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TITLE PAGE

Title: Efficacy of *Helicobacter pylori* Eradication Therapy for Functional Dyspepsia: Updated Systematic Review and Meta-analysis.

Short title: *H. pylori* Eradication Therapy for Functional Dyspepsia.

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Abbreviations:

b.i.d.	twice daily
CI	confidence interval
H. pylori	*Helicobacter pylori*
NNH	number needed to harm
NNT	number needed to treat
o.d.	once daily

PPI	proton pump inhibitor
RCT	randomised controlled trial
RR	relative risk
t.i.d.	three times daily
q.i.d	four times daily

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ABSTRACT

Objective: Functional dyspepsia (FD) is a chronic disorder that is difficult to treat. *Helicobacter pylori* (*H. pylori*) may contribute to its pathophysiology. A Cochrane review from 2006 suggested eradication therapy was beneficial, but there have been numerous randomised controlled trials (RCTs) published since. We evaluated impact of eradication therapy on both cure and improvement of FD, as well as whether any benefit was likely to arise from eradication of *H. pylori*.

Design: We searched the medical literature through October 2021 to identify RCTs examining efficacy of eradication therapy in *H. pylori*-positive adults with FD. The control arm received antisecretory therapy or prokinetics, with or without placebo antibiotics, or placebo alone. Follow-up was for ≥3 months. We pooled dichotomous data to obtain a relative risk (RR) of symptoms not being cured or symptoms not improving with a 95% confidence interval (CI). We estimated the number needed to treat (NNT).

Results: Twenty-nine RCTs recruited 6781 *H. pylori*-positive patients with FD. Eradication therapy was superior to control for symptom cure (RR of symptoms not being cured = 0.91; 95% CI 0.88-0.94, NNT = 14; 95% CI 11-21) and improvement (RR of symptoms not improving = 0.84; 95% CI 0.78-0.91, NNT = 9; 95% CI 7-17). There was no significant correlation between eradication rate and RR of FD improving or being cured (Pearson correlation coefficient = -0.23, P = 0.907) but the effect was larger in patients with successful eradication of *H. pylori* than with unsuccessful eradication (RR = 0.65; 95% CI 0.52-0.82, NNT = 4.5, 95% CI 3-9). Adverse events (RR = 2.19; 95% 1.10-4.37) and adverse events leading to withdrawal (RR = 2.60; 95% CI 1.47-4.58) were more common with eradication therapy.

Conclusion: There is high quality evidence to suggest *H. pylori* eradication therapy leads to both cure and improvement in FD symptoms, although the benefit is modest.

SUMMARY BOX

What is already known about this subject?

- *Helicobacter pylori* (*H. pylori*), colonizes the stomach of approximately 50% of the world's population, and is implicated in the pathophysiology of functional dyspepsia (FD).
- However, randomized controlled trials (RCTs) of eradication therapy for the treatment of *H. pylori*-positive patients with FD demonstrate conflicting results.
- It is unclear whether any potential benefit of eradication therapy stems from eradication of *H. pylori* or from other effects of antibiotics on the upper gastrointestinal microbiome.

What are the new findings?

- Eradication therapy had a significant benefit both on cure of symptoms (relative risk (RR) of symptoms not being cured = 0.91; 95% confidence interval (CI) 0.88 to 0.94, number needed to treat (NNT) = 14; 95% CI 12 to 22), and improvement in symptoms (RR of symptoms not improving = 0.84; 95% CI 0.78 to 0.91, NNT = 9; 95% CI 7 to 17).
- This effect remained stable through multiple subgroup analyses.
- The treatment effect was larger, compared with control therapy, in patients with successful eradication of *H. pylori* (RR of symptoms not being cured = 0.74; 95% CI 0.64 to 0.85, NNT = 6; 95% CI 4 to 10).

How might it impact on clinical practice for the foreseeable future?

- Our updated systematic review and meta-analysis provides high quality evidence that eradication therapy is an efficacious treatment for *H. pylori*-positive patients with FD.
- With inclusion of data from almost 7000 patients, almost 3000 of whom were in newly identified RCTs, our confidence in the estimate of effect has improved, and the magnitude of the effect has increased slightly.

INTRODUCTION

Functional dyspepsia (FD) is a disorder of gut-brain interaction (DGBI) whose symptoms are thought to arise from the gastroduodenum.[1] The cardinal symptoms consist of epigastric pain or burning, early satiety, or postprandial fullness. FD is diagnosed in individuals who fulfil symptom-based criteria, the Rome IV criteria, in the absence of a structural explanation.[2] The prevalence of FD in the community, according to these criteria, is approximately 7%.[3, 4] In the majority of individuals symptoms are chronic and run a relapsing and remitting course.[5] The condition therefore affects quality of life and social functioning;[6, 7] almost 50% of patients would accept a >12% risk of sudden death in return for a 99% chance of cure.[8] There is also a substantial economic impact, estimated at over $18 billion per year in the USA.[9]

The pathophysiology of FD is complex, multifactorial, and incompletely understood.[10] *Helicobacter pylori* (*H. pylori*), which colonises the stomach of approximately 50% of the world's population,[11] may be implicated. Numerous epidemiological studies demonstrate that *H. pylori* infection is associated with dyspepsia in the community, most of which will be due to FD,[12] but the magnitude of this association is modest.[13, 14] Nevertheless, randomised controlled trials (RCTs) show that eradication of the bacterium significantly reduces the prevalence of dyspepsia in the community.[15, 16] In contrast, RCTs of eradication therapy in *H. pylori*-positive patients with FD have demonstrated conflicting results,[17-20] although this may be because the benefit is small and some trials were underpowered to detect a significant difference. In a prior Cochrane collaboration systematic review and meta-analysis eradication therapy had a statistically significant benefit, in terms of symptom cure or improvement in *H. pylori*-positive patients with FD, and appeared to be cost-effective.[21, 22] However, the effect was relatively modest,

based on the number needed to treat (NNT), which was reported as 14. Nevertheless, *H. pylori* eradication therapy is recommended for infected patients with FD.[23]

It is 15 years since the last update of this meta-analysis, and there have been further studies published in the intervening years. In addition, it remains unclear whether the benefit of eradication therapy in *H. pylori*-positive FD relates to cure of the infection. Murine models demonstrate that *H. pylori* infection induces sensorimotor changes in the stomach similar to those seen in patients with FD, which are normalised by eradication of the infection.[24] However, studies suggest that there is duodenal inflammation in FD,[25, 26] and alterations in the duodenal microbiota may also be implicated in its pathophysiology.[27] It could, therefore, be the case that the antibiotics used as part of *H. pylori* eradication therapy are exerting beneficial effects via the treatment of other organisms.[28] Indeed, antibiotics appear to be beneficial in other DGBI, such as irritable bowel syndrome,[29, 30] and in a small RCT from Hong Kong rifaximin, a minimally absorbed broad-spectrum antibiotic, was superior to placebo for the treatment of *H. pylori*-negative FD.[31]

We therefore updated the previous systematic review and meta-analysis.[21, 22] Our aims were to re-examine efficacy of eradication therapy for the treatment of *H. pylori*-positive FD, incorporating new RCTs, as well as to assess if any effect is related to the impact of antibiotics on upper gastrointestinal tract microbiota in general or whether this is specific to eradication of *H. pylori*. We assessed this by evaluating whether the efficacy of eradication therapy was influenced by eradication rates achieved, the antibiotics used, or whether eradication of *H. pylori* was successful or not.

METHODS

Search Strategy and Study Selection

We updated the previous Cochrane review and meta-analysis examining this issue. [21, 22] We searched MEDLINE (1946 to October 2021), EMBASE and EMBASE Classic (1947 to October 2021), and the Cochrane central register of controlled trials to identify potential studies. In addition, we searched clinicaltrials.gov. We hand searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2006 and 2021 to identify studies published only in abstract form. Finally, we performed a recursive search of the bibliographies of all eligible studies.

Eligible RCTs examined the effect of ≥1 week of eradication therapy on symptoms of FD in *H. pylori*-positive adults (≥16 years) (Supplementary Table 1). Trials had to compare a recognised, efficacious, eradication therapy with antisecretory therapy or prokinetics, with or without placebo antibiotics, or a placebo alone. The diagnosis of FD could only be made after a normal upper gastrointestinal endoscopy and was based on either accepted symptom-based diagnostic criteria or a physician's opinion. We required that subjects be followed up for ≥3 months, and trials had to report either cure or improvement of FD symptoms at the last point of follow-up. This was preferably patient reported, but if not then as documented by the investigator or via questionnaire data.

The literature search was conducted by two investigators (YY and ET), independently from each other. The search strategy we used is detailed in the supplementary materials. We evaluated all abstracts identified by the search. Again, this was done by two investigators (YY and ET) independently from each other. We obtained all potentially relevant papers and evaluated them in more detail, using pre-designed forms,

to assess eligibility independently, according to the pre-defined criteria. We resolved disagreements between investigators by discussion. There were no language restrictions; we translated foreign language papers. Chinese language papers were translated and, if they reported definite evidence of a randomization process, were included.

Outcome Assessment

Our primary outcome was the effect of *H. pylori* eradication therapy, compared with antisecretory therapy or prokinetics, with or without placebo antibiotics, or a placebo alone on cure or improvement of FD symptoms. Secondary outcomes included effect of *H. pylori* eradication therapy on FD symptoms according to eradication rates, success or failure of eradication therapy, and antibiotics used, as well as total number of adverse events occurring due to therapy, and adverse events leading to study withdrawal, if reported.

Data Extraction

We extracted all data independently. This was done by two investigators (YY and ET) onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (FD symptoms not improved or not cured). A third investigator (ACF) also extracted all trials independently and compared this with the final data extraction as agreed by the first two investigators. Any disagreements were resolved by consensus (PM, ACF, YY). To study the effect of eradication therapy on FD symptoms according to success or failure of *H. pylori* eradication we also extracted data in the active *H. pylori* eradication therapy arms of the trial according to final *H. pylori* status, where reported. For all included studies, we also extracted the following data for each trial, where available: country of origin, setting, number of centres, criteria used to

define FD, method used to confirm *H. pylori* infection, type of *H. pylori* eradication regimen used (including dose and schedule of individual drugs within it), duration of treatment, eradication rate, duration of follow-up, total number of adverse events, and number of adverse events leading to withdrawal. We extracted all data as intention-to-treat analyses, where we assumed all dropouts to be treatment failures (*i.e.,* symptoms not cured or not improved at last point of follow-up), wherever trial reporting allowed this.

Quality Assessment and Risk of Bias

We assessed risk of bias at the study level. This was done by two investigators independently (YY and ET), using the Cochrane risk of bias tool.[32] We resolved disagreements by discussion. We recorded the method used to generate the randomization schedule and conceal treatment allocation, whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We used a random effects model to pool data,[33] to give a more conservative estimate of the efficacy of eradication therapy in *H. pylori*-positive patients with FD. We expressed the impact of eradication therapy, compared with antisecretory therapy or prokinetics, with or without placebo antibiotics, or a placebo alone as a relative risk (RR) of symptoms not being cured, or symptoms not improving, separately along with 95% confidence intervals (CIs). We used a RR of symptoms not being cured, or symptoms not improving, where if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of *H. pylori* eradication therapy over the control intervention. This

approach is the most stable, compared with a RR of cure or improvement, or using the odds ratio, for some meta-analyses.[34] Similarly, we summarised adverse events data with RRs and 95% CIs. We calculated the NNT, and the number needed to harm (NNH), with a 95% CI, using the formula NNT or NNH = 1 / (assumed control risk x (1 – RR)).

We assessed heterogeneity between studies using both the χ^2 test, with a P value <0.10 used to define a significant degree of heterogeneity, and the I^2 statistic. The I^2 ranges between 0% and 100%, and is typically considered low, moderate, or high for values of 25% to 49%, 50% to 74%, and ≥75% respectively.[35] Review Manager version 5.4.1 (RevMan for Windows 2020, the Nordic Cochrane Centre, Copenhagen, Denmark) was used to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. Where there were sufficient studies (≥10),[36] we assessed funnel plots for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test.[37]

Due to differences in the control interventions used in eligible trials, we performed a subgroup analysis limited to RCTs that compared *H. pylori* eradication therapy to antisecretory therapy and placebo antibiotics, or a placebo alone. We also performed subgroup analyses including only low risk of bias trials, according to study location (Asian versus non-Asian studies), and according to duration of follow-up (12 months versus <12 months). To examine the effect of *H. pylori* eradication therapy on FD symptoms according to either success or failure of eradication therapy, and antibiotic used we performed subgroup analyses. We compared rates of cure or improvement of symptoms in patients with successful or unsuccessful eradication therapy with those in the control arm, as well as with each other. We also pooled trials according to the antibiotic used as part of the eradication therapy regimen and assessed whether there were statistically significant differences between them according to the χ^2 test.

RESULTS

The search identified 6687 citations, of which 29 trials, recruiting 6781 patients, reported dichotomous symptom data, and were judged as being eligible for inclusion (Supplementary Figure 1). [17-20, 38-62] Ten of these trials, recruiting 2896 patients, were identified since the previous systematic review and meta-analysis.[53-62] In total, 3625 patients were randomised to receive *H. pylori* eradication therapy and 3156 antisecretory therapy or prokinetics, with or without placebo antibiotics, or a placebo alone. Characteristics of all included trials are provided in Supplementary Table 2. Risk of bias assessment of all included RCTs is provided in Supplementary Table 3. We classed six trials as being at low risk of bias across all domains.[20, 43, 49, 55, 58, 62]

Effect of *H. pylori* Eradication Therapy on FD Symptoms

In total, there were 18 RCTs reporting on cure of symptoms,[17-20, 42, 43, 45, 47, 48, 50, 51, 53-59] which recruited 4564 *H. pylori*-positive patients with FD, 2432 of whom received eradication therapy. The RR of FD symptoms not being cured with eradication therapy versus control was 0.91 (95% CI 0.88 to 0.94) (Figure 1), with minimal heterogeneity between studies (I^2 = 7%, P = 0.38). However, the funnel plot was asymmetrical, suggesting evidence of publication bias, or other small study effects (Egger test, P = 0.083). The NNT was 14 (95% CI 11 to 21). When we limited the analysis to only the 14 studies, containing 3903 patients,[17-20, 42, 43, 45, 47, 48, 50, 55, 57-59] that compared eradication therapy with either antisecretory therapy with placebo antibiotics, or placebo alone, the RR of symptoms not improving was 0.91 (95% CI 0.89 to 0.94), with a NNT of 14 (95% CI 12 to 22) with no heterogeneity between studies (I^2 = 0%, P = 0.80), and no evidence of funnel plot asymmetry (Egger test, P = 0.24). When the eight RCTs that compared antisecretory therapy and placebo antibiotics with eradication therapy were included,[17, 42,

[43, 45, 47, 48, 58, 59] there was still a benefit (RR = 0.92; 95% CI 0.88 to 0.96, I^2 = 0%, P = 0.73), with a NNT of 16 (95% CI 11 to 33). Similarly, when only the six trials that compared placebo alone with eradication therapy were included,[18-20, 50, 55, 57] the benefit remained (RR = 0.91; 95% CI 0.87 to 0.96, I^2 = 0%, P = 0.47) with a NNT of 14 (95% CI 10 to 31).

There were 22 trials that reported on improvement of FD symptoms,[18-20, 38-41, 44-47, 49-54, 57, 58, 60-62] randomizing 5193 *H. pylori*-positive patients with FD, 2824 of whom received eradication therapy. The RR of FD symptoms not improving with eradication therapy versus control was 0.84 (95% CI 0.78 to 0.91) (Figure 2), with moderate heterogeneity between studies (I^2 = 69%, P < 0.001). The funnel plot was symmetrical, suggesting no evidence of publication bias, or other small study effects (Egger test, P = 0.16). The NNT was 9 (95% CI 7 to 17). When we limited the analysis to only the 16 studies, containing 4224 patients,[18-20, 38, 39, 41, 44-47, 49, 50, 57, 58, 61, 62] that compared eradication therapy with either antisecretory therapy with placebo antibiotics, or placebo alone, the RR of symptoms not improving was 0.86 (95% CI 0.79 to 0.94), with a NNT of 10 (95% CI 7 to 24). Moderate heterogeneity between studies persisted (I^2 = 71%, P < 0.001), but there was no evidence of funnel plot asymmetry (Egger test, P = 0.46). Eight of these trials compared antisecretory therapy and placebo antibiotics with eradication therapy (RR = 0.83; 95% CI 0.73 to 0.95, I^2 = 81%, P < 0.001; NNT = 8; 95% CI 5 to 27),[38, 39, 44-47, 58, 61] and eight compared placebo alone with eradication therapy (RR = 0.90; 95% CI 0.80 to 1.00, I^2 = 49%, P = 0.06).[18-20, 41, 49, 50, 57, 62]

Pooling data from all 29 RCTs, irrespective of whether they reported symptom cure or improvement, but using symptom cure preferentially, where reported, the RR of symptoms not being cured or not improving with *H. pylori* eradication therapy versus control was 0.87 (95% CI 0.83 to 0.92), with moderate heterogeneity between studies (I^2 = 64%, P <0.001) (Supplementary Figure 2). Again, the funnel plot was asymmetrical,

suggesting evidence of publication bias, or other small study effects (Egger test, P = 0.014). The NNT was 10 (95% CI 8 to 16). Limiting the analysis to only the six RCTs at low risk of bias still demonstrated a significant effect of *H. pylori* eradication therapy (RR of symptoms not being cured or improving = 0.90; 95% CI 0.81 to 0.99, I^2 = 46%, P = 0.10) (Supplementary Figure 3),[20, 43, 49, 55, 58, 62] with a NNT of 14 (95% CI 7 to 139). When we performed a subgroup analysis based on study location the effect of *H. pylori* eradication therapy was greater in Asian (RR = 0.82; 95% CI 0.73 to 0.91, NNT = 8; 95% CI 5 to 15, I^2 = 77%, P <0.001) compared with non-Asian studies (RR = 0.92; 95% CI 0.89 to 0.95, NNT = 16; 95% CI 12 to 25, I^2 = 11%, P = 0.32) and this difference was statistically significant (P value for χ^2 = 0.04) (Supplementary Figure 4). Finally, when we performed a subgroup analysis based on study duration a beneficial effect on FD symptoms was seen in studies of 12 months duration (RR = 0.87; 95% CI 0.82 to 0.92, NNT = 10; 95% CI 7 to 17, I^2 = 65%, P <0.001), but not studies of <12 months duration (RR = 0.88; 95% CI 0.77 to 1.00, I^2 =67%, P = 0.01) (Supplementary Figure 5), but this difference was not statistically significant (P value for χ^2 = 0.87).

Effect of *H. pylori* Eradication Therapy on FD Symptoms According to Eradication Rates, Success or Failure of Eradication Therapy, and Antibiotics Used

To assess whether the beneficial effect of eradication therapy was due to eradication of *H. pylori* or an effect related to the use of antibiotics in general, or a particular antibiotic, we first assessed for any correlation between eradication rates observed in the trials and rates of symptom cure or improvement using a Pearson correlation coefficient. There was no significant correlation between the two (Pearson correlation coefficient = -0.23, P = 0.907) (Figure 3).

Second, we compared rates of symptom cure or improvement according to whether *H. pylori* was eradicated successfully in patients in the trial arms that received active *H. pylori* eradication therapy. In these analyses, there were 16 RCTs,[18, 19, 38, 40, 41, 43, 48-50, 54-57, 59-61] containing 2809 patients, where symptom cure or improvement rates could be compared between patients with successful eradication of *H. pylori* and patients in the control arms. The RR of symptoms not being cured or not improving with successful *H. pylori* eradication therapy versus control therapy was 0.74 (95% CI 0.64 to 0.85, I^2 =82%, P <0.001) (Figure 4), and with evidence of funnel plot asymmetry (Egger test, P = 0.076). The number needed to treat was 6 (95% CI 4 to 10). Thirteen trials,[19, 38, 40, 41, 43, 48, 49, 55-57, 59-61] containing 1517 patients, provided data comparing symptom cure or improvement rates between patients with unsuccessful eradication of *H. pylori* and patients in the control arms. In this analysis, the RR of symptoms not being cured or not improving with unsuccessful *H. pylori* eradication therapy versus control therapy was 1.02 (95% CI 0.96 to 1.09, I^2 = 0%, P = 0.63) (Supplementary Figure 6), with no evidence of funnel plot asymmetry (Egger test, P = 0.75). These same 13 RCTs,[19, 38, 40, 41, 43, 48, 49, 55-57, 59-61] containing data from 1259 patients, compared symptom cure or improvement rates between patients receiving eradication therapy with successful or unsuccessful eradication of *H. pylori*. The RR of symptoms not being cured or not improving with successful versus unsuccessful eradication of *H. pylori* was 0.65 (95% CI 0.52 to 0.82, I^2 = 79%, P <0.001) (Figure 5), with no evidence of funnel plot asymmetry (Egger test, P = 0.20). The NNT in this analysis was 4.5 (95% CI 3 to 9).

Finally, we compared efficacy of eradication therapy with control therapy according to the eradication regimen or antibiotics used (Table 1). NNTs were lower, generally, with nitroimidazole-containing regimens, and in regimens consisting of a proton pump inhibitor (PPI) in combination with either amoxicillin and a nitroimidazole, or

Table 1. Relative Risk of Symptoms Not Being Cured or Not Improving and Number Needed to Treat According to *H. pylori* Eradication Regimen Used.

***H. pylori E*radication Regimen Used**	**Number of Trials**	**Number of Patients**	**RR of Symptoms Not Being Cured or Not Improving (95% CI)**	**NNT (95% CI)**	**I^2**	**P value for χ^2**
Amoxicillin-containing	25	6076	0.91 (0.88 – 0.94)	15 (11 – 22)	19%	0.20
Clarithromycin-containing	22	5577	0.87 (0.82 – 0.92)	10 (7 – 17)	67%	<0.001
Nitroimidazole-containing	8	1589	0.79 (0.67 – 0.93)	6.5 (4 – 18.5)	86%	<0.001
Tetracycline-containing	2	223	0.54 (0.16 – 1.77)	N/A	88%	0.005
PPI, amoxicillin, clarithromycin	17	4159	0.92 (0.89 – 0.95)	16.5 (12 – 26.5)	0%	0.61
PPI, amoxicillin, nitroimidazole	2	469	0.87 (0.81 – 0.94)	8.5 (6 – 18)	0%	0.33

PPI, clarithromycin, nitroimidazole	2	482	0.68 (0.47 – 0.98)	4 (2 – 57)	89%	0.003
PPI triple therapy containing a nitroimidazole	5	1112	0.80 (0.66 – 0.97)	6 (4 – 40)	86%	<0.001

N/A; not applicable. No significant benefit of treatment.

clarithromycin and a nitroimidazole. Given this, we assessed for differences in efficacy across all nitroimidazole-containing and non-containing regimens, as well as nitroimidazole-containing and non-containing PPI triple therapy regimens (Supplementary Figures 7 and 8). However, there were no significant differences between these subgroup analyses according to the χ^2 test (P = 0.10 and P = 0.17, respectively).

Adverse Events

Adverse events data were reported incompletely by most trials. Only eight RCTs reported total numbers of adverse events, in 1937 patients.[19, 41, 45, 46, 48, 52, 56, 58] Overall, adverse events were significantly more common with eradication therapy (RR = 2.19; 95% CI 1.10 to 4.37), with high levels of heterogeneity between studies ((I^2 = 92%, P < 0.001) (Supplementary Figure 9) and a NNH of 3 (95% CI 1 to 40). Adverse events leading to withdrawal were reported by 18 trials, recruiting 3694 patients.[18-20, 38, 39, 41-43, 45-47, 49, 50, 52, 53, 55-57] Withdrawals due to adverse events were also significantly more likely with eradication therapy (RR = 2.60; 95% CI 1.47 to 4.58), with no heterogeneity between studies (I^2 = 0%, P = 0.66) (Supplementary Figure 10) and a NNH of 71 (95% CI 32 to 242). There was no evidence of funnel plot asymmetry (Egger test, P = 0.62).

DISCUSSION

This updated systematic review and meta-analysis has confirmed that eradication therapy is efficacious for the treatment of FD in *H. pylori*-positive patients. The RR of either symptoms not being cured or symptoms not improving was significantly lower than with a control intervention, with a NNT of 14 and 9, respectively. Adverse events were more common with eradication therapy, as were adverse events leading to withdrawal, although reporting of these data was incomplete in many trials. Although the effect on cure of symptoms was modest, when applied to entire healthcare systems, and for a highly prevalent condition, this is likely to lead to substantial reductions in management costs. Eradication therapy is particularly likely to be cost-effective as a 2-week course of treatment has an impact for at least 12 months. We judged the evidence for efficacy and safety of eradication therapy in *H. pylori*-positive patients with FD as high quality (Supplementary Table 4).

Whether this relates to the eradication of *H. pylori* or a more general impact on the upper gastrointestinal tract microbiota is unclear from our data. There was no correlation between *H. pylori* eradication rates and rates of symptom cure or improvement, which suggests the effect may relate to a general impact on the gut microbiota. This analysis has the advantage that all data are evaluated and so publication bias is less likely, but as trial level data are being used it is possible that the results are confounded by trial level factors. On the other hand, the RR of FD symptoms not being cured or not improving was significantly lower in those patients receiving eradication therapy who had successful eradication of *H. pylori*, compared with either patients receiving a control intervention or patients randomised to eradication therapy in whom eradication was unsuccessful, with a NNT of 6 and 4.5, respectively, which appear more impressive. This suggests a specific effect of the eradication regimen on *H. pylori*, although over half the trials did not report

these data, so publication bias is probable. Also, patients remaining *H. pylori*-positive are likely to be different to those with successful eradication, and so these results may also be due to bias or confounding. For instance, patients in whom eradication of *H. pylori* was unsuccessful may be less likely to adhere to the trial medication, and hence not receive antibiotics at all. Finally, NNTs were lower with *H. pylori* eradication regimens containing a nitroimidazole, although these differences in efficacy were not statistically significant.

We updated a previous meta-analysis from 2006, using a contemporaneous and exhaustive search strategy, and identified 10 new eligible RCTs, containing almost 3000 patients. Despite this, the estimate of the efficacy of eradication therapy, in terms of cure or improvement of symptoms, remains relatively unchanged from the last version of this meta-analysis.[22] However, in this updated meta-analysis we studied the effect of *H. pylori* eradication therapy on cure or improvement of symptoms separately. Although the NNT of 14 for cure of symptoms is modest, the NNT of 9 for improvement in symptoms is of a similar magnitude to that for other drugs in FD.[63-66] Data extraction was undertaken in triplicate. We used a random effects model and an intention-to-treat analysis, to minimise the possibility that the effect of eradication therapy on symptoms of FD has been overestimated. In addition, all trials had a minimum duration of follow-up of 3 months, and only six trials reported data at less than 12 months of follow-up,[41, 43, 48, 51, 52, 57] meaning that the data we report are likely to indicate long-term efficacy. In fact, in a subgroup analysis based on study duration the effect for symptom cure or improvement increased, with a NNT of 10, when only trials of 12 months duration were included, whereas when RCTs of <12 months duration were included there was no significant benefit. Although the difference between these subgroup analyses was not statistically significant this suggests that future trials should aim to follow participants up for 12 months in order to assess any benefit of eradication therapy in *H. pylori*-positive FD.

Limitations of this meta-analysis include the fact that only six trials were classed as being at low risk of bias across all domains, although a subgroup analysis including only these RCTs still demonstrated a significant effect of *H. pylori* eradication therapy in FD. This means that the quality of evidence underpinning our estimates is of high quality. There was heterogeneity between studies examining the effect of *H. pylori* eradication therapy on symptom improvement, meaning that there is uncertainty in our estimates. This was minimal or low in some of our subgroup analyses based on the comparator regimen, the eradication therapy regimen used, and study location. There was also evidence of publication bias, or other small study effects, in some of our analyses. The eradication regimens used varied considerably between the individual trials and PPI dual therapy or ranitidine bismuth citrate triple therapy would now be considered "historical". However, if anything, suboptimal eradication rates associated with these older regimens may have led to an underestimate of the efficacy of eradication therapy on FD symptoms. In addition, the control intervention also varied between individual trials, from placebo alone, antisecretory therapy plus placebo antibiotics, prokinetics, or antacids. Blinding in some of these RCTs would not have been possible, and these differences in trial design may have contributed to the heterogeneity observed, although results were similar in subgroup analyses including only trials that compared *H. pylori* eradication therapy with antisecretory therapy plus placebo antibiotics, or a placebo alone. Adverse events data were not reported by many of the RCTs we identified, meaning that balancing the benefits and harms of eradication therapy in treating *H. pylori*-positive patients with FD is difficult. Finally, our analyses based on success or failure of eradication therapy, although novel and potentially interesting, were not based on the randomised groups and may have inherent confounding and, in some cases, biases.

Despite these limitations, our results suggest that it is worthwhile testing patients with FD and eradicating the infection if present. With a NNT of 14 for cure of symptoms this is likely to be cost-effective,[21] and there are other benefits from eradication of *H. pylori*, including a reduction in the future incidence of peptic ulcer and gastric cancer,[67-70] as well as the costs of managing these conditions.[71, 72] There is also evidence that testing for and treating *H. pylori* in patients with uninvestigated dyspepsia in the community, the majority of whom will have FD,[12] leads to a significant reduction in the likelihood of needing upper gastrointestinal endoscopy,[73] which is one of the main drivers of the costs of managing dyspepsia. In addition, FD is common,[3, 4] and other treatments are only modestly efficacious in improving symptoms,[63-66] need to be taken long-term, and some, such as prokinetics, are not available in many countries. On the other hand, a course of *H. pylori* eradication therapy only needs to be taken for 2 weeks, and the drugs that are its constituent components are cheap and available widely.

There have been further meta-analyses conducted since the original Cochrane review examining this issue. [21, 22] Our updated meta-analyses contains more trials and more patients that either of the two most recent.[74, 75] Similar to our results, these demonstrated modest benefits of eradication therapy in FD with an increase in adverse events with active treatment, and a greater benefit with increasing duration of follow-up. One of these meta-analyses reported that the NNT was 15, but also suggested that there was no significant benefit of eradicating *H. pylori* in Asian patients with FD.[75] However, the 95% confidence around the estimate of efficacy in this meta-analysis was almost significant. Our results are likely to differ because we included data from a further 11 RCTs. We are not aware of these other meta-analyses having tried to elucidate whether the benefit of eradication therapy stems from the successful eradication of *H. pylori* or the use of antibiotics in general. Another strength of our meta-analysis is the multiple subgroup analyses, including

those comparing eradication therapy with both antisecretory therapy and placebo antibiotics and placebo alone.

How *H. pylori* eradication therapy is having its beneficial effects in FD remains uncertain.[28] Whether it is an effect of antibiotics, *per se*, on the gastrointestinal microbiome or an effect of eradication of *H. pylori* infection remains unclear. Trials of eradication therapy versus a PPI and placebo antibiotics in *H. pylori*-negative patients with FD could answer this question. Nitroimidazole-containing regimens and nitroimidazole-containing PPI triple therapies appeared to lead to a greater treatment effect, compared with eradication regimens or PPI triple therapies without a nitroimidazole, although these differences were not statistically significant. A small trial of rifaximin in *H. pylori*-negative patients with FD in Hong Kong demonstrated a significant benefit over placebo,[31] but there have been no other RCTs of antibiotics conducted, to our knowledge. In addition, follow-up in this trial was only for 8 weeks, and whether repeated courses are required, as is the case in some patients with irritable bowel syndrome,[76] is unknown. An alternative proposed by the Kyoto consensus is that *H. pylori* is itself a cause of dyspepsia,[77] an organic disease termed *H. pylori*-associated dyspepsia, and only if symptoms persist after a course of eradication therapy should the patient be labelled as having FD. However, this is contentious and based on expert opinion rather than RCT evidence. If *H. pylori* eradication were to "cure" dyspepsia in nearly all cases it would support this stance, but the impact observed in this updated meta-analysis was only modest.

Our updated systematic review and meta-analysis provides high quality evidence that eradication therapy is an efficacious treatment for *H. pylori*-positive patients with FD and should, therefore, be first-line therapy in such patients. The NNT for symptom cure was 14, and for symptom improvement it was 9. With the inclusion of data from almost 7000 patients, almost 3000 of whom were in newly identified RCTs, our confidence in the

estimate of effect has improved, and the magnitude of the effect has increased slightly. It is likely that this would be a cost-effective treatment for FD, and it would only need to be applied as a single intervention. It remains unclear how eradication therapy is having its benefits in FD. Future RCTs should consider assessing the efficacy of eradication therapy in patients with FD without *H. pylori* infection.

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CONTRIBUTOR AND GUARANTOR INFORMATION

Guarantor: ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Specific author contributions: ACF, ET, GL, YY, and PM conceived and drafted the study. ACF, ET, YY, and PM collected all data. ACF, ET, YY, and PM analysed and interpreted the data. ACF, YY, and PM drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

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COMPETING INTERESTS DECLARATION

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY STATEMENT

The lead author (ACF, the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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PATIENT AND PUBLIC INVOLVEMENT STATEMENT

We did not involve patients or the public in this work. We will disseminate our findings in lay terms via the national charity for people living with digestive diseases, “Guts UK”.

DATA SHARING

No additional data available.

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FIGURE LEGENDS

Figure 1. Forest Plot of Randomised Controlled Trials of *H. pylori* Eradication Therapy: Effect on Symptom Cure in FD.

Figure 2. Forest Plot of Randomised Controlled Trials of *H. pylori* Eradication Therapy: Effect on Symptom Improvement in FD.

Figure 3. Scatterplot of *H. pylori* Eradication Rate Versus Rate of Symptom Cure or Improvement in Individual Randomised Controlled Trials.

Figure 4. Forest Plot of Randomised Controlled Trials of *H. pylori* Eradication Therapy: Effect on Symptom Cure or Improvement in FD in those with Successful *H. pylori* Eradication Therapy Versus Control Therapy.

Figure 5. Forest Plot of Randomised Controlled Trials of *H. pylori* Eradication Therapy: Effect on Symptom Cure or Improvement in FD in those with Successful *H. pylori* Eradication Therapy Versus Unsuccessful *H. pylori* Eradication Therapy.