General practice

Is *Helicobacter pylori* associated with non-ulcer dyspepsia and will eradication improve symptoms? A meta-analysis

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website extra

Details of the
studies and
additional refer-
ences are included
on the BMJ's
website

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Abstract

Objectives To examine the association between *Helicobacter pylori* infection and non-ulcer dyspepsia, and to assess the effect of eradicating *H pylori* on dyspeptic symptoms in patients with non-ulcer dyspepsia.

Design Systematic review and meta-analysis of (a) observational studies examining the association between *Helicobacter pylori* infection and non-ulcer dyspepsia (association studies), and (b) therapeutic trials examining the association between eradication of *H pylori* and dyspeptic symptoms in patients with non-ulcer dyspepsia (eradication trials).

Data sources Randomised controlled trials and observational studies conducted worldwide and published between January 1983 and March 1999.

Main outcome measures Summary odds ratios and summary symptom scores.

Results 23 association studies and 5 eradication trials met the inclusion criteria. In the association studies the summary odds ratio for *H pylori* infection in patients with non-ulcer dyspepsia was 1.6 (95% confidence interval 1.4 to 1.8). In the eradication trials the summary odds ratio for improvement in dyspeptic symptoms in patients with non-ulcer dyspepsia in whom *H pylori* was eradicated was 1.9 (1.3 to 2.6).

Conclusions Some evidence shows an association between *H pylori* infection and dyspeptic symptoms in patients referred to gastroenterologists. An improvement in dyspeptic symptoms occurred among patients with non-ulcer dyspepsia in whom *H pylori* was eradicated.

Introduction

Although drugs for acid suppression are the mainstay empirical treatment for ulcer-like dyspeptic symptoms¹⁻³ controversy surrounds the role of empirical eradication therapy for *Helicobacter pylori*.^{4,5} Although there is strong evidence of an association between *H pylori* infection, chronic gastritis, and peptic ulcer disease,^{6,7} the relation between dyspeptic symptoms and gastritis caused by *H pylori* is not well described.^{8,9} Systematic reviews examining the relation between non-ulcer dyspepsia and *H pylori* have based their conclusions on qualitative assessments of selected articles¹⁰⁻¹⁵ without any quantitative summary estimate of an association. Only one estimate for *H pylori* infec-

tion among patients with non-ulcer dyspepsia has been quoted in the literature,¹⁶ but this was not based on a systematic selection of articles, no sensitivity analyses of the estimate were included, and there was no assessment for statistical heterogeneity.

If primary care strategies are to be developed for managing non-ulcer dyspepsia or dyspeptic symptoms then evidence needs to be firmly established for a relation between non-ulcer dyspepsia and *H pylori* infection and for an improvement in dyspeptic symptoms with eradication of *H pylori*.

We aimed to review the literature for both observational studies and therapeutic trials. We also aimed to provide quantitative summary estimates for an association between *H pylori* infection and non-ulcer dyspepsia and for change in dyspeptic symptoms in patients with non-ulcer dyspepsia in whom *H pylori* was eradicated.

Methods

Identification of studies

We conducted a Medline search of non-review articles in English from January 1983 to March 1999 with the MeSH headings "dyspepsia," "non-ulcer dyspepsia," "gastritis," "Helicobacter pylori," and "Campylobacter pylori."

Study eligibility was assessed by RLJ and EB who independently reviewed all 654 abstracts. Disagreements were resolved by consensus. On the basis of the abstract, specific criteria were used to retrieve observational studies examining the association between *H pylori* and non-ulcer dyspepsia (association studies). These criteria included a description of a patient or patient group and a control or non-diseased group and an indication that dyspepsia, non-ulcer dyspepsia, or symptoms of dyspepsia was a separate outcome of the study. The study designs were of a prevalence, case-control, or cohort type.

Similarly, abstracts from studies examining *H pylori* eradication and dyspeptic symptoms were retrieved using predefined criteria. These criteria included the symptoms of dyspepsia defined as an outcome measure of the study, all subjects with non-ulcer dyspepsia or dyspeptic symptoms who harboured *H pylori*, and treatment modalities that have shown some efficacy in the eradication of *H pylori*. Only randomised trials were included.

Data extraction

We assessed the association studies with a modified version of a quality assessment form for observational studies,¹⁷ and we assessed the *H pylori* eradication trials with an existing quality assessment system for clinical trials.¹⁸ The methods sections were cut out and coded so that the assessors were blind to the study results, title, authors, publication date, and journal. Agreement between the assessors was evaluated with the κ statistic.^{19, 20}

Data from all articles were abstracted by RLJ and EB independently. The results sections were cut out and coded so that the assessors were blind to the methods, title, authors, publication date, and journal. Disagreements were resolved by consensus. For each association study the number of subjects with non-ulcer dyspepsia or dyspeptic and control subjects with or without *H pylori* infection were extracted from each study and entered into 2x2 tables. The eradication trials gave the number of subjects with improvement in dyspeptic symptoms and those with no improvement or worsening symptoms both for those in whom *H pylori* was eradicated and for those in whom it was not. This allowed the construction of 2x2 tables.

Statistical analysis

We calculated an overall point estimate of the odds ratio and 95% confidence interval with the Mantel-Haenszel statistic,²¹ which is based on the assumption of a fixed effect model.²² Homogeneity was assessed with the Breslow-Day method.²³ The data were entered and analysed with a statistical package.²⁴

Results

The review of abstracts identified 84 potentially eligible studies. Thirty five were eliminated because they did not satisfy the retrieval criteria. This left 26 articles dealing with the association between *H pylori* infection and non-ulcer dyspepsia (association studies) and 23 articles examining dyspeptic symptoms in relation to *H pylori* eradication therapy (eradication trials).

Observational association studies

Study characteristics and quality scores

Three studies did not provide information on *H pylori* infection in the control group and could not be included in the pooled analysis. The box summarises the study characteristics of the 23 association studies (see website). Many studies defined non-ulcer dyspepsia as upper abdominal pain or discomfort with no organic disease identified (16 studies) lasting more than 4 weeks.¹² Most studies included patients with non-ulcer dyspepsia referred to a specialty or gastroenterology clinic¹⁶ and based the *H pylori* assessment on the results of endoscopic biopsy.¹⁵ The rate of *H pylori* infection in patients with non-ulcer dyspepsia was 55.2% (range 9.4 (18.4) to 87.5) and in controls was 40.4% (range 4.7 (22.3) to 83.3).

Out of a possible 100 the mean (SD) quality score for the 23 association studies was 44.2 (11.1), median 41. Most studies lost points on lack of control for confounding and poor definitions of dyspepsia. There was

Study characteristics (number of trials) of the 23 association studies

Case selection

Referred cases (16)^{w1 w2 w4 w5 w8-w12 w14-w20}
Community based (3)^{w3 w6 w22}
Random community sample (4)^{w7 w13 w21 w23}

Control selection

Hospital based (4)^{w4 w5 w11 w16}
Outpatient based (2)^{w2 w17}
Community based (13)^{w1 w3 w6 w8-w10 w12 w14 w15 w18-w20 w22}
Random community sample (4)^{w7 w13 w21 w23}

H pylori assessment

Serology (7)^{w1-w3 w6 w7 w22 w23}
Urea breath test (1)^{w9}
Endoscopically obtained biopsy (15)^{w4 w5 w8 w10-w21}

Definition of non-ulcer dyspepsia

Duration more than 4 weeks (12)^{w1 w2 w4-w6 w8-w11 w13-w15 w18-w22}
No organic disease found on investigation (16)^{w1 w4-w6 w8-w11 w13-w15 w18-w22}
Upper abdominal or epigastric pain or discomfort (16)^{w1 w2 w4-w7 w11-w18 w21 w22}
Symptoms related to meals (9)^{w1 w4-w6 w11 w12 w14 w15 w18}
Other symptoms such as heartburn, nausea, or vomiting (12)^{w2 w5-w7 w12-w15 w17 w18 w21 w23}
Not defined (5)^{w3 w8 w10 w19 w20}

Exclusion criteria

History of:

Gastro-oesophageal reflux disease (6)^{w3 w5 w6 w12 w14 w15}
Peptic ulcer disease (9)^{w3 w8 w9 w12-w14 w16 w20 w21}
Irritable bowel syndrome (5)^{w4 w6 w7 w12 w15}

Concomitant non-steroidal anti-inflammatory drugs (8)^{w2 w5 w6 w9 w12 w17 w18 w20}

Previous eradication therapy for *H pylori* (8)^{w2 w3 w5 w11 w12 w15 w16 w18}

Concomitant acid suppression therapy (4)^{w2 w11 w15 w20}

excellent agreement between the two quality assessors ($\kappa = 0.84$).¹⁹

Summary estimates

Figure 1 shows the odds ratios and summary odds ratio for each association study. Twenty three studies were pooled giving a summary odds ratio of 1.6 (95% confidence interval 1.4 to 1.8) for *H pylori* infection related to non-ulcer dyspepsia ($P < 0.001$). The test for homogeneity was statistically significant ($P < 0.001$). The summary odds ratios and 95% confidence intervals for symptoms of abdominal pain (three studies), abdominal distension, flatulence, bloating, or belching (four), and nausea and vomiting (three) were respectively 1.2 (0.96 to 1.4), 1.2 (0.67 to 21.0), and 0.8 (0.4 to 1.4). All were statistically non-significant.

Sensitivity analysis

The table shows the influence of study design, quality scores, and control of confounders on pooled estimates. Summarised estimates were statistically homogeneous for prevalence studies, studies with quality scores above the median, and studies that controlled for confounding.

Eradication trials

Study characteristics and quality assessment scores

Five eradication trials provided data on change in dyspeptic symptoms in patients in whom *H pylori* had or

Fig 1 Odds ratios and summary odds ratios for association studies

Fig 2 Odds ratios and summary odds ratios for eradication trials

had not been eradicated (see website).^{w24-w28} This change was defined as an improvement, or no change or worsening of dyspeptic symptoms. The 18 other eradication trials could not be included in a pooled analysis because they did not provide data on change in symptoms in relation to *H pylori* eradication.

Sensitivity analysis of trials of *Helicobacter pylori* and non-ulcer dyspepsia that met inclusion criteria for meta-analysis

Pooled group	No of studies	Odds ratio (95% CI)	P value
Association studies			
Summary estimate	23	1.6 (1.4 to 1.8)	<0.001
Study design:			
Prevalence	5	1.3 (1.0 to 1.7)	0.095
Case-control	17	2.0 (1.7 to 2.5)	0.002
Quality score:			
>Median	12	1.5 (1.2 to 1.8)	0.068
<Median	11	1.6 (1.4 to 1.9)	<0.001
Controlled for confounders	7	1.4 (1.2 to 1.6)	0.05
Eradication trials			
Summary estimate	5	1.9 (1.3 to 2.6)	0.046
Treatments:			
Single regimen	3	15.4 (2.2 to 16.7)	0.12
Triple regimen	2	1.4 (1.0 to 2.3)	0.70

Two trials detailed the duration of dyspeptic symptoms. Dyspepsia was defined according to published criteria—pain or discomfort in the upper abdomen in association with other symptoms such as bloating, nausea, or vomiting, relation with meals, worse at night, and reflux. All eradication trials recruited patients from specialty or gastroenterology clinics, and four trials assessed *H pylori* infection from endoscopically obtained biopsies. Three trials used single regimen therapy, and two trials used triple regimen therapy. The single therapy trials followed patients for less than 8 weeks whereas the triple therapy trials assessed *H pylori* eradication and change in dyspeptic symptoms at 12 months.

Out of a possible 100 the mean (SD) quality score for the five eradication trials was 48.4 (16.1), median 42. Most studies lost points for no description of randomisation or blinding, no assessment of treatment compliance, and poor presentation of results. There was good agreement between the two quality assessors ($\kappa = 0.7$).¹⁹

Summary estimates

We compared the change in dyspeptic symptoms in patients with non-ulcer dyspepsia in whom *H pylori* had or had not been eradicated. Figure 2 shows the odds ratios and summary odds ratio for each eradication trial. The odds ratio for symptomatic improvement was 1.9 (1.3 to 2.6) for patients in whom *H pylori* was eradicated ($P = 0.001$). This estimate was statistically homogeneous ($P = 0.046$).

Sensitivity analysis

The table shows the influence of *H pylori* therapeutic regimen and study quality on the summary estimates. The summary odds ratio for single therapy regimens was higher than for triple therapy regimens. Quality scores for the two trials examining triple therapy regimens were above the median as opposed to the three trials examining single therapy regimens.

Discussion

The association studies included in our meta-analysis showed a small yet statistically significant increased risk of non-ulcer dyspepsia in people infected with *H pylori*. Patients with non-ulcer dyspepsia in whom *H pylori* was eradicated were almost twice as likely to show an improvement in their dyspeptic symptoms than patients in whom *H pylori* was not eradicated.

Association studies

The overall summary estimate for the association studies was fairly robust with respect to quality score, the control of confounders, and study design. Interestingly, a higher summary odds ratio was produced from the case-control studies than from the prevalence studies. This may reflect differences in the severity or frequency of dyspeptic symptoms. The prevalence studies utilised structured questionnaires in the general populations to identify subjects with non-ulcer dyspepsia whereas the case-control studies identified such subjects from patients seeking medical treatment. The risk of *H pylori* infection increases with advancing age, lower occupational status, and lower socioeconomic status,²⁵ and controlling for these factors should reduce the

heterogeneity of summary estimates. Statistical heterogeneity was reduced among association studies that controlled for confounding and also among studies with quality scores above the median. The design of the association study did not explain statistical heterogeneity.

Eradication regimens

Triple regimen therapies are the currently accepted treatment for *H pylori* eradication.²⁶ Although the number of trials in the sensitivity analysis was small, pooling the triple regimens produced a lower summary odds ratio than the single therapy regimens (see table). Although *H pylori* eradication was achieved at the time improvements in dyspeptic symptoms were assessed the magnitude of this improvement may have been affected by the regimens used. Colloidal bismuth salicylate is known to improve symptoms irrespective of *H pylori* infection, as does omeprazole.^{27 28} The triple regimens were also used in trials with higher quality scores and longer follow up intervals. Perceived improvements in dyspeptic symptoms may decrease over time and this may explain the lower estimate in the triple than single regimen trials. Therefore, the type of regimen used, the duration of follow up, and the quality of the trial limits the generalisability of this estimate. Further trials that use currently acceptable eradication regimens and that monitor dyspeptic symptoms over longer time intervals are required.

Definitions

Dyspepsia

Inconsistent definitions of dyspepsia may contribute to the conflicting evidence provided by trials of *H pylori* eradication. The definition of dyspepsia has been refined over the years to represent pain or discomfort centred in the upper abdomen described as bloating, distension, fullness, or nausea but not acid regurgitation or heartburn.²⁹ These symptoms should be present for at least a month. Dyspeptic symptoms have generally been poor in discriminating functional from organic disease.^{30 31} Non-ulcer dyspepsia refers to the presence of dyspeptic symptoms in the absence of an identifiable organic disease.³² Depending on the symptoms used to define dyspeptic patients the benefits of treatments may be either augmented or diminished.³³

Symptoms and scores

Similarly, different symptoms and scores have been used to assess treatment response in trials of *H pylori* eradication. Although virtually all scores include upper abdominal pain or discomfort there are a variety of other symptoms included. Likert scales are subject to different interpretations by respondents, leading to misclassification bias.³⁴ In addition to this the weights of scales used in the trials of *H pylori* eradication ranged from three to seven levels. Validated dyspeptic symptom scores would enable comparisons between different treatment modalities assessed in trials, including trials of *H pylori* eradication.

Limitations

Meta-analyses have their limitations.³⁵⁻³⁷ Publication bias tends to lead to the inclusion of studies that only

What is already known on this topic

Although infection with *Helicobacter pylori* is strongly associated with peptic ulcer disease the relation with non-ulcer dyspepsia is controversial

The adoption of empirical eradication regimens for non-ulcer dyspepsia is difficult given the little information about their efficacy

Recently published randomised controlled trials allow an estimation of the change in dyspeptic symptoms among patients

What this paper adds

This meta-analysis found a small yet statistically significant relation between *H pylori* infection and non-ulcer dyspepsia

Eradication of *H pylori* was associated with an almost twofold improvement in dyspeptic symptoms among patients referred to specialty clinics

This quantitative estimate may be used in primary care trials to determine the effectiveness and cost effectiveness of empirical eradication of *H pylori* in non-ulcer dyspepsia

show a positive result. There are limitations to Medline searches as our search failed to identify 16 articles, which were found only when searching the references of papers. A potential for a selection bias exists since the studies included in our meta-analysis did not include information published in textbooks, non-English language articles, and abstract only publications.

Our estimate is slightly lower than the only other quoted one for *H pylori* infection and non-ulcer dyspepsia (2.3, 1.9 to 2.7).¹⁶ Several reasons may explain the difference. Firstly, we included 23 rather than 19 articles with our estimate. Secondly, we restricted the article selection to those published in the English language only whereas the other estimate included two non-English language studies and one abstract. Finally, we selected articles in a systematic manner and evaluated them for methodological quality, and we undertook sensitivity analyses and estimated statistical heterogeneity; none of which was completed in the other study.

Most of the association studies and all the eradication trials recruited patients from secondary or tertiary care populations, therefore the findings may not be generalisable to primary care patients who have less severe disease and symptoms.³⁸ Although eradication therapy for *H pylori* may be beneficial for patients with non-ulcer dyspepsia seen either in specialty clinics or by gastroenterologists this magnitude of symptomatic improvement may not be seen in primary care patients. Only a randomised trial of patients seen and managed by primary care physicians would solve this problem.

In addition, both the clinical and economic costs of *H pylori* eradication need to be considered. Metronida-

zole resistance is found worldwide, with resistance rates of over 70% in developing nations.³⁹⁻⁴⁰ Resistance rates for clarithromycin approach 10%.⁴¹ There is preliminary evidence of a protective association between *H pylori* infection and gastro-oesophageal reflux disease,⁴² with a reduction in efficacy of proton pump inhibitors after cure of *H pylori*.⁴³ Although *H pylori* eradication is cost effective for patients with peptic ulcer disease,⁴⁴⁻⁴⁵ the economic benefits in patients with non-ulcer dyspepsia is equivocal.⁴⁶⁻⁴⁸

Conclusions

A quantitative estimate gives a sense of the magnitude of the relation between a risk factor and a disease. We found that people infected with *H pylori* are about one and a half to twice as likely to have non-ulcer dyspepsia compared with controls. Eradicating *H pylori* results in almost a twofold improvement in dyspeptic symptoms. It is not yet known whether the magnitude of these estimates is large enough to influence clinical guidelines or clinicians, but the summary effect size estimates from our meta-analysis could help with sample size calculations for future studies. Such studies should include primary care patient populations where the efficacy of empirical therapy for dyspeptic patients with *H pylori* infection may be examined.

Contributors: RLJ had the original idea for the study, retrieved articles, extracted data, performed assessments of study quality, and undertook the statistical analysis; she will act as guarantor for the paper. EB extracted data, performed quality assessments, and assisted with the statistical analysis. FT assisted with the interpretation and presentation of the results. RLJ, EB, and FT jointly wrote the paper.

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