

META-ANALYSIS

Is *Helicobacter Pylori* infection inversely associated with atopy? A systematic review and meta-analysis

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Summary

Background The role *Helicobacter Pylori* (*H. pylori*) infection plays in the aetiology of atopy remains unclear, although a possible protective role has been hypothesized.

Objective The aim of this study was to undertake a systematic review and meta-analysis of epidemiological studies to quantify the association between *H. pylori* infection and atopy.

Methods A comprehensive literature search in MEDLINE/PUBMED and EMBASE (up to August 2013) was carried out to identify all observational epidemiological studies (cross-sectional, cohort and case-control) published in English that evaluated the association between *H. pylori* infection and objectively measured atopy (measured by allergen skin tests or specific IgE). The quality of included studies was assessed by the Newcastle–Ottawa scale. Random-effects meta-analyses were performed to obtain pooled estimates of effect.

Results Twenty-two observational studies involving 21 348 participants were identified as eligible for inclusion in the review, of which 16 were included in the meta-analysis.

H. pylori infection was associated with a significantly reduced odds of atopy (pooled odds ratio (OR) 0.82; 95% confidence interval (CI) 0.73 – 0.91; $P < 0.01$). Subgroup analysis according to atopy definition revealed a slightly greater protective effect for atopy defined as raised allergen-specific IgE (OR 0.75; 95% CI 0.62 – 0.92; $P < 0.01$; seven studies). Findings did not differ according to the population age (adult or children), methodological quality or study design.

Conclusion and Clinical Relevance Evidence from epidemiological studies suggests that *H. pylori* infection is associated with an estimated 18% reduction in odds of atopy. If the observed association is causal, more insights into the underlying mechanisms could provide clues to possible therapeutic opportunities in allergic disease.

Keywords *Helicobacter pylori*, hypersensitivity, meta-analysis, skin tests

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Introduction

The prevalence of atopic disorders such as asthma has increased considerably over recent decades, particularly in developed countries [1]. In developing countries, asthma is generally rare in rural subsistence communities, but is increasingly common in towns and cities [2–4]. The exact reasons for this epidemic are unknown, but urbanization and adoption of a westernized lifestyle are likely to play some role [5–7]. The hygiene hypoth-

esis, first proposed by Strachan [8], propounds that decreases in microbial infections may be responsible for the increase in atopic diseases observed, and this theory has gained wide acceptance [9]. As part of this theory, it is proposed that microbial infections, which become less prevalent as hygiene improves, may protect against the development of asthma and allergy [10, 11]. There has been a rapid decline in prevalence of *Helicobacter pylori* (*H. pylori*) infection over the last two decades, particularly amongst children in developed countries

[12, 13], and this has been considered a possible contributor to the hygiene hypothesis. Whilst there is a growing body of epidemiological evidence suggesting that *H. pylori* infection is associated with a reduced risk of allergic disorders, with two recent meta-analyses reporting significant protective effects on asthma [14, 15], to date, no similar quantitative systematic review has been carried out on atopy.

We have therefore carried out a systematic review and meta-analysis of the relevant epidemiologic literature with the aim of quantifying the association between *H. pylori* infection and objectively measured atopy.

Methods

Literature search and study selection

A comprehensive literature search in MEDLINE/PUBMED and EMBASE (up to August 2013) was carried out using the search strategy detailed in Appendix 1, to identify epidemiological studies that met the following criteria: (i) published in English; (ii) design was a cross-sectional, cohort, or case-control study; (iii) atopy was defined using allergen skin sensitization, or the presence of specific IgE (sIgE) to allergens, (iv) *H. pylori* infection was measured either by stool antigen test, serum *H. pylori*-specific IgG using ELISA, ^{13}C - or ^{14}C -labelled urea breath test, histologic identification of organisms, or culture. Articles were excluded if they were reviews, letters to the editor without original data, editorials, or case reports. Studies were first screened on the basis of their titles then their abstracts and full texts were obtained for those potentially fulfilling the inclusion criteria. The reference lists of published reviews and the full text papers were also checked to identify any additional eligible studies. EndNote X5 software (Thomson Reuters Corporation, New York, NY, USA) was used to import the retrieved papers. Two researchers (BT and AT) independently performed the screening of potential studies for eligibility and data extraction. For any discrepancies for which no consensus could be reached between two authors, the opinion of the other authors was sought. Excluded articles and reasons for exclusion were documented.

Study quality assessment

The quality of the studies included was assessed using the Newcastle–Ottawa quality assessment scale (NOS) [16]. A quality score was calculated based on three major components: selection of the groups of study; comparability; and ascertainment of the exposure and outcome. Out of a maximum possible NOS score of 7 for cross-sectional studies and 9 for case-control and

cohort studies, a score of 7 or greater was taken to indicate 'high quality'.

Statistical analysis

Meta-analysis was performed using Stata (version 12 SE; Statacorp, College Station, TX, USA) on those studies which reported relative risks and associated 95% confidence intervals (CIs) for the association between *H. pylori* infection and atopy or for which sufficient raw data were reported for these to be calculated. For the primary analysis, the outcome of any atopy was used (positive skin prick test (SPT) to at least one allergen, raised sIgE to at least one allergen, or a combined measure based on SPT and sIgE). All studies used odds ratios (ORs) as their measure of relative risk, and where adjusted odds ratios were presented, these were used in preference to crude odds ratios. Individual effect estimates from the studies were combined using a random study effects model which accounts for heterogeneity between the estimates of effect. To assess heterogeneity amongst the studies, we used the Cochran Q and I^2 statistics; for the Q statistic, a P value < 0.10 was considered statistically significant for heterogeneity; for I^2 , a value $> 50\%$ is considered a measure of severe heterogeneity [17]. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study ORs against the standard error of the logarithm of the ORs [18]. The degree of asymmetry was tested using Egger's regression asymmetry test [19, 20]. To determine whether individual studies had an undue influence on the overall results, we conducted an influence analysis, which estimates the impact of single studies on the overall pooled estimates [21]. Following the primary analysis, subgroup analyses were then performed according to atopy definition (SPT or raised sIgE or a combined measure), study quality (low or high), study design, and age of study population (children or adults).

Studies not included in the meta-analysis were summarized in narrative format. The present work was performed as per the guidelines proposed by the Meta-analysis of Observational Studies in Epidemiology group (MOOSE) [22]. The protocol developed to undertake this systematic review and meta-analysis was registered at the PROSPERO International prospective register of systematic reviews (registration number; CRD42013005053) to avoid duplication of review [23].

Results

Study characteristics

From the literature search, 732 potentially relevant studies were identified. After the title and abstract screening steps, the full texts of 40 were obtained

(Fig. 1). A total of 22 of these 40 studies were eligible for inclusion, and of these, 16 presented data suitable for inclusion in the meta-analysis (Fig. 1).

Of the 22 studies eligible for review, seventeen used a cross-sectional design [24–40], three used a case-control design [11, 41, 42], and two used a cohort design [43, 44]. The majority of the studies were undertaken in adults from 18 to 74 years, with only six performed in children (aged 3–17 years) [28, 32, 36, 37, 39, 43] and one in both children and adults [38]. The total number of individuals in all 22 studies eligible for review was 21 348 (Table 1).

Of the 16 studies included in the meta-analysis, atopy was defined using a positive skin sensitization test (wheal sizes of ≥ 3 mm) in six studies [33–36, 39, 43], using specific IgE in seven [25–28, 30, 37, 44, 45], and using a combined measure (SPT and SIgE) in three. [11, 41, 42] (Table 1).

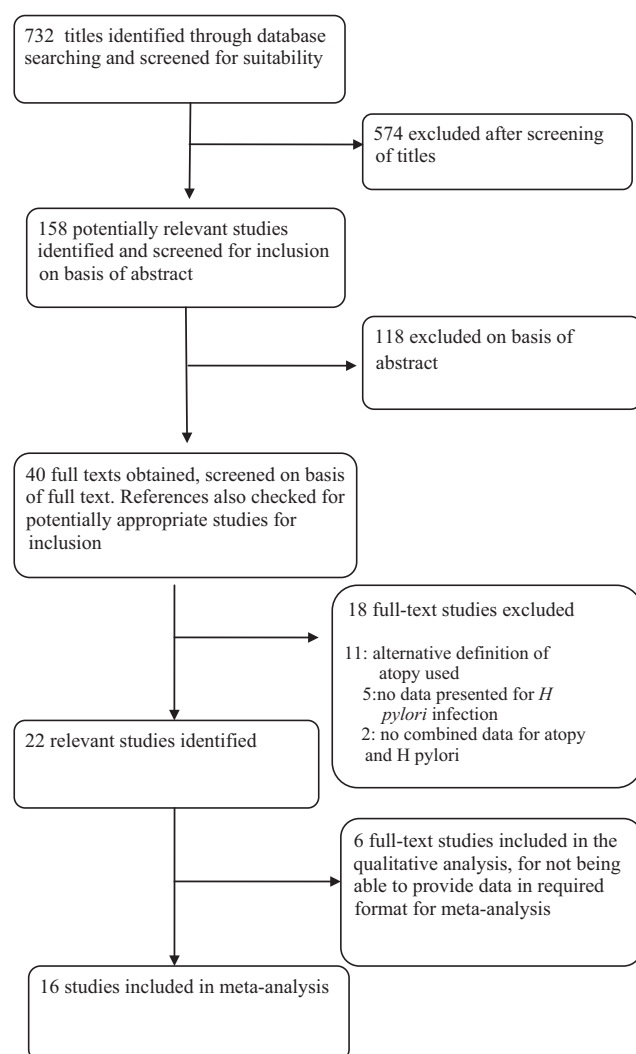


Fig. 1. Flow diagram of study selection procedure.

Quality assessment

A total of 14 of the 22 studies eligible for review were classified as being of higher methodological quality (score ≥ 7) and eight were judged to be lower quality because of inadequate definition of their control population, failure to adjust for confounding variables, or not reporting response rates. The median overall score was 7 (range 4–8) indicating that the quality was generally high (Table 1).

Meta-analysis of association between *H. pylori* infection and atopy

Figure 2 shows an overall pooled OR for the association between *H. Pylori* and any atopy (defined by SPT, SIgE, or a combination of both) of 0.82 (95% CI 0.73–0.91), which was highly statistical significant ($P < 0.001$). Thirteen of the 16 studies individually reported an OR less than 1, and heterogeneity in estimated effect size between the studies was very low and no more than expected by chance ($I^2 = 0.0\%$). No marked departures from symmetry were seen in the funnel plot that would be suggestive of publication bias (Fig. 3). The Egger regression asymmetry test also showed no statistically significant publication biases (Egger's test; $\beta = 0.0935$, $P = 0.851$). When the robustness of the estimate was examined by sequentially removing each study and re-analysing the remaining data sets, no single study exerted undue influence on the pooled OR estimate (Online supplement Fig. S1).

Subgroup analyses

When the meta-analysis was split by atopy definition, a nonsignificantly reduced OR of 0.88 (95% CI 0.76–1.03, $P = 0.11$, $I^2 = 0.0\%$) was obtained from pooling the six studies that assessed atopy using SPT [33–36, 39, 43], whilst the pooled OR for the seven studies [25–28, 30, 37, 44, 45] that assessed atopy based on SIgE was stronger and statistically significant (OR = 0.75, 95% CI; 0.63–0.92, $P < 0.01$, $I^2 = 17.6\%$). Only three studies used a combined measure to define atopy [11, 41, 42] resulting in a reduced but nonsignificant pooled OR of 0.82 (95% CI; 0.59–1.14, $P = 0.24$, $I^2 = 0.0\%$, Fig. 4).

Findings did not materially alter when analysis was restricted to the 12 high-quality studies (OR = 0.82, 95% CI 0.73–0.91; $P < 0.01$; $I^2 = 0.0\%$; Fig. S2). Assessing adults only, the pooled OR was 0.80 (95% CI 0.71–0.90; $P < 0.01$; $I^2 = 0.0\%$; 11 studies) compared with 0.88 for children (0.69–1.13; $P = 0.31$; $I^2 = 0.4\%$; five studies; Fig. S3). The 11 cross-sectional studies resulted in a pooled OR of 0.82 (95% CI; 0.71–0.94; $P < 0.01$, $I^2 = 11.2\%$), and whilst there were only three case-control and two cohort studies, the magnitude of effect for

Table 1. Descriptive characteristics of studies eligible for the review

First Author, Year	Country	Study design	Outcome* measures	Cut-off value	Exposure measure	Age in years	Number of participants	NOS†
Bodner, (2000)	UK (Scotland)	Case-control	SPT and SIgE	SPT ≥ 3 mm, SIgE > 0.35 IU/L	IgG ELISA	39-45	97 cases and 208 controls	7
Matricardi, (2000)	Italy	Case-control	SPT and SIgE	SigE > logRU 1.2, SPT ≥ 3 mm	IgG ELISA	17-24	240 cases and 240 control	5
Cullinan, (2003)	UK	Cohort	SPT	SPT ≥ 3 mm	IgG ELISA	Mean (SD) = 28 (5)	896	8
Linneberg, (2003)	Denmark	Cross-sectional	SigE	SigE ≥ 0.35 ku/L	IgG ELISA	15-69	1101	7
Jarvis, (2004)	UK	Cross-sectional	SigE	SigE ≥ 0.35 ku/L	IgG ELISA	20-44	907	7
Radon, (2004)	Germany	Cross-sectional	SigE	SigE > 0.70 ku/L	IgG ELISA	18-44	321	7
Kolho, 2005	Finland	Cross-sectional	SigE	SigE ≥ 0.35 ku/L	IgG/IgA ELISA	5-5; mean 9.3	74	4
Janson, (2007)	Iceland, Sweden, Estonia	Cross-sectional	SigE	SigE ≥ 0.35 ku/L	IgG ELISA	Mean 42.1 ± 7.2	1249	7
Bacciglu, (2008)	Turkey	Cross-sectional	SPT	SPT ≥ 3 mm	Histology	17-74, mean 38	90	4
Konturek, (2008)	Germany	Case-control	SPT and SIgE	Not provided	UBT*	Mean 46.5 and 49.1 for cases and control respectively	42 cases and 20 controls	4
Seiskari, (2009)	Finland	Cohort	SigE	SigE ≥ 0.35 ku/L	IgG ELISA	Median 26, 28, 29, 29 in 1983, 1989, 1995, 2001, respectively	958; n = 232, 240, 243, and 243 in 1983, 1989, 1995 and 2001, respectively	8
Cam, (2009)	Turkey	Cross-sectional	SPT	SPT ≥ 3 mm	UBT*	13-17	74	4
Fullerton, (2009)	UK	Cross-sectional	SPT	SPT ≥ 3 mm	IgG ELISA	18-70, mean 44 (SD = 13.6)	2437	8
Amberbir, (2011)	Ethiopia	Cross-sectional	SPT	SPT ≥ 3 mm	Stool antigen	3	616	7
Michos, (2011)	Greece	Cross-sectional	SigE	Positive vs. negative	IgG ELISA	5-15	216	8
Alcantara-Neves, (2012)	Brazil	Cross-sectional	SPT	SpT ≥ 3 mm	IgG ELISA	4-11	1182	8
Studies not included in the meta-analysis								
Kosunen, (2002)	Finland	Cross-sectional	SigE	SigE > 0.35 IU/L	IgG/IgA ELISA	15-54	326 and 319 in 1973 and 1994, respectively	7
von Hertzen, (2006)	Eastern Finland, Western Russia	Cross-sectional	SPT	SPT ≥ 3 mm	IgG ELISA	25-54	790 from Finland and 387 from Russia	7
Seiskari, (2007)	Finland and Russian	Cross-sectional	SigE	SigE ≥ 0.35 ku/L	IgG ELISA	7-15, mean 11.4	266 from Finland and 266 from Russia	4
Chen, (2007)	USA	Cross-sectional	SPT	SPT ≥ 3 mm	IgG ELISA	20-59, mean 43	7633	8
Imamura, (2010)	Japan	Cross-sectional	SigE	5, 5.1-20, > 20 IU/mL; mild, moderate severe	ELISA	Mean 32.7 and 49.8 for healthy and patients, respectively	97 healthy 211 patients	5
Serrano, (2011)	Chile	Cross-sectional	SPT and SIgE	SPT ≥ 3 mm, no cut-off value for SIgE	IgG ELISA	Mean 11.8 and 43.2 for children and adults, respectively	98 children and 67 adults	5

*SPT (skin prick test), SIgE (specific IgE).

†Newcastle-Ottawa Quality Assessment Scale, a maximum score of 7 for cross-sectional studies and nine for case-control and cohort studies *UBT ¹³C-labelled urea breath test.

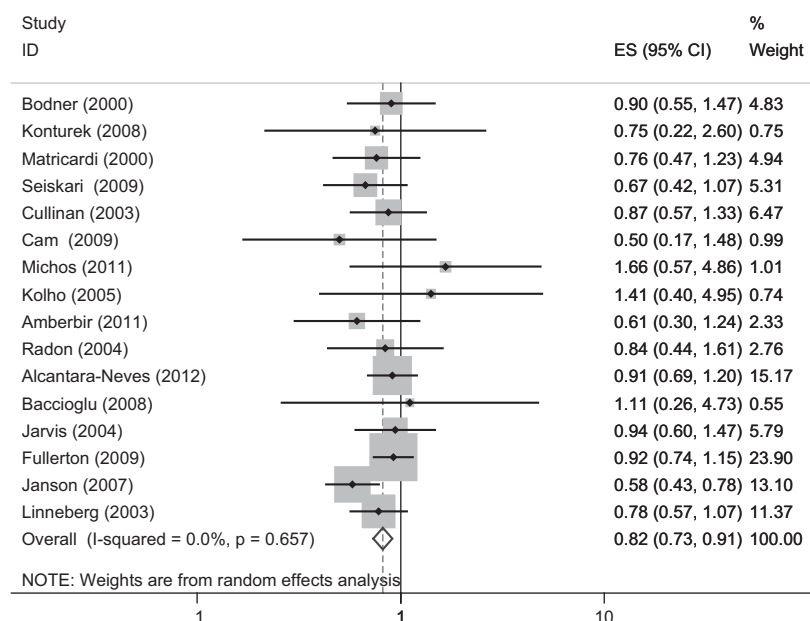


Fig. 2. Forest plot of the association between atopy and *H. pylori* infection. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis. Test for overall effects: $z = 3.70$; $P < 0.001$, Heterogeneity chi-squared test = 12.29 (df = 15), $P = 0.657$.

these designs was similar (OR 0.82 and 0.77, respectively; Fig. S4). Limiting analysis to those studies adjusted their analysis for potential confounders resulted in a pooled OR 0.86 (95% CI: 0.76 – 0.97; $P < 0.01$, $I^2 = 0.0\%$; 11 studies) compared with 0.62 for unadjusted analyses (0.47 – 0.81; $P < 0.01$; $I^2 = 0.0\%$; five studies; Fig. S5).

Studies not included in meta-analysis

Six studies [24, 29, 31, 32, 38, 40] were identified as eligible but could not be included in the meta-analysis.

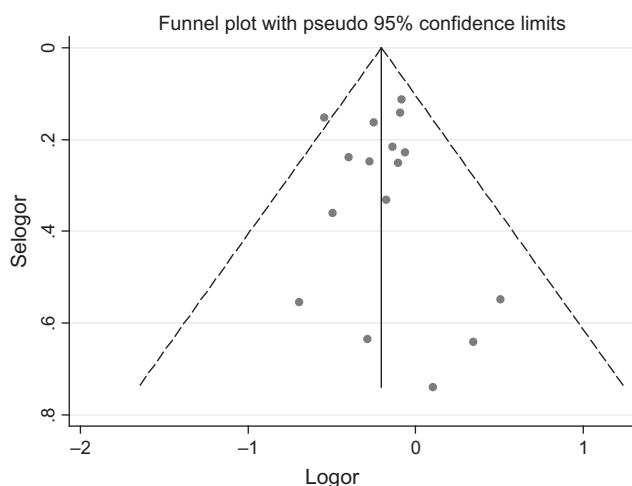


Fig. 3. Funnel plot with pseudo 95% CIs for the association between atopy and *H. pylori* infection. Egger's test; $\beta = 0.0935$, $P = 0.851$.

Chen et al. [31] presented separate data for six specific allergens only and reported a reduced risk of skin sensitization to several pollen and moulds amongst individuals infected with the more virulent Cag A+ *H. pylori* strain. Imamura et al. [40] also found *H. pylori* infection to be associated with a statistically significant decrease in the likelihood of having raised specific IgE to pollen. Two studies reported higher prevalence of atopic sensitization in Finland than Russia amongst children [32] and adults [29], respectively, and it appeared that this was due to an inverse association with *H. pylori* infection. Kosunen et al. [24] also reported a 3.5-fold increase in the incidence of allergy between 1973 and 1994 in Finland, accompanied by a 30% decrease in *H. pylori* infections over the same period. Serrano et al. [38] found a significantly lower prevalence of skin sensitization to any specific allergen amongst *H. pylori* positive children, but not in adults.

Discussion

To our knowledge, this study is the first systematic review and meta-analysis of the epidemiological evidence for an association between *H. pylori* infection and objectively measured atopy. Our meta-analysis of 16 eligible studies showed *H. pylori* infection to be associated with an estimated 18% reduction in odds of atopy, which was highly statistically significant. A broadly similar magnitude of association was observed regardless of atopy definition, study quality, adult or

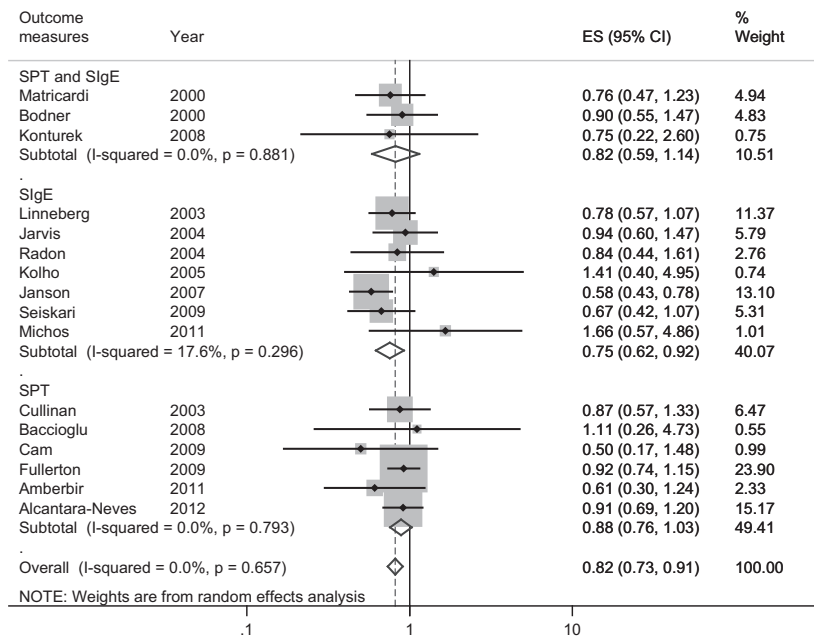


Fig. 4. Forest plot of the association between atopy and *H. pylori* infection according to definition of outcome. Skin prick test (SPT) indicates positive skin sensitization to at least one allergen, SIgE indicates raised specific IgE level to at least one allergen, both SPT and SIgE indicate combined measures used at the same time. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis. Test for overall effects: Both SPT and SIgE, $z = 1.17$; $P = 0.24$; Skin prick test (SPT), $z = 1.58$; $P = 0.11$; SIgE, $z = 2.77$; $P < 0.01$; Overall $z = 3.70$; $P < 0.001$.

child population, and study design, although the estimated protective effect was slightly stronger for atopy defined using raised SIgE than atopy defined using SPT.

A strength of this review was the comprehensive search strategy in two separate journal databases (i.e. PUBMED and EMBASE) used to identify potentially suitable studies. By limiting to English language only, however, it is possible that some relevant studies published in the non-English literature could have been missed. Study eligibility was rigorously assessed by two independent reviewers, and reference lists checked to further minimize the possibility of missing eligible studies. No evidence of publication bias was identified from our funnel plot, although the possibility that some unpublished studies have been missed cannot be completely ruled out. The degree of heterogeneity between the studies was very low, and it was therefore appropriate to pool the findings using meta-analysis. Furthermore, the meta-analysis was based on data from 16 studies and over 20 000 individuals, resulting in high statistical power.

The majority of the studies included in our analysis scored highly for methodologically quality, and findings were consistent when the small number of lower quality studies were excluded. Only studies that used an objective definition of atopy were eligible for inclusion in the review, hence reducing reporting bias that may arise from use of subjective self-reported measures.

Consistency in the cut-point used to define atopy was seen across the studies, with all those based on SPT using a wheal size of ≥ 3 mm to define positive, and all but three that assessed atopy on SIgE adopting the cut-off value of ≥ 0.35 ku/L to define atopy. This may have led to some misclassification, but it is unlikely to have had a major influence on our findings as the pooled estimate was similar when these were excluded. The exposure of interest, *H. pylori* infection, also had to have been measured objectively to meet our eligibility criteria, with most studies defining infection by the detection of anti *H. pylori* IgG antibodies using ELISA-based technology, an inexpensive, noninvasive, and validated method to ascertain *H. pylori* exposure [46]. However, as *H. pylori* infection status was presented solely as positive or negative rather than level of infection, dose-response effects could not be assessed in our meta-analysis.

Most studies adjusted their analyses for major important confounders. Limiting analysis to studies that did not adjust their analyses for potential confounders showed a higher magnitude of effect estimate, suggesting that the association between *H. pylori* and atopy from pooled data could be partly explained by unmeasured or residual confounding.

The possibility of reverse causation is difficult to fully eliminate as all but two studies in our meta-analysis were case-control or cross-sectional in design. How-

ever, the results of the two available cohort studies were consistent with our overall findings, which provide, in part, an indication that reverse causation was unlikely.

According to the hygiene hypothesis, it is biologically plausible that individuals with *H. pylori* infection are less likely to develop atopy [9]. This premise is supported by several mechanistic disease models; allergic diseases and asthma are caused by exaggerated T helper 2 (Th2)-biased immune response in genetically susceptible individuals [47]. One possibility is that *H. pylori* drives a more generalized Th1 response that suppresses Th2 effects; the latter are elicited by infectious agents and are able to induce the production of IFN- γ , IL-12, IL-18, and IL-23 [48]. Furthermore, a high level of T regulatory cells (Tregs), associated with *H. pylori* colonization [49, 50], might also play an important role in controlling Th2-biased responses, in which impaired expansion of natural or adaptive Tregs is hypothesized to lead the development of allergy and asthma [47].

Our findings also fit with recent meta-analyses of *H. pylori* and asthma by both Zhou et al. [14] and Wang et al. [15], who report a significant inverse association between *H. pylori* infection and asthma from 14 and 19 studies, respectively. Our findings for *H. pylori*

and atopy are also in accordance with those for other micro-organisms which have similar Th1-type immune responses, for example a meta-analysis of 11 studies that found a statistically significant inverse association between current intestinal parasite infection and atopy [51].

In conclusion, this review and meta-analysis provide evidence that *H. pylori* infection is inversely associated with atopy. However, further studies, particularly high-quality cohort studies, are needed to help establish causality, something that has potentially important implications in terms of improved understanding of the pathogenesis of allergic disease and possible therapeutic opportunities.

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Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Sensitivity analysis for atopy and *H. pylori* infection. The horizontal axis shows the omitted study. Each circle indicates the pooled odds ratio (OR) when the named study is omitted from this meta-analysis. The two ends of each broken line represent the respective 95% confidence interval (CI).

Figure S2. Forest plot of the association between atopy and *H. pylori* infection according to NOS quality scale. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

Figure S3. Forest plot of the association between atopy and *H. pylori* infection according to the type of

study population used. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

Figure S4. Forest plot of the association between atopy and *H. pylori* infection according to study design. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

Figure S5. Forest plot of the association between atopy and *H. pylori* infection according to the type of analysis (i.e. Adjusted vs. Unadjusted for potential confounders). For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

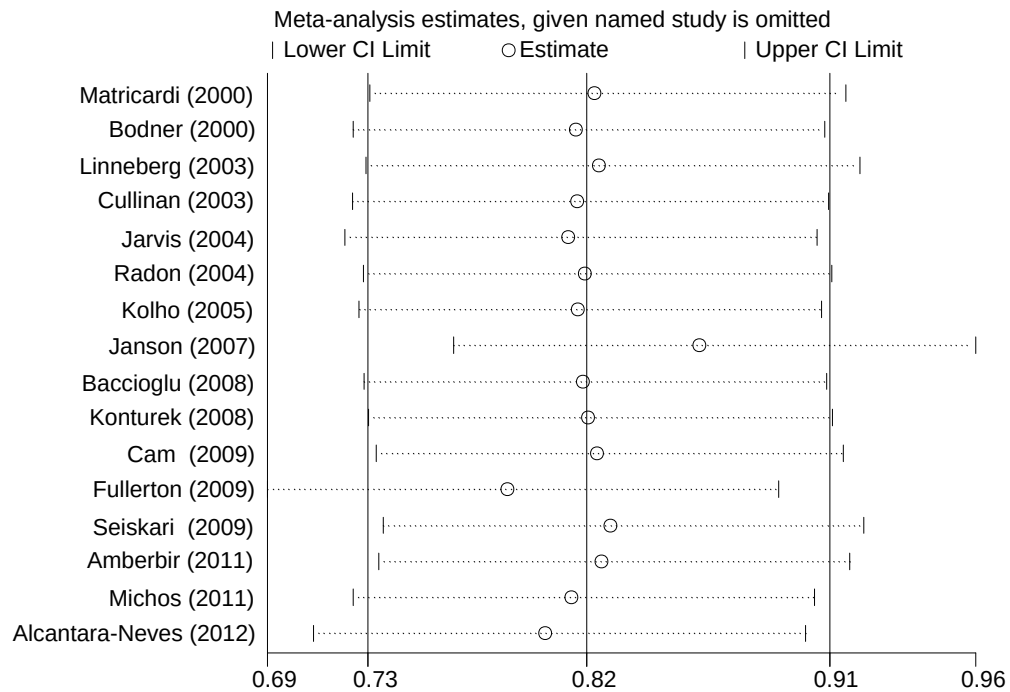


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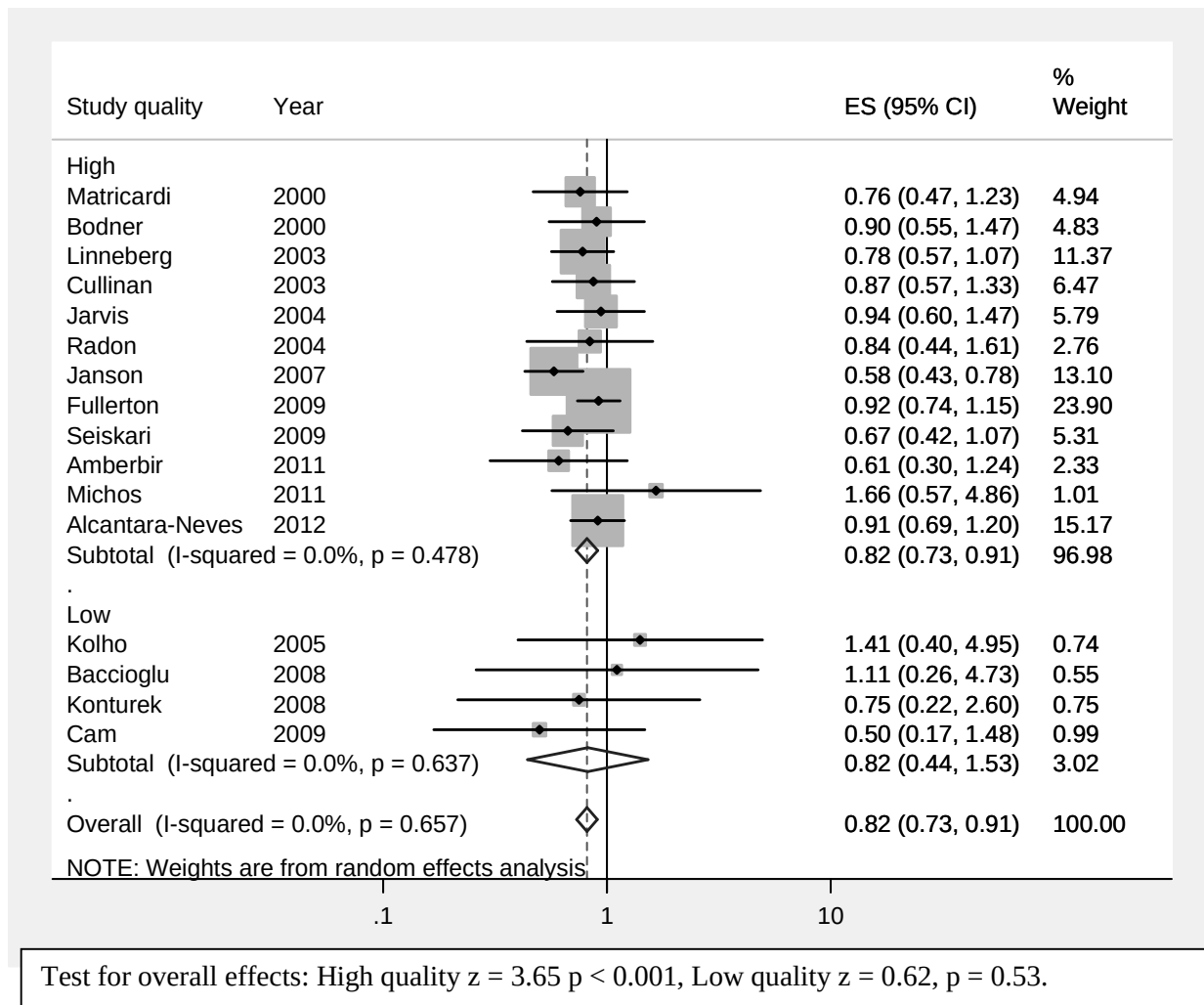


Fig. S2. Forest plot of the association between atopy and *H. pylori* infection according to NOS quality scale. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

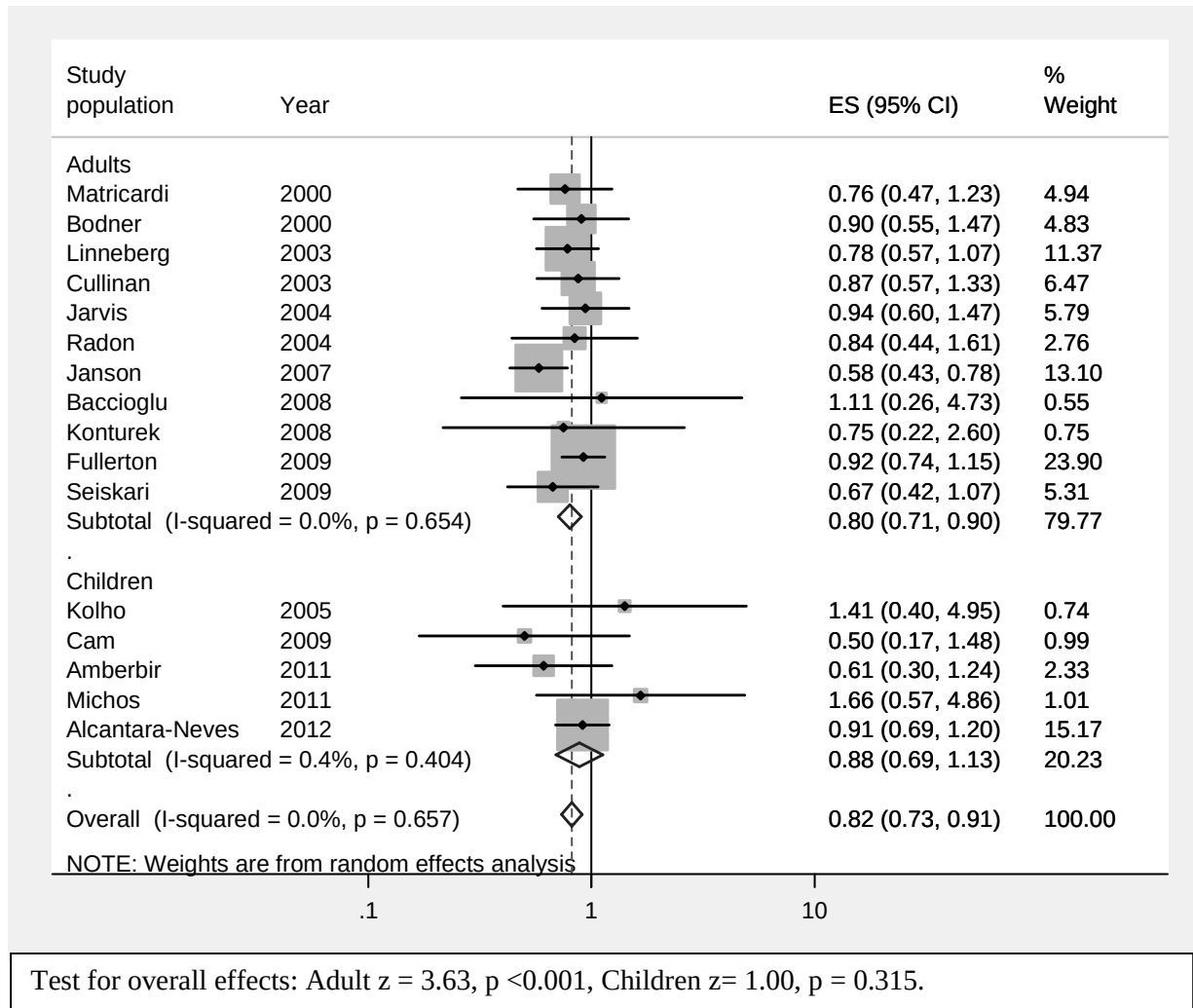


Fig. S3. Forest plot of the association between atopy and *H. pylori* infection according to the type of study population used. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

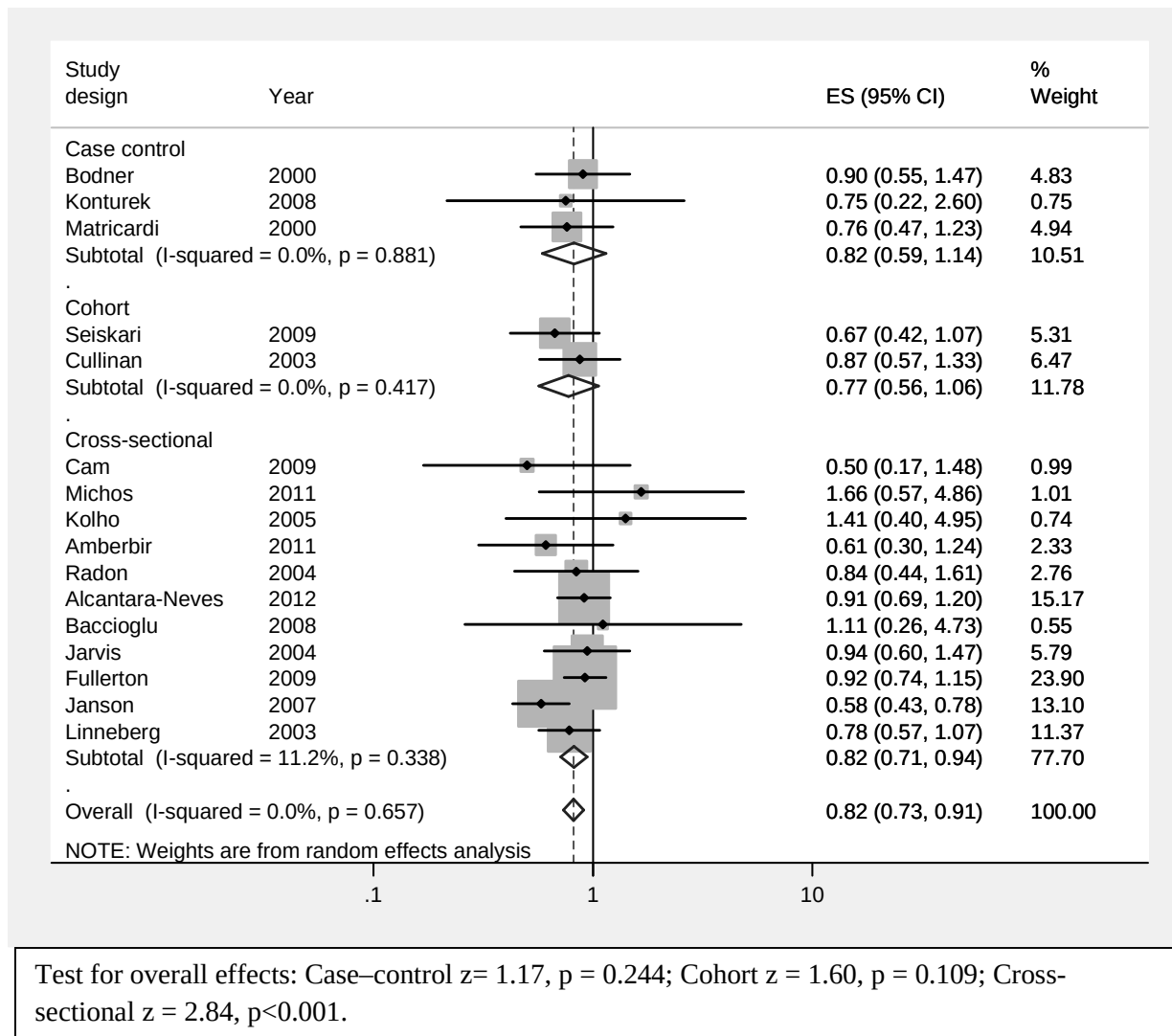


Fig. S4. Forest plot of the association between atopy and *H. pylori* infection according to study design. For each study, the box represents the random effects odds ratio and the line the 95% confidence intervals. The size of each box indicates the relative weight of each study in the meta-analysis.

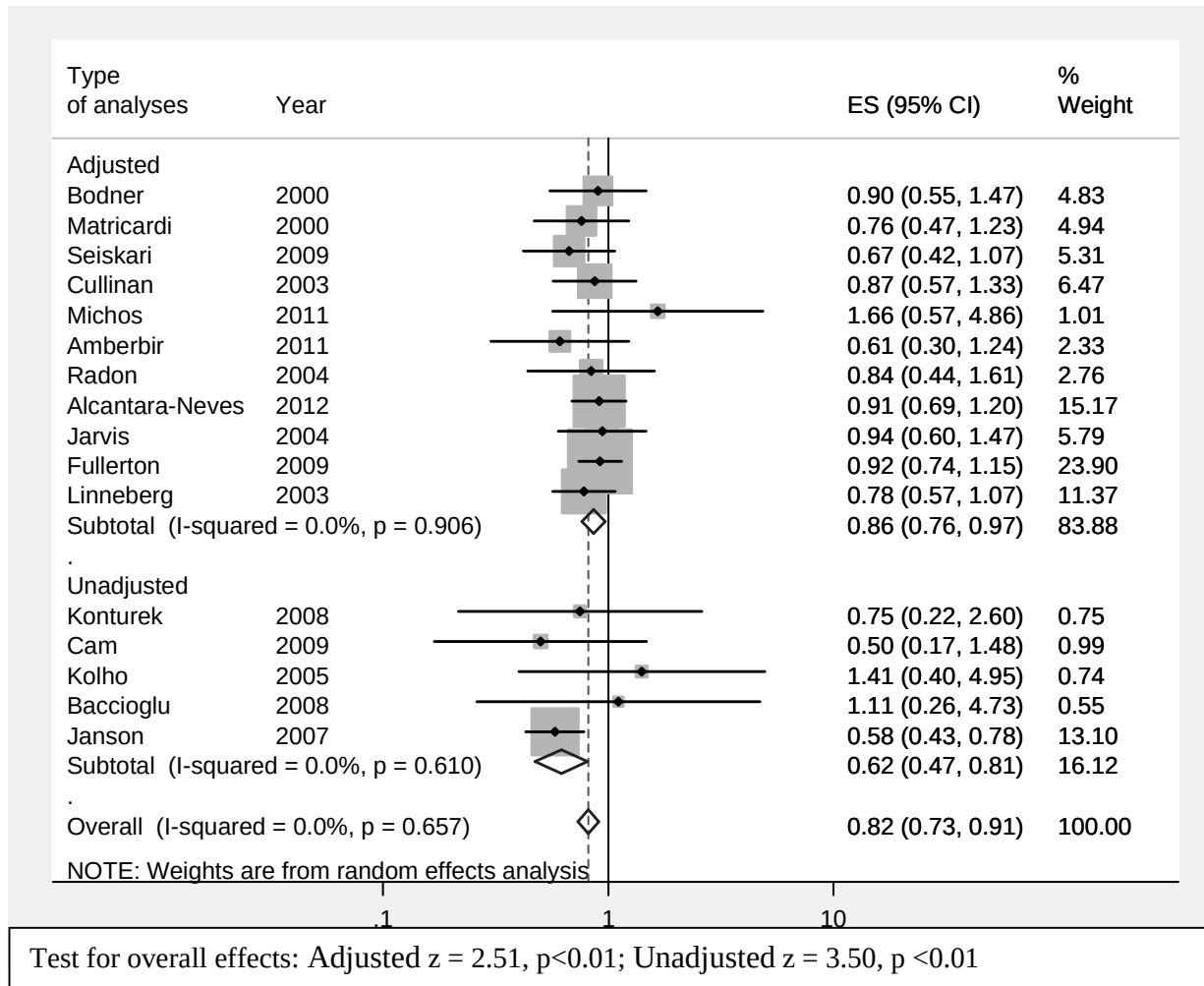


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