter-negative participants.

† anti-vacuolating toxin. †† anti-cytotoxin-associated gene product. # SIBO = small intestinal bacterial overgrowth.

Table 5. Observational studies of comparative frequency of associated *Helicobacter* and idiopathic parkinsonism and its age relationship

Study	Helicobacter Positivity Assessment	Country	Number of Participants or Samples	Participant/Sample Source	Findings
Dobbs *et al.* [61]	Anti-urease-IgG serology (ELISA)	UK	105 with IP, 210 controls	Volunteers with and without IP screened for inclusion/exclusion criteria	Controls exhibited a birth cohort effect for Helicobacter positivity, which was absent in IP. Higher Helicobacter positivity in IP up to age 72.5 years compared to controls.
Weller *et al.* [51]	Immunoblot serology, Anti-urease-IgG serology (ELISA)	UK	124 with IP, 196 without	Consecutive IP patients from clinic and healthy volunteers from the same locality, with similar inclusion/exclusion criteria (except IP diagnosis excluded in controls)	Birth cohort effect for VacA antibody odds in controls, absent in IP. Highest IP probability with CagA-positivity, VacA-negativity, and urease-B negativity. ELISA did not enhance discrimination.

Nielsen *et al.* [62]	Helicobacter eradication course	Denmark	4484 with IP, 22416 controls	Danish National Patient Register for IP diagnosis (2001–2008), National Prescription Registry for eradication, Civil Registration System for 5 matched controls per IP patient	Increased frequency of historical Helicobacter eradication in IP, even when limited to eradications ≥5 years before IP diagnosis.
Blaecher *et al.* [63]	H. pylori: culture and PCR in culture-negative; H. suis: PCR	UK	60 DNA extracts from IP, 256 from endoscopy departments	Serial archived DNA extracts from Helicobacter Reference Laboratory, selected for documentation and IP clinic status	Relative risk of H. suis vs. H. pylori 10 times higher in IP compared to controls.
Fasano *et al.* [59]	Urea breath test (UBT)	Italy	33 with IP, 30 spouses of IP probands	Consecutive IP patients and their spouses from a hospital	Similar frequency of Helicobacter positivity in IP patients and their spouses.
Bu *et al.* [53]	Anti-urease-IgG serology (ELISA)	China	131 with IP, 141 controls	Consecutive IP patients from hospital, controls randomly recruited from hospital clinics	Higher frequency of Helicobacter positivity in IP compared to controls.
Esmael *et al.* [55]	Anti-urease-IgG serology (ELISA)	Egypt	50 with IP, 20 controls	IP patients from neurology outpatients, age- and gender-matched controls without neurological disease	Higher frequency of Helicobacter positivity in IP compared to controls.
Huang *et al.* [64]	Endoscopic biopsy, UBT for those not tolerating endoscopy	Taiwan	9186 Helicobacter-positive (9105 after matching), 9105 Helicobacter-negative	2000 Longitudinal Health Insurance Database, propensity score matching (age, sex, income, urbanization, comorbidities, medication), follow-up 2000–2012	Increased estimated IP incidence in Helicobacter-positive individuals ≥60 years, regardless of eradication therapy.
Roshan *et al.* [56]	Anti-urease-IgG serology (ELISA)	Iran	99 with IP, 297 controls (excluded if history of Helicobacter eradication)	Consecutive IP patients from neurology clinic, controls from Amirkola Health and Ageing Project matched for age and gender	Lower frequency of Helicobacter positivity in IP compared to controls.

Study Findings

Helicobacter eradication trials in idiopathic parkinsonism

Randomized controlled trials on IP severity and motor features

In the first RCT [45] **(Table 1)**, analysis of 6-weekly observations over one year revealed that participants receiving blinded active Helicobacter eradication therapy experienced a mean increase in stride length of 7.3 cm compared with the placebo group. This improvement occurred regardless of whether participants were treatment-naïve or on long half-life anti-parkinsonian medications. By contrast, four participants with failed eradication showed a substantial decline in stride length (29 cm), even though in two cases H. pylori persistence was only detectable at the molecular level. Corresponding global visual analogue scores for stance and gait also reflected these changes. Notably, improvement in hypokinesia was observed despite a slight post-eradication increase in rigidity. This dissociation between hypokinesia and rigidity persisted in the open-label post-placebo phase. Hypokinesia gains plateaued after one year and remained stable through the three-year study endpoint, whereas rigidity plateaued in the second year and showed minor deterioration in year three.

In the second RCT [46], three months post-treatment, participants receiving eradication therapy demonstrated improved daily total UPDRS motor scores across repeated assessments, except for two individuals in whom eradication failed. In contrast, the allopurinol comparator group exhibited either no improvement or worsening. Measurements of "on-time" (the duration of at least 20% improvement from baseline UPDRS motor scores) mirrored these findings.

Non-Randomized trials on IP severity and motor features

Among four open-label trials **(Table 2)**, one study [49] reported substantial improvement in the total UPDRS motor score and the PDQ-39 mobility domain at 12 weeks after eradication. Another [50] observed improvement over baseline in total UPDRS motor scores and upper/lower limb bradykinesia subscores at one year post-eradication, after excluding two participants with eradication failure. These gains exceeded changes seen in a comparator group of IP patients with untreated Helicobacter infection.

In two trials that specifically included participants with motor fluctuations, one [47] found that the UPDRS motor score, measured two hours after levodopa administration,

improved at two weeks following active eradication compared with the preceding placebo phase. The other [48] showed a numerical, though not statistically significant, improvement in total UPDRS motor scores three months after eradication, after excluding a participant with eradication failure.

Biological gradients of helicobacter serology and disease severity in IP

The first observational study [51] **(Table 3)** highlighted pronounced biological gradients linking Helicobacter serology to clinically meaningful differences in IP severity. Using a discriminant index derived from Western blot IgG antibody patterns against electrophoretically separated H. pylori antigens, higher index values were correlated with shorter stride lengths and greater overall severity on the Webster scale. Moreover, participants with higher index scores experienced a more pronounced decline in stride length over a four-year follow-up period.

Cross-Sectional associations of helicobacter status in IP

With global and facet measures

Among other studies in **Table 3**, Helicobacter-positive individuals consistently demonstrated worse total UPDRS motor scores [49, 54, 55], higher PDQ-39 scores [49, 55], and slower performance on timed walking and pegboard tests indicative of brady/hypokinesia [54]. Most of these studies assessed current infection status, with the exception of one [55]. In contrast, two studies [52, 56] reported no significant differences in total UPDRS scores between Helicobacter-positive and -negative participants (assessed via stool antigen or serology). One study [53] combined Helicobacter seropositivity with broader measures of infection burden. Functional staging using Hoehn and Yahr scores generally showed no sensitivity to Helicobacter status.

With Other Outcomes

Four cross-sectional studies **(Table 4)** explored additional outcomes: body mass index [57], serum autoantibodies [58], and motor complications of levodopa therapy [59, 60]. For BMI, seropositivity for the H. pylori virulence factor VacA was associated with nearly threefold increased odds of being underweight, independently of IP status [57]. Elevated autoantibodies targeting proteins critical for neurological function were more common among H. pylori-positive IP patients compared to seronegative IP participants [58].

Effects of helicobacter eradication or status on levodopa

Pharmacokinetics

Eradication of H. pylori has been linked to increased area under the curve (AUC) for levodopa over both 4-hour and 11-hour periods in a pilot study [47] and an RCT [46], assessed via serology and endoscopic biopsy. However, a cross-sectional study found no significant effect of current H. pylori status on either levodopa AUC or its long half-life metabolite, 3-O-methyldopa, whether measured over 4 hours or extrapolated beyond [52].

Pharmacodynamics

Motor complications associated with levodopa—either decreased, increased, or unchanged—have been variably linked to Helicobacter infection, with most reports indicating reduced complications. Post-eradication, improvements included shorter onset time for levodopa, longer periods of being "on," and reduction of end-of-dose wearing-off [46, 48, 49]. Cross-sectional studies indicated that UBT- or seropositivity was associated with delayed onset and shorter "on-time" [48, 55], particularly when co-occurring with small intestinal bacterial overgrowth (SIBO) [59]. Contradictory findings include one study reporting less wearing-off with UBT positivity [60], and others observed no differences in dyskinesias or motor fluctuations between seropositive and seronegative groups [56].

Longitudinal Follow-Up of untreated helicobacter infection

In one study [50], 12 UBT-positive IP participants who declined eradication were followed for one year. Rigidity improved numerically, while brady/hypokinesia and rest tremor worsened. By contrast, the placebo arm in a year-long blinded RCT [45] showed no significant changes in objective measures of brady/hypokinesia, rigidity, or hand tremor during stance or walking.

An inception cohort [64] demonstrated that Helicobacter infection, confirmed by biopsy or UBT, was associated with increased risk of subsequent IP diagnosis over four years, regardless of whether eradication therapy was administered.

Inter-Relationship between helicobacter and IP

Prevalence of IP with or following helicobacter infection

Two studies [62, 64] explored the risk of IP in the context of Helicobacter exposure. Danish national registry data indicated that prior prescription of Helicobacter eradication therapy (≥5 years before) was associated with a 45% higher likelihood of IP diagnosis [62]. Similarly, Taiwan's National Health Insurance Registry revealed a 129% elevated risk of developing IP among individuals with confirmed H. pylori infection via endoscopic biopsy [64].

Prevalence of helicobacter in IP

Among three cross-sectional studies comparing Helicobacter seropositivity in individuals with and without IP **(Table 5)**, two reported a significant positive association [50, 52], whereas one found a lower frequency of seropositivity in IP patients [53]. The reduced prevalence in the latter study may partly reflect the exclusion of participants with prior Helicobacter eradication therapy. Another study found no difference in urea breath test (UBT) positivity between IP patients and controls; however, the control group consisted of IP probands' spouses, raising the possibility of shared environmental exposure [59]. Interestingly, infections with non-H. pylori Helicobacter species appear more frequent in IP: the relative prevalence of H. suis detected by PCR on gastric biopsies was tenfold higher in IP patients compared to routine gastroenterology patients undergoing endoscopy [63].

Influence of age on the Helicobacter-IP relationship

One study [61] **(Table 5)** demonstrated that anti-urease IgG seropositivity was higher in IP patients compared with controls up to 72 years of age. This finding contrasts with the typical birth cohort effect—an increasing prevalence of seropositivity with age—observed in controls of comparable social backgrounds. Furthermore, a specific profile of H. pylori virulence marker antibodies [51] was associated with the highest predicted probability of developing IP. For individuals with this antibody profile, the odds of parkinsonism began to rise around age 70, reaching a fivefold increase by age 80.

Risk of bias

Table 6 summarizes risk of bias in the two double-blind RCTs evaluating Helicobacter eradication [44–46]. Overall, both trials were judged to have a low risk of bias. Nevertheless, one study [46] had unclear allocation concealment and did not clearly report whether analyses were restricted to participants with proven eradication. Additionally, repeated subjective assessments introduced potential detection bias, including the possibility of carry-over effects.

Table 6. Risk of bias assessment of randomised placebo-controlled trials

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
Citation	**Random Sequence Generation**	**Allocation Concealment**	**Blinding of Participants & Personnel**	**Blinding of Outcome Assessment**	**Incomplete Outcome Data**	**Selective Reporting**
[44,45]	low	low	low	low	low	low
[46]	low	unclear *	low	moderate †	low	unclear #

* Patients allocated to either 7 days of twice daily *Helicobacter* eradication triple-therapy or 15 days of a twice daily allopurinol pill. All participants "received the same number of tablets", but 7 (rather than 8) days of placebo specified at end of triple therapy. † "An expert neurologist unaware of study design clinically evaluated patients." This involved serial within-day and between-day subjective scoring. # Whether intention-to-treat or protocol analysis of proven eradication.

Discussion

Our central focus is whether Helicobacter infection plays a causative role in idiopathic parkinsonism (IP) and, if so, through which mechanisms. Understanding this requires examining the interplay between Helicobacter and IP, as well as the effects of eradication therapy compared with no treatment or failed eradication. Given the long prodromal phase and heterogeneity of IP, where different disease facets progress at varying rates, it is unlikely that a single pathogenic driver explains all outcomes [65]. Eradicating Helicobacter may interrupt one pathological pathway while allowing progression along others. Additional modifiers, such as host genetics or environmental factors like smoking, may influence disease trajectory.

Three prior systematic reviews and meta-analyses have addressed Helicobacter in IP. A 2011 review of six studies through 2006 concluded that potential benefits of eradication must be weighed against screening and treatment costs, without integrating the observed improvement in hypokinesia with successful eradication [66]. A 2017 meta-analysis of eight studies through 2015 reported a positive association between IP and Helicobacter [67]. The 2018 meta-analysis of ten studies through 2017 confirmed this association, noting higher global IP severity in infected individuals (seven studies) and improvements following eradication (five studies) [68]. In contrast, our review of 20 studies through 2019 addresses additional evidence and three specific questions.

Key questions addressed by this systematic review

Effect of helicobacter eradication therapy in IP

This review builds on the 2018 meta-analysis [68] by elevating the level of Oxford Centre for Evidence-Based Medicine (OCEBM) evidence to Level 1 for the question, "Does Helicobacter eradication help?" This upgrade incorporates Level 2 evidence from RCTs [44–46] and a high-impact observational study [51], as well as supportive Level 3 evidence from three of four non-randomised trials [47, 49, 50]. In one non-randomised trial [48], improvements did not reach statistical significance.

The clinical benefit of eradication manifested as reductions in global motor severity and brady/hypokinesia. Short-term effects may reflect non-specific benefits of infection clearance [46, 47], but longer follow-up data—including a three-year RCT [45] and a one-year open eradication study [50]—demonstrate sustained improvement. Cross-sectional studies also link Helicobacter infection to brady/hypokinesia [51, 54], while hypokinesia improves after eradication [45, 50] and worsens with failed eradication [44, 45]. The latter may reflect immune activation triggered by bacterial antigens released during unsuccessful therapy.

Eradication appears to be disease-modifying: in IP patients (mean age 60), hypokinesia improved while rigidity increased [44, 45]. In contrast, untreated patients showed reciprocal trends, with worsening brady/hypokinesia and reduced rigidity [50]. A pilot study tested whether the same antimicrobial intervention for other indications would produce similar effects; IP patients negative for H. pylori showed no disease-modifying benefit [57].

Further evidence from surveillance of antimicrobial prescriptions in IP patients on stable anti-parkinsonian therapy confirmed that improvements in hypokinesia and bradykinesia were specific to Helicobacter infection (mean stride length 15 cm/year; free walking speed 0.2 m/s/year) [69]. However, the effect on rigidity was non-specific, increasing cumulatively after successive antimicrobial courses for unrelated indications (18% after a second course, further 17% after a third). This suggests that H. pylori may suppress rigidity-promoting inflammation, or that eradication may allow the emergence of rigidity-inducing intestinal microbiota. Indeed, in IP, H. pylori presence is inversely related to small intestinal bacterial overgrowth (SIBO) [70]. Supporting this, longitudinal data show a plateau in rigidity progression following the introduction of maintenance laxatives, further implicating gut dysbiosis in rigidity [71].

Consequences of not eradicating helicobacter in IP

Level-1 OCEBM evidence from inception cohort studies [50, 64], supplemented by the placebo arm of an RCT [44, 45], addresses the question, "What happens if Helicobacter is not eradicated?" At first glance, short-term follow-up (1–4 years) suggests little change. However, this period is insufficient to capture the evolution of IP, a disease that develops over decades with a median age at diagnosis of 60–69 years [72]. Given the carcinogenic potential of Helicobacter, leaving the infection untreated for more than a year—even after ruling out neoplasia endoscopically—is generally inadvisable [44, 45]. In fact, many participants had pangastritis or corpus-predominant gastritis, and a third showed atrophy or intestinal metaplasia.

In one cohort [64], biopsy-confirmed infection and the decision to treat or not at a mean age of 51 years did not influence the increased risk of IP diagnosis four years later. Although eradication did not prevent disease, its potential disease-modifying effects remain uncertain [4.1.1]. In another cohort [50] (mean age 63 years), untreated patients had numerically lower rigidity scores after one year, though not statistically significant. Similarly, the placebo arm of a year-long blinded RCT showed no notable changes in brady/hypokinesia or rigidity [45]. Prospective recording of sensitive biomarkers, such as plasma interleukin-6, is required to better evaluate disease evolution [73].

Inter-Relationship between helicobacter and IP

Level-1 evidence on "How common is Helicobacter in IP?" comes from registry-based studies with matched controls [62, 64], emphasizing that prior infection may be as relevant as current infection to IP pathogenesis. This is reinforced by systematic reviews [67, 68] and non-registry surveys [51, 53, 55, 61, 63], indicating that historical or current Helicobacter infection is more frequent in IP than expected, albeit with regional variation.

Geographical differences are notable: the association appears stronger in Taiwan [64] than Denmark [62], likely due to increased virulence conferred by East Asian-type cag pathogenicity island genes, which trigger gastric inflammation, interleukin-8 secretion, and CagA translocation [74]. Even in Europe, specific antibody profiles against pathogenicity markers predict disease burden and progression [51]. Interestingly, the birth cohort effect seen in gastric cancer does not apply to IP: IP patients lack the expected age-related increase in anti-urease and anti-VacA antibodies [51, 61].

Infection with non-H. pylori Helicobacter (NHPH), such as H. suis, is also relevant. Endoscopic biopsy positivity for H. suis in IP patients is associated with a 12-fold increase in all-cause mortality [75]. H. suis is 10 times more frequent relative to H. pylori in IP [63] and may occupy the gastric niche after H. pylori eradication, consistent with its differing antibiotic susceptibilities [76]. Human NHPH infection is typically sparse, often undetectable by UBT [63, 75]. One case report describes successful eradication of NHPH in an IP patient, resulting in improved mobility, weight gain, and resolution of gastritis over four years [57]. In contrast, repeated failed eradication attempts were associated with persistent disease and pangastritis.

Evidence for a causal relationship

Applying Koch's postulates (1884) to Helicobacter in IP:

1. **Presence in disease:** H. pylori is not found in every IP case, and other Helicobacter species are generally unexamined.

2. **Isolation and culture:** H. pylori has been isolated and cultured from IP patients in RCTs [44–46].
3. **Reproduction of disease:** IP occurs only in humans, but Helicobacter may exacerbate parkinsonism in genetically modified animal models.
4. **Recovery from experimentally infected host:** Marshall's self-infection experiments confirm gastritis induction, but the decades-long latency of IP complicates direct replication.

Bradford Hill's concept of a dose–response relationship is illustrated by the discriminant index of anti-H. pylori antibodies, which correlates with IP severity and progression [51]. Understanding the underlying mechanisms remains a key challenge.

Limitations and avoiding a priori assumptions

Several limitations are intrinsic to this systematic review. First, study timeframes are short relative to IP's decades-long prodrome [65, 73]. A narrow definition of IP was avoided, as clinical diagnosis remains critical even without early biomarkers [77, 78].

Second, objective assessments of IP facets were used in only a few studies [44, 45, 51, 54]. Measures such as mean stride length are highly sensitive for detecting treatment effects [40, 79] and reduce bias from global scoring or observer carry-over. Composite scores may mask effects on specific IP features.

Third, inclusion of patients with levodopa-induced motor fluctuations may confound results. Studying anti-parkinsonian treatment-naïve individuals is ideal, while those on stable long-half-time medications are a secondary option.

Finally, failed Helicobacter eradication and low bacterial load—particularly relevant for NHPH—may lead to false-negative conclusions. Accurate determination of Helicobacter status requires endoscopic biopsy with histology, culture, and molecular methods, which is optimal for mechanistic research in IP [65].

Avoiding A Priori Assumptions

Assuming that improvements in IP following Helicobacter eradication are solely due to enhanced levodopa bioavailability diverts attention from the central hypothesis that Helicobacter itself drives disease pathogenesis. The first RCT [44, 45] addressed this by excluding participants on levodopa, though most subsequent studies included patients receiving the drug.

Whether Helicobacter truly alters levodopa pharmacokinetics remains unclear. Levodopa absorption is inherently complex, with multiple plasma peaks [52] and delayed gastric emptying affecting its own uptake [80]. Faster gastric emptying post-eradication has been documented in both dyspepsia [81] and IP [57]. Some studies report that eradication increases the area under the levodopa concentration/time curve [46, 47], but these findings lack robust comparisons with uninfected individuals [52].

Improved performance after eradication may arise independently of altered levodopa kinetics. Elevation of baseline motor function following eradication [4.1.1] would naturally shorten apparent levodopa onset, prolong "on-time," and reduce wearing-off. Notably, an increased area under the curve does not necessarily reduce motor fluctuations; in fact, higher effective levodopa levels may exacerbate them over time [82]. Dyskinesia and on/off fluctuations are likely influenced by time spent outside therapeutic windows and by pulsatile dopaminergic stimulation [83]. Inflammation may further lower thresholds for motor complications, as exemplified by a case report where severe dyskinesia coincided with NHPH recurrence [57]. Coexisting Helicobacter and SIBO also amplify fluctuations [59]. Accumulation of the long half-life metabolite 3-O-methyldopa may contribute to wearing-off [84].

Processes, Mechanisms, and Explanations

Genetic associations between IP and HLA-DR loci suggest a role for classical autoimmunity [65], though cross-reactivity via innate recognition of Helicobacter or the broader microbiome may also be relevant. In IP, hypokinesia improvement after H. pylori eradication appears independent of bacterial load [45]; even low-density infections are detrimental. All eradication failures were ANA-positive, with ANA positivity reducing the benefits of successful eradication. Autoantibodies potentially harmful to neurons correlate with H. pylori seropositivity [58].

A distinct antibody profile—anti-CagA positivity combined with anti-VacA and urease B negativity—predicts global IP severity, hypokinesia, and its progression over four years [51]. CagA is linked to autoimmunity, as demonstrated in thrombocytopenic purpura [85], where anti-CagA antibodies decline after eradication and platelet counts improve. VacA, conversely, modulates immune tolerance, skewing T-cell responses toward regulatory functions [86]. The absence of VacA may predispose to autoimmunity, and reliance on anti-urease B antibodies alone could misclassify prior infection [87].

Clinical and research implications

The association between Helicobacter and IP is well-established. In later adulthood, H. pylori eradication is disease-modifying but not preventive. Early-life eradication may reduce IP risk. Clinically, eradication regresses hypokinesia and improves overall motor function but may also facilitate the emergence of rigidity,

highlighting the need for interventions targeting intestinal transit [69, 71].

Screening for H. pylori and considering eradication should become a routine aspect of IP management. From a research perspective, this provides a foundation for unraveling IP pathogenesis. Helicobacter virulence markers offer mechanistic insights, and the impact of eradication on gastrointestinal microbiota—including interactions with NHPH species—warrants further study.

IP is an ideal starting point for investigating Helicobacter's role in neuropsychiatric disease because its cardinal signs are objectively measurable, allowing for the definition of pre-symptomatic stages [34, 41].

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

Ethics statement: None.

References

1. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of Helicobacter pylori infection: Systematic review and meta-analysis. Gastroenterology. 2017;153:420–9.
2. Mishra S, Singh V, Rao GRK, Jain AK, Dixit VK, Gulati AK, et al. Detection of Helicobacter pylori in stool specimens: Comparative evaluation of nested PCR and antigen detection. J Infect Dev Ctries. 2008;2:206–10.
3. Kao CY, Sheu BS, Wu JJ. Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. Biomed J. 2016;39:14–23.
4. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983;321:1273–5.
5. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984;323:1311–5.
6. Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, et al. Association between Helicobacter pylori eradication and gastric cancer incidence: A systematic review and meta-analysis. Gastroenterology. 2016;150:1113–24.
7. Zullo A, Hassan C, Ridola L, Repici A, Manta R, Andriani A. Gastric MALT lymphoma: Old and new insights. Ann Gastroenterol. 2014;27:27–33.
8. Zheng Y, Liu M, Shu H, Chen Z, Liu G, Zhang Y. Relationship between oral problems and Helicobacter pylori infection. Arch Oral Biol. 2014;59:938–43.
9. Ogaya Y, Nomura R, Nakano K, Watanabe Y. Detection of Helicobacter pylori DNA in inflamed dental pulp specimens from Japanese children and adolescents. J Med Microbiol. 2015;64:117–23.
10. Nilsson HO, Taneera J, Castedal M, Glatz E, Olsson R, Wadström T. Identification of Helicobacter pylori and other Helicobacter species by PCR, hybridization, and partial DNA sequencing in human liver samples from patients with primary sclerosing cholangitis or primary biliary cirrhosis. J Clin Microbiol. 2000;38:1072–6.
11. Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, et al. Management of Helicobacter pylori infection—The Maastricht V/Florence Consensus Report. Gut. 2016;66:6–30.
12. Wenzhen Y, Yumin L, Kehu Y, Bin M, Quanlin G, Donghai W, et al. Iron deficiency anemia in Helicobacter pylori infection: Meta-analysis of randomized controlled trials. Scand J Gastroenterol. 2010;45:665–76.
13. Bai Y, Wang Z, Bai X, Yu Z, Cao L, Zhang W, Ruan C. Cross-reaction of antibody against Helicobacter pylori urease B with platelet glycoprotein IIIa and its significance in the pathogenesis of immune thrombocytopenic purpura. Int J Hematol. 2009;89:142–9.
14. Akcam M, Ozdem S, Yilmaz A, Gultekin M, Artan R. Serum ferritin, vitamin B12, folate, and zinc levels in children infected with Helicobacter pylori. Dig Dis Sci. 2007;52:405–10.
15. Vijayvergiya R, Vadivelu R. Role of Helicobacter pylori infection in pathogenesis of atherosclerosis. World J Cardiol. 2015;7:134–43.
16. Kim BJ, Kim HS, Jang HJ, Kim JH. Helicobacter pylori eradication in idiopathic thrombocytopenic purpura: A meta-analysis of randomized trials. Gastroenterol Res Pract. 2018;2018:6090878.
17. Gasbarrini A, Gabrielli M, Fiore G, Candelli M, Bartolozzi F, De Luca A, et al. Association between Helicobacter pylori cytotoxic type I CagA-positive strains and migraine with aura. Cephalalgia. 2000;20:561–5.
18. Yang X. Relationship between Helicobacter pylori and rosacea: Review and discussion. BMC Infect Dis. 2018;18:4–9.
19. Gravina AG, Zagari RM, De Musis C, Romano L, Loguercio C, Romano M. Helicobacter pylori and extragastric diseases: A review. World J Gastroenterol. 2018;24:3204–21.
20. Wong F, Rayner-Hartley E, Byrne MF. Extraintestinal manifestations of Helicobacter pylori: A concise review. World J Gastroenterol. 2014;20:11950–61.

21. Franceschi F, Covino M, Roubaud Baudron C. Review: Helicobacter pylori and extragastric diseases. Helicobacter. 2019;24:e12636.
22. Rubenstein JH, Inadomi JM, Scheiman J, Schoenfeld P, Appelman H, Zhang M, et al. Association between Helicobacter pylori and Barrett's esophagus, erosive esophagitis, and gastroesophageal reflux symptoms. Clin Gastroenterol Hepatol. 2014;12:239–45.
23. Zhang H, Dai Y, Liu Y, Wu T, Li J, Wang X, Wang W. Helicobacter pylori colonization protects against chronic experimental colitis by regulating Th17/Treg balance. Inflamm Bowel Dis. 2018;24:1481–92.
24. Lin KD, Chiu GF, Waljee AK, Owyang SY, El-Zaatari M, Bishu S, et al. Effects of anti–Helicobacter pylori therapy on incidence of autoimmune diseases, including inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2019;17:1991–9.
25. Schwab R. Symptomatology and medical treatment of Parkinson's disease. Int J Neurol. 1961;2:61–75.
26. Strang RR. The association of gastro-duodenal ulceration and Parkinson's disease. Med J Aust. 1965;51:842–3.
27. Szabo S. Dopamine disorder in duodenal ulceration. Lancet. 1979;2:880–2.
28. Altschuler E. Gastric Helicobacter pylori infection as a cause of idiopathic Parkinson disease and non-arteric anterior optic ischemic neuropathy. Med Hypotheses. 1996;47:413–4.
29. Sikiric P, Rotkvic I, Mise S, Petek M, Rucman R, Seiwerth S, et al. Dopamine agonists prevent duodenal ulcer relapse—A comparative study with famotidine and cimetidine. Dig Dis Sci. 1991;36:905–10.
30. Dobbs SM, Dobbs RJ, Weller C, Charlett A. Link between Helicobacter pylori infection and idiopathic parkinsonism. Med Hypotheses. 2000;55:93–8.
31. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Exploring the association between rosacea and Parkinson disease. JAMA Neurol. 2016;73:529–34.
32. Fischer M, Gemende I, Marsch WC, Fischer PA. Skin function and skin disorders in Parkinson's disease. J Neural Transm. 2001;108:205–13.
33. Scher AI, Ross GW, Garcia M, Gudmundsson LS, Wagner AK. Midlife migraine and late-life parkinsonism. Neurology. 2014;83:1246–52.
34. Charlett A, Dobbs R, Dobbs S, Weller C, Brady P, DW P. Parkinsonism: Siblings share Helicobacter pylori seropositivity and facets of syndrome. Acta Neurol Scand. 1999;99:26–35.
35. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ. 2015;349:g7647.
36. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. Mov Disord. 2007;22:41–7.
37. Webster DD. Critical analysis of the disability in Parkinson's disease. Mod Treat. 1968;5:257–82.
38. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res. 1995;4:241–8.
39. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. Neurology. 1967;17:427–42.
40. Schwab R, England AG. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson ML, editors. Third Symposium on Parkinson's Disease. Edinburgh: Churchill Livingstone; 1969. p. 152–7.
41. Kirollos C, O'Neill CJA, Dobbs RJ, Charlett A, Bowes SG, Weller C, et al. Quantification of the cardinal signs of parkinsonism and of associated disability in spouses of sufferers. Age Ageing. 1993;22:20–6.
42. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford: Centre for Evidence-Based Medicine; 2011.
43. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
44. Bjarnason IT, Charlett A, Dobbs RJ, Dobbs SM, Ibrahim MAA, Kerwin RW, et al. Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 2: Response of facets of clinical idiopathic parkinsonism to Helicobocter pylori eradication. A randomized, double-blind study. Helicobacter. 2005;10:276–87.
45. Dobbs SM, Dobbs RJ, Weller C, Charlett A, Bjarnason I, Lawson A, et al. Differential effect of Helicobacter pylori eradication on time-trends in brady/hypokinesia and rigidity in idiopathic parkinsonism: Report on completion of a randomized, double-blind, placebo-controlled efficacy study. Helicobacter. 2010;15:279–94.
46. Pierantozzi M, Pietroiusti A, Brusa L, Galati S, Stefani A, Lunardi G, et al. Helicobacter pylori eradication and L-dopa absorption in patients with PD and motor fluctuations. Neurology. 2006;66:1824–9.

47. Pierantozzi M, Pietroiusti A, Sancesario G, Lunardi G, Fedele E, Giacomini P, et al. Reduced L-dopa absorption and increased clinical fluctuations in Helicobacter pylori-infected Parkinson's disease patients. Neurol Sci. 2001;22:89–91.
48. Lee WY, Yoon WT, Shin HY, Jeon SH, Rhee PL. Helicobacter pylori infection and motor fluctuations in patients with Parkinson's disease. Mov Disord. 2008;23:1696–700.
49. Hashim H, Azmin S, Razlan H, Yahya NW, Tan HJ, Manaf MRA, et al. Eradication of Helicobacter pylori infection improves levodopa action, clinical symptoms and quality of life in patients with Parkinson's disease. PLoS ONE. 2014;9:e112330.
50. Liu H, Su W, Li S, Du W, Ma X, Jin Y, et al. Eradication of Helicobacter pylori infection might improve clinical status of patients with Parkinson's disease, especially on bradykinesia. Clin Neurol Neurosurg. 2017;160:101–4.
51. Weller C, Charlett A, Oxlade NL, Dobbs SM, Dobbs RJ, Peterson DW, et al. Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 3: Predicted probability and gradients of severity of idiopathic parkinsonism based on H. pylori antibody profile. Helicobacter. 2005;10:288–97.
52. Naroz˙an´ska E, Białecka M, Adamiak-Giera U, Gawron´ska-Szklarz B, Sołtan W, Schinwelski M, et al. Pharmacokinetics of levodopa in patients with Parkinson disease and motor fluctuations depending on the presence of Helicobacter pylori infection. Clin Neuropharmacol. 2014;37:96–9.
53. Bu XL, Wang X, Xiang Y, Shen LL, Wang QH, Liu YH, et al. The association between infectious burden and Parkinson's disease: A case-control study. Park Relat Disord. 2015;21:877–81.
54. Tan AH, Mahadeva S, Marras C, Thalha AM, Kiew CK, Yeat CM, et al. Helicobacter pylori infection is associated with worse severity of Parkinson's disease. Parkinsonism Relat Disord. 2015;21:221–5.
55. Esmael A, El-Sherif M, Shabana HR, Elazzouny AA. Helicobacter pylori infection in Egyptians with Parkinson's disease: Incidence and the effect on motor fluctuation and response to levodopa. Egypt J Neurol Psychiatry Neurosurg. 2016;53:84–8.
56. Roshan TB, Bihani A, Seyed RH, Bagherzade M, Saadat P, Zamani M. The association between Helicobacter pylori infection and Parkinson's disease: A case-control study. J Clin Diagn Res. 2018;12:5–8.
57. Dobbs RJ, Dobbs SM, Weller C, Bjarnason IT, Oxlade NL, Charlett A, et al. Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 1: Eradication of Helicobacter in the cachexia of idiopathic parkinsonism. Helicobacter. 2005;10:267–75.
58. Suwarnalata G, Tan AH, Isa H, Gudimella R, Anwar A, Loke MF, et al. Augmentation of autoantibodies by Helicobacter pylori in Parkinson's disease patients may be linked to greater severity. PLoS ONE. 2016;11:e0153725.
59. Fasano A, Bove F, Gabrielli M, Petracca M, Zocco MA, Ragazzoni E, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. Mov Disord. 2013;28:1241–9.
60. Rahne KE, Tagesson C, Nyholm D. Motor fluctuations and Helicobacter pylori in Parkinson's disease. J Neurol. 2013;260:2974–80.
61. Dobbs R, Charlett A, Dobbs S, Weller C, Peterson D. Parkinsonism: Differential age-trend in Helicobacter pylori antibody. Aliment Pharmacol Ther. 2000;14:1199–205.
62. Nielsen HH, Qiu J, Friis S, Wermuth L, Ritz B. Treatment of Helicobacter pylori infection and risk of Parkinson's disease in Denmark. Eur J Neurol. 2013;19:864–9.
63. Blaecher C, Smet A, Flahou B, Pasmans F, Ducatelle R, Taylor D, et al. Significantly higher frequency of Helicobacter suis in patients with idiopathic parkinsonism than in control patients. Aliment Pharmacol Ther. 2013;38:1347–53.
64. Huang HK, Wang JH, Lei WY, Chen CL, Chang CY, Liou LS. Helicobacter pylori infection is associated with an increased risk of Parkinson's disease: A population-based retrospective cohort study. Park Relat Disord. 2018;47:26–31.
65. Dobbs SM, Dobbs RJ, Weller C, Charlett A, Augustin A, Taylor D, et al. Peripheral aetiopathogenic drivers and mediators of Parkinson's disease and co-morbidities: Role of gastrointestinal microbiota. J Neurovirol. 2016;22:22–32.
66. Rees K, Stowe R, Patel S, Ives N, Breen K, Clarke CE, Ben-Shlomo Y. Helicobacter pylori eradication for Parkinson's disease. Cochrane Database Syst Rev. 2011;2011:CD008800.
67. Shen X, Yang H, Wu Y, Zhang D, Jiang H. Meta-analysis: Association of Helicobacter pylori infection with Parkinson's diseases. Helicobacter. 2017;22:e12398.
68. Dardiotis E, Tsouris Z, Mentis AFA, Siokas V, Michalopoulou A, Sokratous M, et al. H. pylori and Parkinson's disease: Meta-analyses including clinical severity. Clin Neurol Neurosurg. 2018;175:16–24.
69. Dobbs SM, Charlett A, Dobbs RJ, Weller C, Iguodala O, Smee C, et al. Antimicrobial

surveillance in idiopathic parkinsonism: Indication-specific improvement in hypokinesia following Helicobacter pylori eradication and non-specific effect of antimicrobials for other indications in worsening rigidity. Helicobacter. 2013;18:187–96.
70. Dobbs RJ, Charlett A, Dobbs SM, Weller C, A Ibrahim MAA, Iguodala O, et al. Leukocyte-subset counts in idiopathic parkinsonism provide clues to a pathogenic pathway involving small intestinal bacterial overgrowth: A surveillance study. Gut Pathog. 2012;4:1–16.
71. Augustin AD, Charlett A, Weller C, Dobbs SM, Taylor D, Bjarnason I, et al. Quantifying rigidity of Parkinson's disease in relation to laxative treatment: A service evaluation. Br J Clin Pharmacol. 2016;82:441–50.
72. Pagano G, Yousaf T, Wilson H, Niccolini F, Polychronis S, Chaudhuri KR, Politis M. Constipation is not associated with dopamine transporter pathology in early drug-naïve patients with Parkinson's disease. Eur J Neurol. 2018;25:307–12.
73. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. Am J Epidemiol. 2008;167:90–5.
74. Yuan XY, Yan JJ, Yang YC, Wu CM, Hu Y, Geng JL. Helicobacter pylori with East Asian-type cagPAI genes is more virulent than strains with Western-type in some cagPAI genes. Braz J Microbiol. 2017;48:218–24.
75. Augustin AD, Savio A, Nevel A, Ellis RJ, Weller C, Taylor D, et al. Helicobacter suis is associated with mortality in Parkinson's disease. Front Med. 2019;6:188.
76. Vermoote M, Theo T, Vandekerckhove M, Flahou B, Pasmans F, Smet A, et al. Genome sequence of Helicobacter suis supports its role in gastric pathology. Vet Res. 2011;42:1–11.
77. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55:181–4.
78. Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. Ann Neurol. 1992;32:S125–7.
79. Weller C, O'Neill C, Charlett A, Bowes S, Purkiss A, Nicholson P, et al. Defining small differences in efficacy between anti-parkinsonian agents using gait analysis: A comparison of two controlled release formulations of levodopa/decarboxylase inhibitor. Br J Clin Pharmacol. 1993;35:379–85.
80. Robertson D, Renwick A, Wood N, Cross N, Macklin B, Fleming J, et al. The influence of levodopa on gastric emptying in man. Br J Clin Pharmacol. 1990;29:47–53.
81. Miyaji H, Azuma T, Ito S, Abe Y, Ono H, Suto H, et al. The effect of Helicobacter pylori eradication therapy on gastric antral myoelectrical activity and gastric emptying in patients with non-ulcer dyspepsia. Aliment Pharmacol Ther. 1999;13:1473–80.
82. Dobbs RJ, Dobbs SM, Weller C, Charlett A, Taylor D. Time-lag between establishing clinical pharmacology principles and advances in practice: The case of tolerance to levodopa. J Pharmacol Clin Toxicol. 2017;5:1084.
83. Chase TN, Engber TM, Mouradian MM. Contribution of dopaminergic and glutamatergic mechanisms to the pathogenesis of motor response complications in Parkinson's disease. Adv Neurol. 1996;69:497–501.
84. Bowes S, Clark P, Charlett A, O'Neill C, Leeman A, Weller C, et al. Objective outcome criteria in trials of anti-parkinsonian therapy in the elderly: Sensitivity, specificity and reliability of measures of brady- and hypo-kinesia. Br J Clin Pharmacol. 1991;31:295–304.
85. Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. Helicobacter pylori and autoimmune disease: Cause or bystander. World J Gastroenterol. 2014;20:613–29.
86. Lehours P, Ferrero RL. Review: Helicobacter: Inflammation, immunology, and vaccines. Helicobacter. 2019;24:e12644.
87. Ekström AM, Held M, Hansson LE, Engstrand L, Nyrén O. Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection. Gastroenterology. 2001;121:784–91.