MAJOR ARTICLE

The Role of Breast-Feeding in the Prevention of *Helicobacter pylori* Infection: A Systematic Review

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Background. The benefits of breast-feeding for the prevention of infection in infants and young children have been widely recognized, but epidemiologic studies regarding the role of breast-feeding in protecting against *Helicobacter pylori* infection have produced conflicting results.

Methods. We performed a systematic review of relevant epidemiologic studies conducted during the period 1984–2007 after abstracting data from articles that met our inclusion criteria. Study quality was assessed using the Newcastle-Ottawa scale. With use of the random effects model, we calculated the summary odds ratios (ORs) and 95% confidence intervals (CIs) for *H. pylori* infection according to history of breast-feeding.

Results. For the 14 studies that met inclusion criteria, the summary OR for *H. pylori* infection was 0.78 (95% CI, 0.61–0.99; 1-sided $P = .02$). Nine of the 14 studies reported ORs of <1.0, and 6 of these studies reported statistically significant protective effects. Only 1 study reported a statistically significant OR of >1.0. In studies in which the subjects resided in middle- or low-income nations, the summary OR was 0.55 (95% CI, 0.33–0.93; $P = .01$), compared with 0.93 (95% CI, 0.73–1.19; $P = .28$) in studies in which subjects resided in high-income nations. The summary OR for studies that use the ^{13}C-urea breath test was 0.67 (95% CI, 0.32–1.39), compared with 0.91 (95% CI, 0.74–1.11) for studies that used the *H. pylori* IgG serologic test. We found no statistically significant dose-dependent protective effect against *H. pylori* associated with increasing duration of breast-feeding.

Conclusions. Breast-feeding is protective against *H. pylori* infection, especially in middle- and low-income nations.

Helicobacter pylori is a major contributor to the gastrointestinal disease burden worldwide and is the causative agent in peptic ulcer disease [1], gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma [2]. Although it is generally accepted that infection occurs early in life [3], routes of transmission and protective factors against infection have not been firmly established. One source of controversy has been breast-feeding and its relationship with *H. pylori* infection status.

Breast-feeding has been firmly established as a method of preventing infectious disease in infants [4]. Among Gambian infants, Thomas et al. [5] demonstrated that anti–*H. pylori* IgA in human breast milk was associated with delayed age of onset of *H. pylori* infection. However, previous epidemiologic studies of the relationship between breast-feeding and *H. pylori* infection have reported conflicting results. In a cross-sectional study of 327 Turkish preschool children, Ertem et al. [6] reported an OR of 0.22 (95% CI, 0.05–0.96) for *H. pylori* infection among children who were breast-fed. In contrast, in a cross-sectional study of 946 German preschool children, Rothenbacher et al. [7] reported an OR of 2.57 (95% CI, 1.19–5.55). Given these conflicting findings in the literature, we conducted a systematic review of the role of breast-feeding in *H. pylori* infection and examined potential sources of heterogeneity in these data.

METHODS

Search strategy and identification of studies. We searched databases, including the Medline, the Cochrane Library, and Lilacs databases, for all epidemiologic studies of *H. pylori* and exposure to breast-feeding. Our

Received 26 May 2008; accepted 13 October 2008; electronically published 9 January 2009.

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Clinical Infectious Diseases 2009; 48:430–7

1058-4838/2009/4804-0010$15.00
DOI: 10.1086/596499

searches accounted for names by which the bacterium was previously called, including *Campylobacter pyloridis* and *Campylobacter pylori.* We limited searches to human studies starting from 1984, the year that *H. pylori* was first described [8], and included combinations of the following keywords: "*Helicobacter pylori,*" "breast-feeding," "nursing," and "breast milk." We also searched the bibliographies of identified review articles for additional studies.

Inclusion and exclusion criteria. We included studies published in scientific journals that provided information about breast-feeding history and *H. pylori* infection status using any diagnostic test. We excluded studies that did not include relative risks, ORs, or 95% CIs or the crude data to calculate them. We also excluded case reports and review articles from our analysis but searched their bibliographies for relevant articles. We defined breast-feeding as reported by authors; most studies did not define breast-feeding and only reported whether mothers breast-fed their children or not, providing few other details. If a study reported the effects of different durations of breast-feeding, we used the OR for the longest time in our meta-analysis, to maximize the chance of showing a dose-response relationship. If a study separated its data into subgroups, we included these data but analyzed them separately in their respective categories. We used adjusted ORs, when available, in lieu of crude data.

Data analysis and statistical methods. All studies reported ORs, and none reported risk ratios or rate ratios. Thus, we calculated summary OR estimates using the fixed-effects inverse variance–weighting method [9]. We assessed heterogeneity using the Q statistic, with degrees of freedom equal to the number of studies in the meta-analysis minus 1 [10]. In the presence of heterogeneity, the random effects model was used [11]. All reported *P* values are 1-tailed, because our a priori hypothesis was unidirectional (i.e., that breast-feeding protected from, and did not cause, *H. pylori* infection).

To assess the quality of studies included in the meta-analysis, we used the Newcastle-Ottawa scale [12], which uses a "star" rating system to judge the quality of observational studies. We determined a priori that only studies that received a rating of $\geqslant$7 stars (of 9 possible stars) would be judged as "high quality." Because there is currently no rating system for cross-sectional studies, we assigned these to the "lower quality" category on the basis of the inherent limitations of this type of design.

We conducted 4 subgroup analyses in addition to the summary meta-analysis. All 4 subgroup analyses were planned a priori. First, we compared data collected from studies in which subjects resided in middle- and low-income countries and in high-income nations. Countries were placed in their respective income categories on the basis of the World Bank's classification by gross national income per capita [13]. Second, we determined whether a dose-dependent relationship existed between length of breast-feeding time and *H. pylori* infection. Third, we compared data from studies that used the ^{13}C-urea breath test (^{13}C-UBT) and the IgG serologic test as a method of diagnosing *H. pylori.* Finally, we compared "high-quality" studies with "lower-quality" studies.

Forest plots and examination for publication bias. We generated a forest plot with use of Stata software, version 8.0 (Stata). We used Egger's test [14] and Begg's test [15] to assess for publication bias, as well as a funnel plot of the log each study's OR versus its SE.

RESULTS

Search Results

Of the 583 articles retrieved, 43 completed articles were reviewed, and 14 studies met all inclusion criteria (table 1); these included 3 cohort studies, 1 case-control study, and 10 cross-sectional studies. Two additional studies, which otherwise met all inclusion criteria, did not provide ORs or 95% CIs or the crude data to calculate them and were excluded [28, 29].

Summary Estimates

The overall summary OR for all 14 studies combined was 0.78 (95% CI, 0.61–0.99; $P = .02$). Six studies reported statistically significant protective effects of breast-feeding on *H. pylori* infection, whereas only 1 study reported a statistically significant OR of >1.0. Figure 1 shows the forest plot of the studies included in our meta-analysis for the fixed-effects model. The summary ORs for cohort studies (0.80; 95% CI, 0.68–0.94; $P = .003$) was similar to that for the cross-sectional studies (0.81; 95% CI, 0.58–1.14; $P = .12$), whereas the single case-control study that we identified found a substantially greater protective effect (OR, 0.14; 95% CI, 0.38–0.49).

The study by Rothenbacher et al. [7] was the only study to report that breast-feeding may increase one's risk of *H. pylori* infection. When this study was removed from the analysis, the summary OR became 0.73 (95% CI, 0.58–0.93; $P = .006$). The study by Ueda et al. [23] was statistically weighted heavily in our analysis, because it was a large study with a consequently smaller SE. We performed a separate analysis after removing this study that yielded similar results (OR, 0.75; 95% CI, 0.56–0.99; $P = .02$).

Subgroup Analyses

Middle- and low-income versus high-income nations. Seven studies had patient populations residing in middle- or low-income countries, including Turkey, Brazil, Vietnam, Egypt, and Bangladesh. Among these studies, the summary OR was 0.55 (95% CI, 0.33–0.93; $P = .01$) (table 2). When the analysis was limited to the 7 studies in which the patient populations resided in high-income nations (United Kingdom, United States, Japan, Germany, and Italy), the summary OR

Table 1. Studies used for meta-analysis, with point estimates and 95% CIs, for the effect of breast-feeding (BF) on *Helicobacter pylori* infection.

Reference	Location of study (patient subgroup)	No. of cases of *H. pylori* infection in the BF group	Duration of BF, months	Diagnostic test	Point estimate of effect of BF on *H. pylori* infection (95% CI)	Weight, %		Covariate(s) adjusted for in study
						Random-effects model	Fixed-effects model	
Cohort studies								
Pearce et al. [16]	UK (men)	NR	1.4[a]	IgG serologic test	0.71 (0.54–0.93)	9.20	20.70	Social class, housing conditions
Pearce et al. [16]	UK (women)	NR	Any	IgG serologic test	0.90 (0.60–1.35)	7.70	4.50	Social class, housing conditions
Naficy et al. [17]	Egypt	16	Any	IgG serologic test	1.40 (0.37–5.80)	2.40	0.40	Age
Fall et al. [18]	UK (men)	215	Any	IgG serologic test	0.72 (0.35–1.51)	5.20	1.40	None
Fall et al. [18]	UK (women)	114	Any	IgG serologic test	0.57 (0.19–1.71)	3.20	0.60	None
Case-control study: Süoglu et al. [19]	Turkey	12	⩾4	Biopsy	0.14 (0.38–0.49)	2.60	0.50	Age, socioeconomic status
Cross-sectional studies								
Braga et al. [20]	Brazil	35	>6	^{13}C-UBT	1.69 (0.84–3.41)	5.40	1.50	None
Nguyen et al. [21]	Vietnam	69	>6	IgG serologic test	0.60 (0.40–0.80)	8.10	6.20	None
Rodrigues et al. [22]	Brazil	87	>6	^{13}C-UBT	0.64 (0.35–1.18)	6.00	2.00	Age, nutritional status, maternal *H. pylori* infection, education of mother and/or parents, history of antibiotic use, smoking of mother and/or parents, housing density, number of siblings
Ueda et al. [23]	Japan	1748	Any	IgG serologic test	1.07 (0.94–1.22)	9.50	42.60	Age, sex, district
Ertem et al. [6]	Turkey	154	Any	^{13}C-UBT	0.22 (0.05–0.96)	2.20	0.40	Age, socioeconomic status, heating system type, child weight-to-height ratio, no. of siblings, education of mother and/or parents, housing density
Rothenbacher et al. [7]	Germany	41	>6	^{13}C-UBT	2.57 (1.19–5.55)	4.90	1.30	Age, sex, nationality, birthplace, birth weight, maternal *H. pylori* infection, education of mother and/or parents, history of antibiotic use, smoking of mother and/or parents, housing density, number of siblings
Dore et al. [24]	Italy (rural residents)	311	Any	IgG serologic test	1.25 (0.91–1.67)	8.50	8.10	Age
Dore et al. [24]	Italy (urban residents)	177	Any	IgG serologic test	1.67 (0.09–2.50)	6.80	2.90	Age
Malaty et al. [25]	US	13	Any	^{13}C-UBT	0.33 (0.17–0.67)	5.50	1.60	Age
McCallion et al. [26]	UK	16	>0.5	IgG serologic test	0.54 (0.28–1.06)	5.60	1.70	Age, social class, housing density
Mahalanabis et al. [27]	Bangladesh	187	Any	^{13}C-UBT	0.34 (0.21–0.52)	7.30	3.60	None

NOTE. NR, not reported; ^{13}C-UBT, ^{13}C-urea breath test; UK, United Kingdom; US, United States.

[a] Median value.

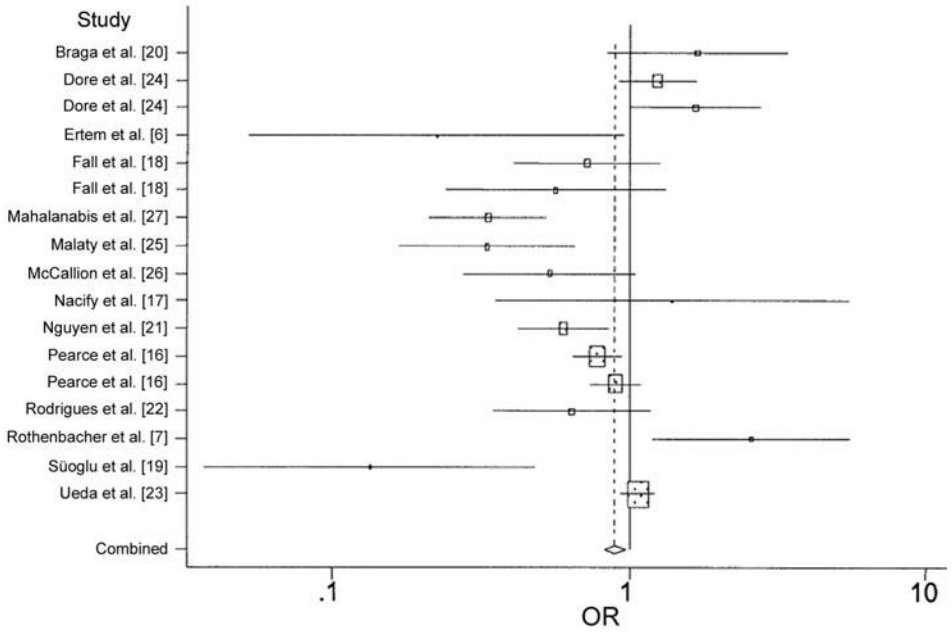

Figure 1. Forest plot of all included studies in the meta-analysis. *Horizontal lines,* 95% CIs of each study; *rectangles,* ORs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond* and *dotted, vertical line,* summary estimate; *solid, vertical line,* null value.

became 0.93 (95% CI, 0.73–1.19; $P = .28$). Of the studies that were conducted in high-income nations, only that by Malaty et al. [25] revealed that breast-feeding had a statistically significant protective effect on *H. pylori* infection (OR, 0.33; 95% CI, 0.17–0.67). It was also the only study from a high-income nation to specifically involve subjects from low socioeconomic backgrounds.

Length of time breast-feeding. In the 5 studies that specified that the subject breast-fed for ⩾4 months, the summary OR was 0.81 (95% CI, 0.40–1.66; $P = .28$). Because this analysis was based on a relatively small number of studies, the summary OR was highly dependent on the results of the individual studies. If the Rothenbacher et al. [7] study was removed from this analysis, the OR decreased to 0.63 (95% CI, 0.32–1.24; $P = .09$). When the 9 studies that did not specify a length of time breast-feeding were analyzed separately, the OR was found to be 0.76 (95% CI, 0.59–0.99; $P = .02$).

^{13}C-UBT versus IgG serologic tests. In the 6 studies that used ^{13}C-UBT for the diagnosis of *H. pylori*, the OR was 0.67 (95% CI, 0.32–1.39), compared with 0.91 (95% CI, 0.74–1.11) for the 7 studies that used the IgG serologic test.

"High-quality" versus "lower-quality" studies. On the basis of the Newcastle-Ottawa scale, each of the cohort studies received 7 stars, and the case-control study received 8 stars; these were classified as "high-quality" studies. The summary OR for these 4 studies was 0.73 (95% CI, 0.52–1.01). The other studies, all of which were cross-sectional studies, were classified as "lower quality" and had a summary OR of 0.81 (95% CI, 0.58–1.14).

Publication Bias

There was no evidence of publication bias according to the results of Egger's test [14] and Begg's test [15]. In the summary analysis, which involved all 14 studies, the Begg's test Kendall score was −20 ($P = .43$), and the Egger's test P value for bias was .17. The funnel plot (figure 2) suggests a paucity of data in the area representing smaller studies with ORs of >1.0, although there are very few small studies for comparison, and this interpretation is highly subjective. Note that none of the standard methods used to assess publication bias are completely reliable, and publication bias may still be occurring despite their findings.

DISCUSSION

Overall, our data suggest that breast-feeding is protective against *H. pylori* infection. The one-sided P value of .02 from our summary analysis and the finding that 6 studies reported statistically significant results for the protective effect of breast-feeding, compared with only 1 study to show the opposite effect, all suggest that these results are not due to chance. Our subgroup analysis also provides evidence that this effect may be greater in middle- and low-income countries. Although we did not find evidence of a dose-response effect based on duration of breast-feeding, our analysis was based on a small number

of studies and subject to type II error. The lower OR in studies that used the ^{13}C-UBT, which is generally more specific than the IgG serologic test, also supports the conclusion that breast-feeding decreases the risk of *H. pylori* infection and suggests that some of the studies could have missed this effect by using the less accurate IgG serologic test. This result, however, is also based on a small number of studies, and the summary 95% CIs are wide. The lower OR and narrower 95% CI in "high-quality" studies also supports the conclusion that breast-feeding is protective against *H. pylori* infection, whereas less rigorous studies could have missed this effect because of limitations in study design.

Our finding—that breast-feeding is protective against *H. pylori* infection—is consistent with other known scientific literature. Clyne et al. [30] showed that human milk inhibits the adherence of *H. pylori* to a gastric adenocarcinoma cell line by 50%–70% in vitro. Furthermore, Appelmelk et al. [31] reported that lactoferrin from human breast milk was able to bind to *H. pylori* liposaccharide e, leading to its inactivation. Thomas et al. [32] also found that anti–*H. pylori* urease antibodies protect against colonization during infancy. As a whole, these studies support the biological plausibility of our results.

We also found that the protective effect of breast-feeding on *H. pylori* infection may most clearly be seen in middle- and low-income countries, compared with high-income countries. Low socioeconomic status has been strongly associated with *H. pylori* infection [33, 34] and likely explains the higher prevalence of the bacterium in the developing world. Magalhães Queiroz and Luzza [35] reported that the prevalence can vary from 8.9% (in developed nations) to 72.8% (in developing nations). Thus, it is biologically plausible that mothers in de-

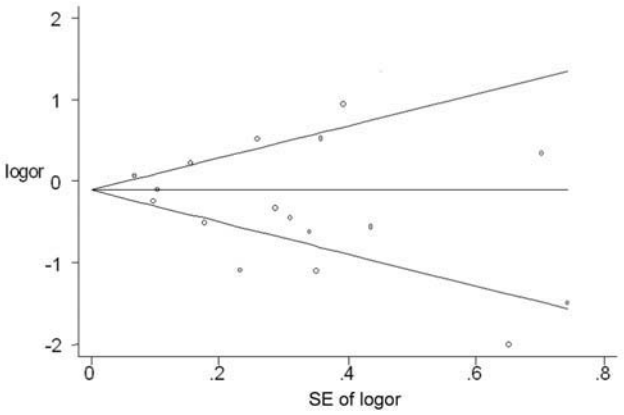

Figure 2. Funnel plot created by the Begg's test [15] to assess publication bias in the meta-analysis. logor, log of the OR.

Table 2. Summary estimates of effect of breast-feeding on *Helicobacter pylori* infection in subgroup analyses.

Variable	No. of Studies	Summary estimate (95% CI)		Heterogeneity, %[a]	P[b]
		Random-effects model	Fixed-effects model		
All studies	14	0.78 (0.61–0.99)	0.9 (0.83–0.98)	77.48	.00
National economic status					
Middle- and low-income nation	7	0.55 (0.33–0.93)	0.56 (0.44–0.70)	22.81	.00
High-income nation	7	0.93 (0.73–1.19)	0.98 (0.89–1.07)	34.28	.00
Duration of breast-feeding					
⩾4 months	5	0.81 (0.40–1.66)	0.77 (0.60–0.99)	23.75	.00
<4 months or not specified	9	0.76 (0.59–0.99)	0.92 (0.84–1.01)	52.09	.00
Diagnostic test[c]					
^{13}C-urea breath test	6	0.67 (0.32–1.39)	0.61 (0.47–0.80)	33.07	.00
IgG serologic test	7	0.91 (0.74–1.11)	0.95 (0.87–1.04)	26.31	.00
Study design[d]					
Cohort[e]	3	0.8 (0.68–0.94)	0.8 (0.68–0.94)	1.47	.83
Cross-sectional	10	0.81 (0.58–1.14)	0.96 (0.86–1.06)	64.07	.00
Study quality[f]					
High quality	4	0.73 (0.52–1.01)	0.77 (0.66–0.91)	8.78	.12
Low quality	10	0.81 (0.58–1.14)	0.96 (0.86–1.06)	64.07	.00

[a] Determined by the χ^2 test.
[b] P value is for the Q statistic.
[c] The study by Süoglu et al. [19] was excluded because it used endoscopic biopsy.
[d] The study by Süoglu et al. [19] was excluded because it was a case-control study.
[e] The random-effects and fixed-effects summary estimates were identical because the χ^2 value was less than the number of degrees of freedom.
[f] Study quality was judged on the basis of the Newcastle-Ottawa scale [12].

veloping countries have higher titers of *H. pylori* IgA in their breast milk or that a greater proportion of mothers have protective levels of anti–*H. pylori* IgA as a result of the higher prevalence of infection in those areas. The scientific literature is scant on the subject of *H. pylori* IgA levels in breast milk and has produced results that are not directly comparable [36, 37]. Nonetheless, Thomas et al. [5] reported that increased titers of *H. pylori* IgA in breast-feeding Gambian mothers can delay acquisition of infection in their children, suggesting that higher titers may indeed translate into greater degrees of protection.

The protective effect that we found is likely due to passive immunity [5] and may not be long-lasting. As such, the prevalence of *H. pylori* infection has been shown to increase with age, especially in developing nations [6], although seroreversions have been noted in children aged <3 years [17]. Thus, it seems that breast-feeding is an important intervention early in life, but prevention of *H. pylori* infection after the protective effects of breast-feeding have waned is of equal, if not greater, importance. As some authors suggest, the existence of naturally occurring human IgA antibodies providing passive protection against *H. pylori* infection supports the possibility that vaccines could be used to induce active immunity against colonization [32].

Several biases could have impacted the studies in our analysis, although most data suggest that these biases were unlikely to have substantially affected our conclusions. We found that the ORs of cross-sectional studies and cohort studies were similar (0.81 and 0.80, respectively). This similarity suggests that biases specifically related to cross-sectional study design had little impact on our summary results. As stated, few studies defined breast-feeding, and studies may have used different definitions of breast-feeding. Importantly, use of less-accurate definitions of breast-feeding would most likely cause bias toward the null, not toward the protective effect that we found [38]. The choice of diagnostic test (^{13}C-UBT or *H. pylori* IgG serologic test) could have also biased the results of the studies included in the meta-analysis. In the 6 studies that used the ^{13}C-UBT, the OR was 0.67 (95% CI, 0.32–1.39), whereas in the 7 studies that used the IgG serologic test, the OR was 0.91 (95% CI, 0.74–1.11). The use of a less accurate test will generally bias toward the null and may cause some studies to miss a true protective effect [38]. The specificity of the *H. pylori* IgG serologic test has been reported to be as low as 76% for some assays [39]; thus, the test will produce more false-positive results than does the ^{13}C-UBT, which has reported specificities as high as 100% [40, 41]. Our result is consistent with other scientific literature that has called the overall accuracy of the IgG serologic test into question [42]. The lower OR we identified in studies that used the ^{13}C-UBT, compared with the OR for studies that used the IgG serologic test, although not statistically significant, could be an indication that some studies that used the IgG serologic test missed a true effect because of use of this less accurate test.

Several studies in our meta-analysis presented only data that were not adjusted for potential confounding variables (table 1). Factors such as housing density and lack of running water have been linked to increased risk of *H. pylori* infection [33, 34]. However, these factors are unlikely to have caused substantial confounding in our study, because they are not strongly related to breast-feeding—that is, they are found in groups both exposed and unexposed to breast-feeding [43]. Furthermore, the inflammatory bowel diseases may be potential confounders of the relationship between breast-feeding and *H. pylori* infection [44], but they are unlikely to have caused significant confounding because of their relatively low prevalence at the population level. As a whole, although we cannot completely exclude the possibility that some other agent caused the effects we identified, most evidence suggests that confounding is not the likely cause.

Comparison of crude and adjusted data from the few studies that reported these data can provide some indication of the magnitude of potential confounding and suggest logical adjustors that may be used in future studies. In the study by Naficy et al. [17], the crude data (OR, 3.1; the 95% CI was unreported) and age-adjusted data (OR, 1.4; 95% CI, 0.37–5.8) differed, suggesting that age may be an important confounding variable, and future studies related to *H. pylori* infection should consider adjusting for it. Rodrigues et al. [22] adjusted for maternal *H. pylori* infection, age, nutritional status, education of mother, history of antibiotic use, whether the mother smoked, and household density. In this study, the OR was lower in the adjusted results (OR, 0.64; 95% CI, 0.35–1.18) than in the crude results (OR, 0.86; 95% CI, 0.56–1.35), although this difference was small and not statistically significant.

Of all the articles included in our analysis, the study by Rothenbacher et al. [7] was the only to have reported a statistically significant OR of >1.0. Interestingly, the crude OR in that study was 1.46 (95% CI, 0.77–2.75), whereas the OR after adjustment for only maternal *H. pylori* infection was 2.38 (95% CI, 1.20–4.72). As discussed above, important confounders must be associated with both exposure and outcome [43]. Although the data from Rothenbacher and colleagues do show a strong association between maternal *H. pylori* infection and *H. pylori* infection in the child, the magnitude of the association between maternal infection and breast-feeding appears to be small and does not seem to be of sufficient magnitude to cause such a large difference in crude and adjusted ORs. In contrast, Rodrigues et al. [22] also adjusted for maternal *H. pylori* infection, but they instead found that breast-feeding was protective. These conflicting results underscore the importance of assessing maternal *H. pylori* status in future studies. It is intriguing to consider that close maternal contact may be a pos-

sible route of transmission of *H. pylori* infection. On balance, no other obvious differences separate the study by Rothenbacher et al. [7] from the other cross-sectional studies in the meta-analysis, and reasons for its divergent results remain unclear at this time. Furthermore, the study by Rothenbacher and colleagues may highlight possible weaknesses inherent in cross-sectional study design. The case-control study by Süoglu et al. [19] is arguably the most rigorous of the studies included in our meta-analysis, and it reported the greatest protective effect against *H. pylori* infection, compared with all of the other studies.

In conclusion, the results of our analysis suggest that breast-feeding is protective against *H. pylori* infection with the effect primarily seen in studies conducted in middle- and low-income nations. The biologic plausibility of our findings is further supported by the other human and laboratory data. Our findings, however, are based on a relatively small number of studies, and additional longitudinal studies are required for further investigation and to clarify the relationship between breast-feeding and *H. pylori* infection.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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