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REVIEW

Helicobacter pylori infection is associated with a poor response to levodopa in patients with Parkinson's disease: a systematic review and meta-analysis

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Abstract

Background *Helicobacter pylori* (HP) infection has been reported to be associated with increased severity of Parkinson's disease (PD) and have negative effects on drug response in patients. We aimed to investigate the influence of HP infection on patients with PD using a systematic review and meta-analysis approach.

Methods PubMed and EMBASE databases for relevant articles published before October 2020 were searched. Two authors independently screened records, extracted data, and evaluated the quality of the included studies. The odds ratios (ORs) or standardized mean differences (SMDs) with their corresponding 95% confidence intervals (CIs) were used to calculate the pooled results by employing a random or fixed-effects model. Sensitivity analyses were conducted, and potential publication bias was assessed.

Results A total of 13 studies were included in our meta-analysis. Overall, PD patients with HP infection had significantly higher levodopa equivalent daily dose (UPDRS) motor scores (SMD = 0.266; 95% CI 0.065–0.467; $P = 0.009$) and more units of levodopa equivalent daily dose (LEDD) (SMD = 0.178; 95% CI 0.004–0.353; $P = 0.046$) than those of patients without HP infection. Additionally, the time to achieve 'ON' state was significantly longer (SMD = 0.778; 95% CI 0.337–1.220; $P = 0.001$) and the duration of 'ON' state was significantly shorter (SMD = −0.539; 95% CI = −0.801 to −0.227; $P = 0.001$) in patients with HP infection than in those without HP infection.

Conclusion Our pooled results of this meta-analysis demonstrated that HP infection was associated with worse motor symptoms, higher LEDD, and worse response to drugs in patients with PD. This evidence emphasizes the importance of considering subsequent eradication of HP infection in patients with PD.

Keywords *Helicobacter pylori* · Parkinson's disease · Motor symptoms · Levodopa equivalent daily dose · Response to levodopa

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and represents various motor symptoms (bradykinesia, rigidity, and tremor at rest) and non-motor symptoms (pain, depression, dementia, digestive system problems, and sleep disorders) [1, 2]. The incidence of PD is low before the age of 50 years; however, PD increases rapidly with aging and affects approximately 1% of the population over 60 years [3, 4].

Helicobacter pylori (HP) is a highly prevalent bacterial infection of the digestive tract and is significantly associated with the risk of gastroduodenal diseases [5]. In recent years, more attention has been paid to the association between HP infection and PD [6, 7]. Evidence from a population-based cohort study established that HP infection was associated with an increased risk of PD [8]. The incidence rate of HP infection is higher in patients with PD than that in the general population [9, 10]. Additionally, HP infection may affect the motor symptoms and PD patients' response to levodopa (LD). Previous observational studies have made

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great contributions to this field. For example, a study by Lee et al. indicated that PD patients with HP infection had longer LD "onset" time and shorter "on-time" duration than that in PD patients without HP infection, showing the effect of HP infection on the drug responses in PD [11]. Tan et al. recently reported that HP infection was associated with increased severity of PD motor symptoms in patients [12]. However, several studies failed to identify such relationships [13, 14].

In the past decades, multiple studies have been performed to investigate the role of HP infection in PD and its effect on drug response [11, 12, 15, 16]. However, some of the findings seem to be conflicting, complicating our knowledge on this topic. To date, no comprehensive meta-analysis on this topic has been performed. Therefore, it is necessary to perform a comprehensive systematic review and meta-analysis via an extensive search of observational studies to identify the effect of HP infection on patients with PD.

Methods

This meta-analysis adhered to the MOOSE guidelines for meta-analysis of observational studies and PRISMA guidelines [17].

Literature search strategy

Two independent reviewers (Zhong and Chen) systematically searched PubMed and EMBASE databases for relevant articles published before October 2020. The following search strategy was used: "Parkinson" OR "Parkinson'" OR "Parkinson's" OR "Parkinson disease" OR "Parkinson' disease" OR "Parkinson's disease" OR "parkinsonism" OR "parkinsonian" AND "*Helicobacter pylori*" OR "*H. pylori*" OR "Helicobacter" OR "campylobacter pylori" OR "*Helicobacter pylori*". We also reviewed the reference lists of all included studies and existing reviews for additional studies. Any differences in the literature search process were resolved through a full discussion. Consultation from a third reviewer (Zhang) was acquired if necessary.

Selection criteria

Eligible studies were included if they fulfilled the following criteria: (1) the study design was either a retrospective or prospective observational study (for prospective study, we used baseline data); (2) participants were adults diagnosed with PD; (3) the status of HP infection was evaluated by specific validated methods; (4) the study aimed to identify the effect of HP infection on PD, such as motor symptoms and drug response; and (5) provided sufficient data to pool the results. Studies were excluded if they did not meet the inclusion criteria. We also excluded duplicated articles and non-original research (reviews, meta-analyses, commentaries, letters, and editorials). If two studies used the same data based on the same population, we chose the study with a larger sample size. Any discrepancy in the study selection process was discussed among the two reviewers (Zhong and Chen) to reach a consensus. Consultation from a third reviewer (Zhang) was acquired if necessary.

Data extraction and quality assessment

A standard pre-extraction form was used to initially extract the data needed for this meta-analysis.

The following data were extracted from each study: name of the first author, publication year, country, sample size, study design, age, sex proportion, the evaluation method of HP infection, and diagnostic criteria of PD. Data extraction was performed by two independent reviewers. If there was a disagreement, a third reviewer would help to make the final decision. We evaluated the quality of included studies using the Newcastle–Ottawa Quality Assessment Scale (NOS) [18]. Wherein a maximum score of 9 reflects the highest quality, and a NOS score of ≥ 7 indicates high quality [19].

Statistical analysis

We performed a meta-analysis if a related factor was described by at least three studies. The odds ratios (ORs) or standardized mean differences (SMDs) with their corresponding 95% confidence intervals (CIs) were used to calculate the pooled results. The I^2 statistic and Q statistic were employed to assess heterogeneity across studies [20]. $I^2 > 50\%$ and $P < 0.05$ indicated significant heterogeneity across the included studies; hence, a random-effect model was subsequently used to pool these results. A fixed-effect model was employed when heterogeneity was not significant. We performed a sensitivity analysis by removing one study per time to test the robustness of the results. We used funnel plots, Begg's test, and Egger's test to test for the presence of publication biases. Statistical significance was set at $P < 0.05$ in two-sided tests. Analyses were performed using STATA version 12.0 (StataCorp, Texas).

Results

Literature search

We initially identified 296 potentially eligible studies after the literature search process. Of the 296 identified articles, 232 remained after excluding duplicates, of which 65 were identified as potentially eligible after scanning the titles and abstracts. Twelve articles met the

inclusion criteria after reviewing the full article text. Further, we reviewed the reference lists of all included studies and existing reviews, and one study was added. Eventually, 13 studies were eligible for inclusion in our meta-analysis. The literature search process is illustrated in Fig. 1.

Characteristics of included studies

There were 13 studies [11–14, 21–29] published between 2008 and 2019 included in our meta-analysis. Detailed characteristics of the included studies are presented in Table 1. Our meta-analysis involved 826 patients with PD from Asia (8 studies), Europe (3 studies), Northern America (1 study), and Africa (1 study), including 383 patients in the HP-infected group and 443 patients in the HP non-infected group. All included studies adopted a retrospective observational design. PD diagnosis was most often performed following the UK Parkinson's Disease Brain Bank Criteria. The ^{13}C urea breath test was used to define the status of HP infection in most studies. According to the NOS guidelines, the mean quality score of all included studies was 7.5.

Meta-analysis results

Considering the smaller pooled population reported for some factors (such as age at diagnosis), we only analyzed the factors with a relatively large population (reported by at least three studies) to avoid the error of estimates. All these factors were classified into the following groups: demographic characteristics, PD duration and motor symptoms, and medication.

Association with demographic characteristics

The association between age and HP infection in patients with PD was described in ten studies. The pooled results of ten studies indicated that age was not associated with the risk of HP infection in patients with PD (SMD = 0.081; 95% CI −0.090 to 0.252; $P = 0.352$). A fixed-effect model was used to pool the results because of the low heterogeneity across these studies ($I^2 = 42.3\%$; $P = 0.076$). The results of the meta-analysis are shown in Table 2.

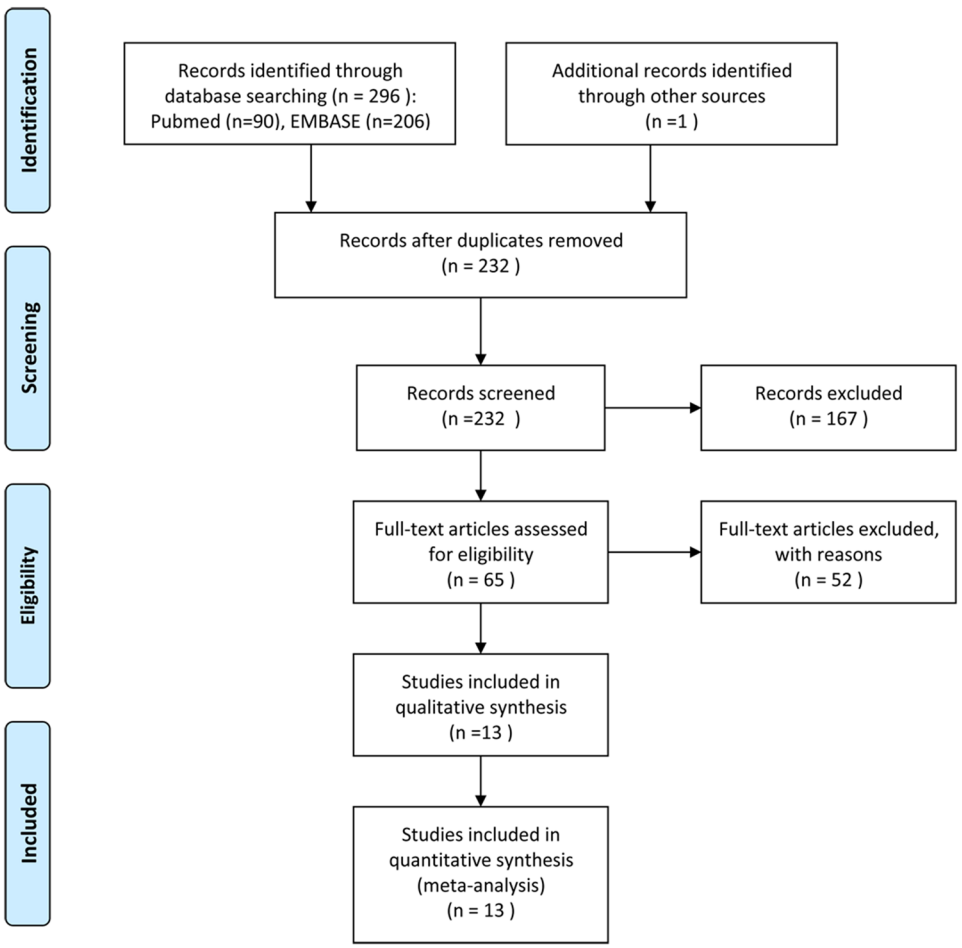

Fig. 1 Flow diagram of study selection

Table 1 Characteristics of 13 included studies

First author	Publication (year)	Country	Sample size	Study design	Mean age (years)	Sex (%, female)	Evaluation of HP infection	PD diagnosis	Factors reported	NOS scores
Won Yong Lee	2008	Korea	65	Retrospective study	60.1	29 (44.6%)	^{13}C urea breath test	UK Parkinson's Disease Brain Bank Criteria	F1, F2, F3,F4,F5, F6,F7,F8	8
A.H. Tan	2013	Canada	74	Retrospective study	NA	NA	^{13}C urea breath test	NA	F6	6
Alfonso Fasano	2013	Italy	33	Retrospective study	67.8	15 (45.5%)	^{13}C urea breath test	UK Parkinson's Disease Brain Bank Criteria	F1,F2, F3, F4, F5, F6, F7, F8	8
Karl-Erik Rahne	2013	Sweden	75	Retrospective study	60.1	39 (52%)	^{13}C urea breath test	UK Parkinson's Disease Brain Bank Criteria	F1, F2, F3, F4, F5	8
Ewa Narożańska	2014	Poland	37	Retrospective study	62.6	18 (48.6%)	*H. pylori* antigen test	UK Parkinson's Disease Brain Bank Criteria	F1, F2, F3, F4, F5, F6	8
Hasriza Hashim	2014	Malaysia	76	Retrospective study	66.9	42 (55.3%)	^{13}C urea breath test	NA	F1, F2, F3, F4, F5, F7, F8	7
Ai Huey Tan	2015	Malaysia	102	Retrospective study	65.3	41 (40.2)	^{13}C urea breath test	Queen Square Brain Bank criteria	F1, F2, F3, F4, F5, F6	8
Ahmed Esmael	2016	Egypt	50	Retrospective study	64.2	23 (46%)	Serum *H. pylori* IgG antibodies test	UK Parkinson's Disease Brain Bank Criteria	F3, F4, F5, F7, F8	7
Gunasekaran Suwarnalata	2016	Malaysia	58	Retrospective study	64.5	29 (50%)	*H. pylori* antigen and CagA serological tests	Queen Square Brain Bank criteria	F1, F2, F3, F4, F5	7
Huijing Liu	2017	China	38	Retrospective study	63.4	20 (52.6%)	^{13}C urea breath test	UK Parkinson's Disease Brain Bank Criteria	F1, F2, F3, F4, F5	8
Kandadai Rukmini Mridula	2017	India	36	Retrospective study	60	17 (47.2%)	Serum *H. pylori* IgG antibodies test	UK Parkinson's Disease Brain Bank Criteria	F1, F2, F3, F5, F6, F7, F8	8
Tahereh Babajani Roshan	2018	Iran	99	Retrospective study	70.5	41 (41.4)	Serum *H. pylori* IgG antibodies test	UK Parkinson's Disease Brain Bank Criteria	F1, F2, F4, F6	7
Murat ÇALIK	2019	Turkey	83	Retrospective study	68.7	NA	Serum *H. pylori* IgG antibodies test	UK Parkinson's Disease Brain Bank Criteria	F4	7

Factors: F1, sex; F2, age; F3, PD duration; F4, Hoehn and Yahr scale; F5, levodopa equivalent daily dose; F6: UPDRS part III score; F7: Time to achieve "ON" State; F8: Duration of the "ON" State; NA, not available; HP, *Helicobacter pylori*; PD, Parkinson's disease; UK, United Kingdom; NOS, Newcastle–Ottawa Quality Assessment Scale

Table 2 The results of meta-analysis

Factors	Number of included studies	Sample size	Pooled effects			Heterogeneity		Analysis model	Publication bias	
			OR/SMD	95% CI	*P* value	I^2, %	*P* value		Begg's test	Egger's test
Age	10	619	0.081	−0.090–0.252	0.352	42.30	0.076	Fixed-effect model	0.721	0.926
Sex	10	621	1.058	0.755–1.483	0.744	30.20	0.168	Fixed-effect model	0.474	0.523
PD duration	10	570	0.172	-0.005–0.348	0.056	0	0.905	Fixed-effect model	0.21	0.109
UPDRS-III score	7	446	0.266	0.065–0.467	0.009	50	0.062	Fixed-effect model	0.764	0.971
Hoehn and Yahr scale	11	716	0.098	-0.064–0.261	0.236	0	0.593	Fixed-effect model	0.533	0.154
LEDD	10	570	0.178	0.004–0.353	0.046	0	0.733	Fixed-effect model	0.152	0.433
Time to achieve 'ON' state	5	260	0.778	0.337–1.220	0.001	58.30	0.048	Random-effect model	0.221	0.416
Duration of 'ON' state	5	260	-0.539	−0.801 to −0.227	0.001	0	0.949	Fixed-effect model	1	0.88

OR odds ratio; *SMD* standardized mean difference; *CI* confidence interval; *PD* Parkinson's disease; *LEDD* levodopa equivalent daily dose

There were ten studies on the relationship between sex and HP infection in patients with PD. The pooled results showed that sex was not associated with HP infection in patients with PD (OR = 1.058; 95% CI 0.755–1.483; $P = 0.744$). A fixed-effect model was used to pool the results because of the low heterogeneity across these studies ($I^2 = 30.2\%$; $P = 0.168$).

Association with PD duration and motor symptoms

Our meta-analysis included ten studies on the association between PD duration and HP infection. Our results showed no significant association between PD duration and HP infection in patients with PD (SMD = 0.172; 95% CI −0.005 to 0.348; $P = 0.056$). A fixed-effect model was used to pool the results because of the low heterogeneity across these studies ($I^2 = 0\%$; $P = 0.905$).

Seven studies were about UPDRS motor scores (UPDRS-III) and HP infection in PD patients. The pooled association showed that PD patients with HP infection had significantly higher UPDRS motor scores compared to those without HP infection (SMD = 0.266; 95% CI 0.065–0.467; $P = 0.009$). A fixed-effect model was used to pool the results since no significant heterogeneity was detected across these studies ($I^2 = 50\%$; $P = 0.062$).

Eleven studies reported the association between Hoehn and Yahr stages (HY) and HP infection in patients with PD. The pooled evidence of 11 studies showed no significant difference in HY stages between patients with and without HP infection (SMD = 0.098; 95% CI −0.064 to 0.261; $P = 0.236$) (Fig. 2). We used a fixed-effect model because of the low heterogeneity across these studies ($I^2 = 0\%$; $P = 0.593$).

Association with medication

The association between levodopa equivalent daily dose (LEDD) and HP infection was reported in ten studies. The pooled effect of the meta-analysis showed that patients with HP infection had more units of LEDD than those recorded for patients without HP infection (SMD = 0.178; 95% CI 0.004–0.353; $P = 0.046$) (Fig. 3). We employed a fixed-effect model because of the low heterogeneity across these studies ($I^2 = 0\%$; $P = 0.733$).

Five studies investigated the effect of HP infection on the amount of time taken to achieve the 'ON' state in patients with PD. The pooled evidence showed that the time to achieve 'ON' state was significantly longer in patients with HP infection than in those without HP infection (SMD = 0.778; 95% CI 0.337–1.220; $P = 0.001$). We employed a random-effect model since significant heterogeneity was detected across these studies ($I^2 = 58.3\%$; $P = 0.048$).

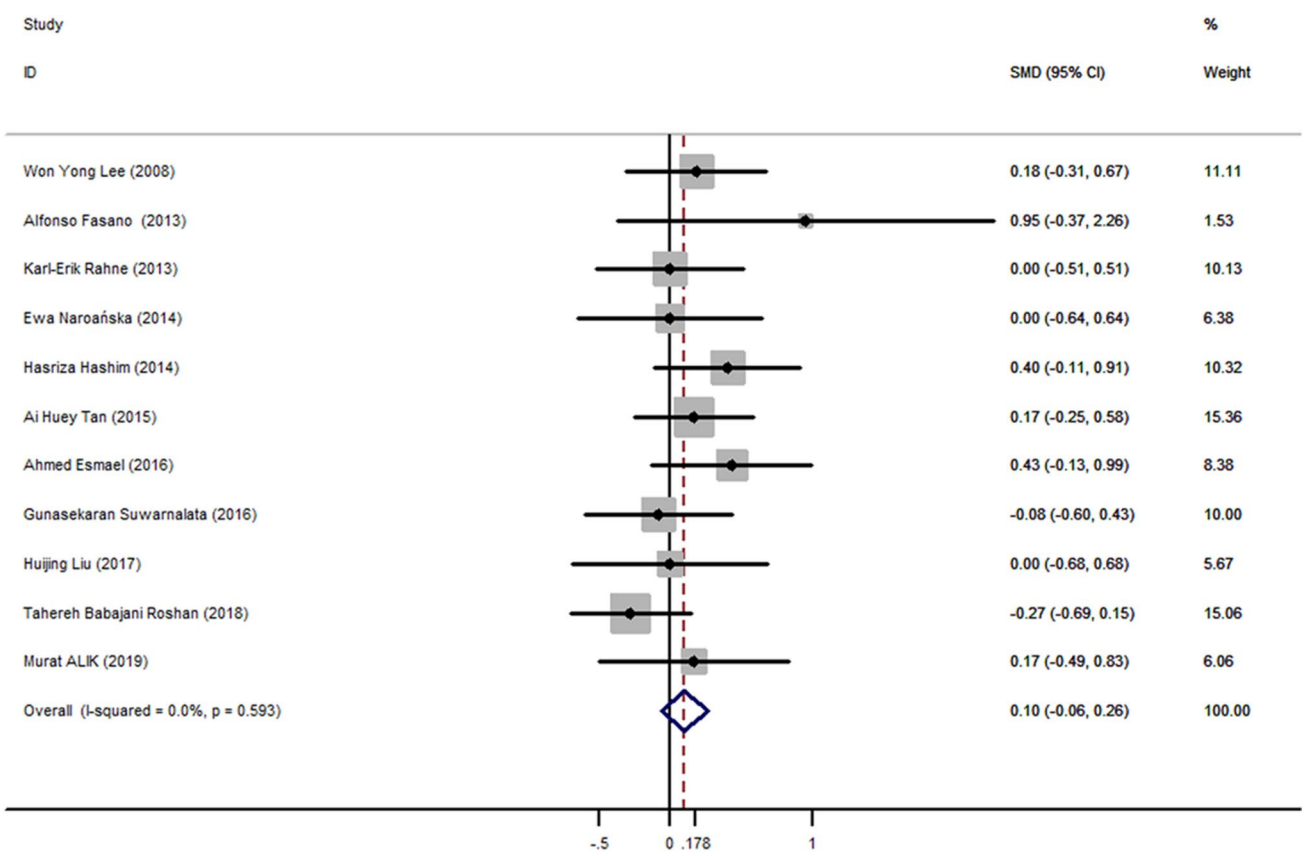

Fig. 2 Forest plot of studies examining the association between Hoehn and Yahr stages and HP infection

Five studies investigated the effect of HP infection on the duration of the 'ON' state in patients with PD. The pooled results showed that the duration of 'ON' state was significantly longer among patients without HP infection that in those with HP infection (SMD = −0.539; 95% CI −0.801 to −0.227; $P = 0.001$). We employed a fixed-effect model to pool the results due to low heterogeneity across these studies ($I^2 = 0\%$; $P = 0.949$).

Sensitivity analysis and publication bias

The results of the sensitivity analysis demonstrated the stability of outcomes in most meta-analyses. However, after excluding one single study per time, the pooled associations were changed for the following two factors: LEDD and UPDRS-III score. Based on the results of the funnel plot, Begg's test, and Egger's test, no evidence for publication bias was detected in all analyses.

Discussion

In this meta-analysis, we established pooled evidence that HP infection represents a higher risk of worse motor symptoms (UPDRS-III score) in patients with PD. Additionally, we found that HP infection was associated with more units of LEDD, longer time to achieve 'ON' state, and shorter duration of 'ON' state in PD patients, indicating a negative effect of HP infection on the response to LD. However, sensitivity analysis showed that the pooled associations with HP infection in PD were changed for LEDD and UPDRS-III scores. Hence, the evidence on LEDD and UPDRS-III score is less persuasive, mostly due to sampling size limitations.

Our findings on the relationship between UPDRS-III score and HP infection were partially in line with a previous meta-analysis by Dardiotis et al. [30], which showed that patients with HP infection had a higher total UPDRS score than those without HP infection. However, sensitivity analysis and publication bias were not assessed in the published meta-analysis by Dardiotis et al., which could not evaluate the robustness of the results. Additionally, we also investigated the associations of HP infection with other demographic and clinical characteristics (such as age and PD duration) and its effect on drug response in PD. In this

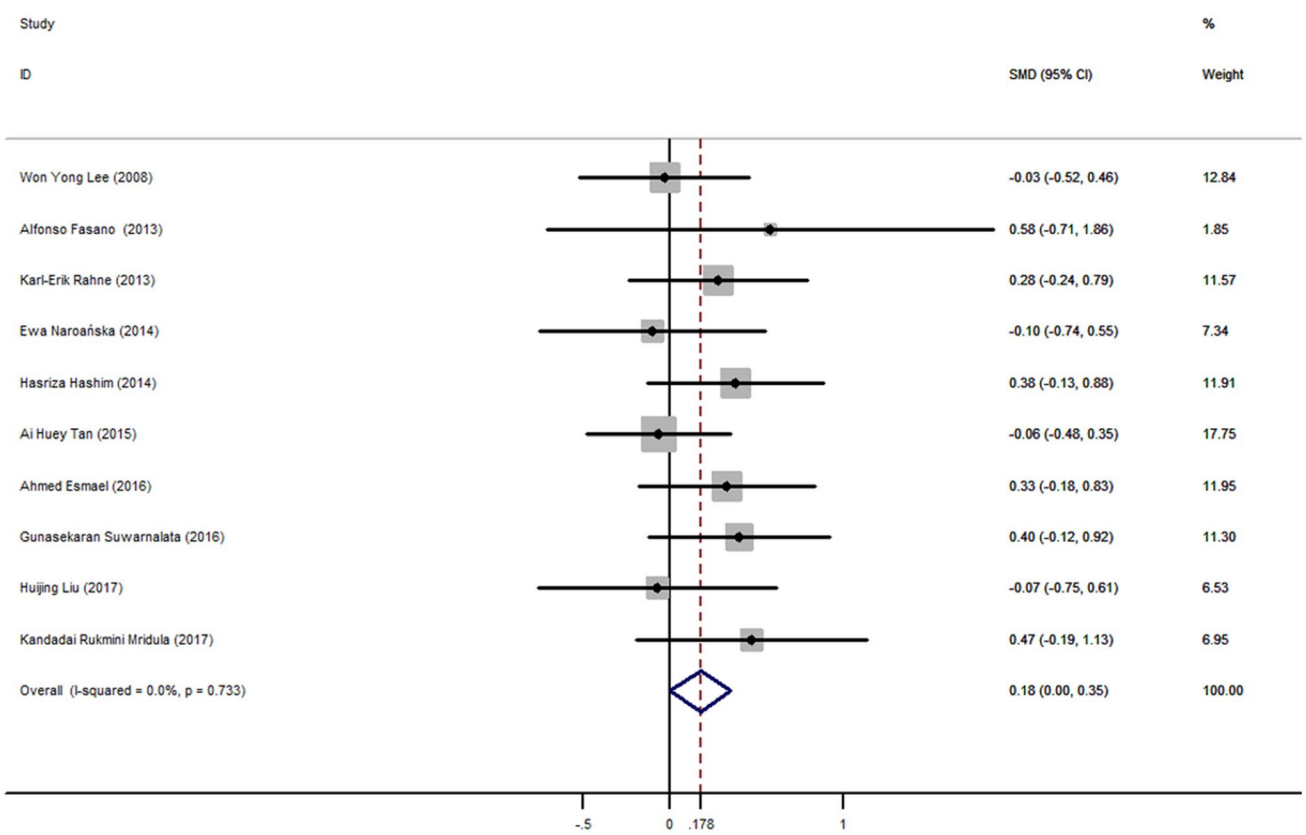

Fig. 3 Forest plot of studies examining the association between LEDD and HP infection

work, we pooled the results of 13 studies with 826 individual enrolments, which may have more statistical power and reliability of the findings.

PD patients with HP infection compared to non-infected patients may present with increased severity of motor symptoms [13, 21]. Its positive association with motor symptom severity in patients with PD was also revealed in our meta-analysis. HP infection may play a causative role in the pathogenesis of PD [6]. Schulz et al. proposed a hypothesis based on their experiments that cholesterol glucosides generated by HP infection may act as neurotoxins, leading to the degeneration of dopaminergic (DAergic) neurons [31]. Khabazian et al. found in vitro studies that sterol glucosides lead to the release of excitotoxic glutamate [32], a process that has been implicated in parkinsonian pathogenesis in multiple studies [33–35]. In addition, prior studies in mice have indicated that cycad toxins cause oxidative stress, caspase activation, and changes in glutamate transporters, among other neuropathologies associated with parkinsonism [31, 36]. Another hypothesis is that HP infection permits immunologically activated molecules to pass the blood–brain barrier, causing damage to dopaminergic cells in the brain [37]. For example, chronic HP infection can generate cytokines such as IL-6 and TNF-α, associated with the inflammation observed in the parkinsonian brain [38]. These cytokines may gain access to the CNS and activate the brain's immune system directly [39]. The CSF from PD patients was observed to contain auto-antibodies against DAergic neurons, which may be generated by chronic nervous system inflammation [40]. However, the association between HP infection and severity of motor symptoms was not statistically significant after carrying out a sensitivity analysis by excluding one study per time. The results of the sensitivity analysis indicated that the evidence on the relationship between HP infection and UPDRS-III score is less stable, and the results should be interpreted with caution. One possible explanation for this is the relatively small sample size in our analysis. Another explanation may be the relatively high heterogeneity across the included studies. We highlight the need to conduct more studies with a large sample size to verify our findings.

It has been reported by some researchers that PD patients with HP infection tended to receive more units of LEDD compared to non-infected patients [25, 28]. However, this result was not duplicated by other studies [11, 14]. Our meta-analysis analyzed the impact of HP infection on LEDD in patients with PD. Our pooled results showed that there were indeed differences between LEDD received by HP-infected patients and HP non-infected patients. This may

be explained partly by the fact that compared to HP non-infected patients, those with HP infection were more likely to have worse motor symptoms, which necessitated the use of more units of LEDD to control these symptoms.

A previous study by Lee and colleagues reported that PD patients with HP infection than those without HP infection had a greater delay in LD "onset (kick-in)" time and shorter "on-time" duration after every single dose of LD [11]. Similarly, our pooled results also provided an evidence-based association between HP infection and the worse clinical response to LD. This may be explained by the increasing evidence about the relevant role of HP infection in reported erratic LD absorption in patients with PD. HP-induced reduction of LD absorption may lead to the need for more units of LEDD for motor control in patients [41]. The disruption of L-dopa absorption by HP infection also has a negative impact on L-dopa "onset" time and "on-time" duration and may be associated with worse motor symptoms. Several potential mechanisms might explain the effect of HP infection on LD absorption, such as the degradation of the drug by chemical processes, delayed delivery into the duodenum, or increased transformation of L-dopa into dopamine [47, 48]. It has been proposed that HP infection could impair LD absorption in PD patients. Clinical data showed a reduction in LD absorption in 189 HP-infected patients under replacement treatment with LD, and further eradication of this infection improves drug absorption [49]. Additionally, HP infection may influence the pharmacokinetic properties with subsequent impact on levodopa efficacy [42].

The present meta-analysis sheds light on the role of HP infection in PD and its negative effect on drug response. This evidence emphasizes the importance of considering subsequent eradication of HP infection in patients with PD. However, our meta-analysis has several limitations. First, some potential studies may be missed with the language restricted to English. A meta-analysis may be biased when the literature search fails to identify all relevant studies. Second, the sample size was relatively small in our meta-analysis. The sample size is also an important factor that influences the results. Third, the association of HP infection with worse motor symptoms and higher LEDD was not statistically significant according to the results of the sensitivity analysis, indicating instability of the pooled evidence. This may be explained by the relatively small sample size.

Conclusions

In summary, our pooled results of this meta-analysis demonstrated that HP infection was associated with worse motor symptoms, higher LEDD, and worse response to drugs in patients with PD. Further large-scale studies are required to confirm our findings due to the inevitable limitations of this meta-analysis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-021-10473-1.

Author contributions RZ, QC, XZ, and ML: literature search, data extraction, statistical analysis, and drafting of the manuscript. RZ and WL: design of the study, quality evaluation, comment on important intellectual content.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standards This article does not contain any experiments performed by any of the authors, on with human participants/animal subjects. As a systematic review and meta-analysis, no ethical approval or consent to participate was required.

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