

BCG vaccination and allergy: A systematic review and meta-analysis

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Background: There is conflicting evidence on whether BCG vaccination might represent an effective primary preventative strategy against the development of allergic sensitization and disease.

Objectives: We sought to systematically review the relationship between BCG vaccination and the risk of sensitization, eczema/atopic dermatitis, allergic rhinoconjunctivitis, asthma, and other allergic conditions, such as food allergy and anaphylaxis. **Methods:** Four international databases were searched for published epidemiologic or interventional studies. Additional online study databases were searched and vaccine manufacturers and a panel of international experts were contacted in an attempt to locate unpublished or ongoing studies. Quality assessment was undertaken by using internationally established criteria. Meta-analyses were undertaken by using fixed- or random-effects modeling. Funnel plots were used to assess for the risk of publication bias.

Results: We identified 767 articles, of which 17 satisfied our inclusion criteria; there was only 1 randomized controlled trial, with the remaining studies being epidemiologic investigations. Meta-analyses did not show any protective effect of vaccination against the risk of sensitization, as judged by specific IgE tests (odds ratio [OR], 1.31; 95% CI, 1.07-1.60) or skin prick testing (OR, 0.87; 95% CI, 0.67-1.13); the risk of atopic eczema/dermatitis (OR, 0.84; 95% CI, 0.64-1.09); or the risk of allergic rhinoconjunctivitis (OR, 1.07; 95% CI, 0.89-1.28). BCG vaccination was associated with a protective effect against the risk of asthma (OR, 0.73; 95% CI, 0.56-0.95), although this might be explained by publication bias.

Conclusions: BCG vaccination is unlikely to be associated with protection against the risk of allergic sensitization and disease. The observed possible benefit in relation to the development of asthma is unlikely to be due to allergic sensitization. (*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: Allergy, asthma, atopy, BCG vaccination, meta-analysis, systematic review

Abbreviations used

OR: Odds ratio

RCT: Randomized controlled trial

The prevalence of atopic allergic disorders has increased dramatically in many parts of the world in recent decades such that it has now reached epidemic proportions in some countries, with approximately 50% of young people experiencing symptoms highly suggestive of 1 or more allergic disorders at some point in their lives.^{1,2} Allergic problems can have a considerable effect on the quality of life of affected subjects, and they now also pose a substantial economic burden to health care systems and the state.³⁻⁵ There is then a pressing need to identify safe and effective interventions for the primary prevention of allergy.

Late pregnancy and early infancy are critical times for the development of the acquired immune system and therefore offer potentially important windows of opportunity for preventative measures. Earlier formulations of the hygiene hypothesis suggested that decreases in exposure to infectious diseases in early life might have prevented the shifting of the immune system's initial dominant T_H2 (allergic) response to a more T_H1-dominant immunologic profile (nonallergic) that is characteristic in subjects exposed to infectious antigens, thereby increasing the risk of sensitization and allergic disease.⁶ More recently, however, a number of other biological explanations of the hygiene hypothesis have been advanced, including the critical role of regulatory T and T_H17 immune cells and reasons for the failure to achieve immune tolerance.⁷⁻¹⁰

Childhood vaccinations are an important early influence on the development of the immune system. The association between vaccination and the risk of atopic disorders was first proposed in 1994 by Odent et al,¹¹ and since then, numerous epidemiologic studies have investigated this hypothesis. Of particular interest in this respect, however, is the possible effect of vaccination with BCG on preventing allergic disease.

The BCG vaccine, which is given to prevent tuberculosis and leprosy, is a potentially useful therapeutic model to investigate the effect of early-life stimulation of T_H1 cells. This is because BCG has a T_H1 stimulatory effect, which results in it altering cytokine response patterns in such a way that the T_H2 immunologic response is inhibited, thus antagonizing atopy, as has now been demonstrated both in animal models and human subjects.¹² On this basis, it has been suggested that BCG vaccination administered in infancy might have a protective effect against the development of atopic diseases.¹³

Randomized controlled trials (RCTs) are the only study design to allow the effectiveness of interventions to be reliably assessed. Using such gold standard designs is particularly important to establish the

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D. L. A. was supported by a Socrates Studentship.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

Received for publication January 21, 2010; revised June 14, 2010; accepted for publication July 19, 2010.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2010.07.039

evidence for primary preventative interventions because one is by definition intervening in healthy subjects; therefore the strength of evidence needed before intervening needs (appropriately) to be very high. However, recognizing the likely very limited trial evidence to date, we decided to include both experimental and epidemiologic studies that have investigated the relationship between BCG vaccination and the risk of allergic sensitization and disease to make explicit the evidence and to inform deliberations on the appropriateness of future possible primary prevention trials.

METHODS

Overview

We conducted a systematic review of the literature using agreed-upon international standards for appraising experimental and epidemiologic studies. This included a clearly described search strategy for identifying all potentially relevant studies, with study selection, quality assessment, and data extraction independently undertaken by 2 reviewers.

Inclusion criteria

Types of participants. We were interested in studies conducted on children aged 17 years or less at either high or low risk of sensitization, allergic disorders, or both of any ethnic group.

Types of exposure. We were interested in studies that investigated BCG vaccination administered in early childhood (ie, up until the age of 5 years).

Types of outcomes. Outcome measures of interest were risk of sensitization and all potentially relevant diseases, including atopic eczema/dermatitis, asthma, allergic rhinoconjunctivitis, food allergies, urticaria, angioedema, and anaphylaxis.

Types of studies. We were willing to consider RCTs, controlled trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies with or without modeling.

Search strategy

A detailed search strategy was developed using both MeSH terms and text searches (see Appendix E1 in this article's Online Repository at www.jacionline.org), and this was applied to searching the following major biomedical databases: MEDLINE, EMBASE, ISI Web of Science, and BIOSIS. There were no restrictions in terms of language or year of publication. The bibliographies of included studies were scrutinized for additional possibly eligible studies.

In an attempt to locate relevant unpublished and in-progress work, we searched the following additional databases: Index to Thesis, Clinical trials.gov, Current clinical trials.gov, digital dissertations, open SIGLE, and Google Scholar. In addition, we contacted manufacturers of the BCG vaccine and a panel of international experts to ask whether they were aware of any other published or unpublished studies that might be relevant.

Study selection, quality assessment, and data extraction

All relevant articles identified were independently scrutinized by 2 reviewers (D. L. A. and M. L.) on the basis of their titles, key words, and abstracts. Articles were excluded when both reviewers agreed that the article did not match the inclusion criteria. When reviewers disagreed, a solution was initially sought through discussion among the reviewers. Where the title, abstract, or both did not provide sufficient information to come to a consensus decision, the full text of the article was obtained for evaluation. Both reviewers then independently assessed the full report for eligibility. Any disagreements were resolved by discussion between the reviewers; if necessary, a third reviewer (A. S.) arbitrated.

Two reviewers (D. L. A. and M. L.) independently performed the quality assessment of included articles using the Cochrane approach detailed in

section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* for experimental studies¹⁴ and a quality assessment checklist for epidemiologic studies using relevant data fields derived from the Strengthening the Reporting of Observational studies in Epidemiology checklist.¹⁵ Based on these assessments, we classified the studies into the following categories: A, high quality and at low risk of bias; B, moderate quality and therefore at moderate risk of bias; and C, low quality and at high risk of drawing erroneous conclusions. Disagreements were resolved by means of discussion, with arbitration by A. S. if necessary.

Data were independently extracted onto a customized data extraction form. Disagreements were resolved by discussion, with arbitration by A. S. if necessary.

Statistical methods. Data were, where appropriate, pooled by using the software program Review Manager to calculate summary odds ratios (ORs) with corresponding 95% CIs. To investigate heterogeneity, we used the I^2 statistic, assuming statistical heterogeneity if the I^2 value was greater than 40%. If significant heterogeneity was present, we used random-effects modeling to undertake meta-analysis; in the absence of such heterogeneity, however, we used fixed-effects modeling.

If heterogeneity was detected, we used, where possible, *a priori*-defined subgroup analyses to investigate this heterogeneity, focusing in particular on the risk of allergy based on family history, region of birth, or both as explanatory factors. Geography was considered potentially important because children born into regions of the world in which helminth infections and tuberculosis are endemic might derive particular benefits from BCG vaccination.¹⁶

The risk of publication bias was assessed graphically by using funnel plots. The robustness of the overall estimates obtained was, where appropriate, assessed by using sensitivity analyses by excluding studies judged to be at high risk of bias.

RESULTS

Our searches identified 767 potentially relevant articles, of which 17 ultimately satisfied our inclusion criteria.¹⁷⁻³⁴ Fig 1 describes the study selection process, including details of the reasons for excluding studies. Our searches for unpublished material did not identify any other eligible studies (see Fig E1 in this article's Online Repository at www.jacionline.org).

The main features of the 17 included studies are detailed in Table I.¹⁷⁻³⁴ Of particular note was that there was only 1 RCT³²; the remaining 16 studies used either cohort (n = 7, 6 of which were retrospective and only 1 of which was prospective),^{17,18,22-24,26-27} case-control (n = 2)^{20,30} or cross-sectional (n = 7) designs.^{19,21,25,28,31,33}

Sensitization to common allergens

Ten studies investigated the relationship between BCG vaccination and allergic sensitization.^{17-19,23,25,27,29-30,32,34} Five of these studies considered sensitization as judged by increased specific IgE levels to 1 or more allergens (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org for details about these studies and the specific IgE measures assessed).^{18,23,25,30,32} Seven studies considered evidence of sensitization as determined by a positive skin prick test (SPT) response, this being determined by at least 1 positive reaction, where a positive reaction was described as a wheal size of 2 mm or greater or 3 mm or greater (see Table E3 in this article's Online Repository at www.jacionline.org).^{17-19,23,27,29,34}

The pooling of the 5 studies investigating specific IgE levels estimated an overall OR of 1.31 (95% CI, 1.07-1.60) for the risk of sensitization in those who were vaccinated compared with those who were not (Fig 2). Sensitivity analysis found that the OR

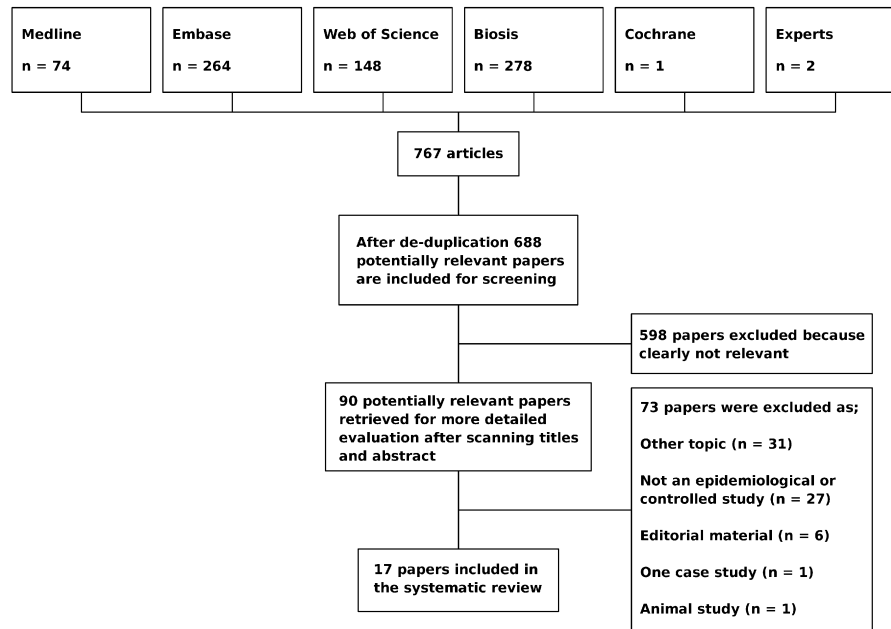


FIG 1. Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) diagram of published studies.

was unchanged when excluding studies judged to be at high risk of bias (OR, 1.34; 95% CI, 1.05-1.69; see Fig E2, A, in this article's Online Repository at www.jacionline.org). The funnel plot suggested that publication bias was unlikely (see Fig E2, B).

It was possible to pool data from 5 studies investigating sensitization using SPTs; this estimated an overall OR of 0.87 (95% CI, 0.67-1.13; Fig 3). Sensitivity analysis found that the OR was unchanged when excluding studies judged to be at high risk of bias (OR, 0.92; 95% CI, 0.76-1.12; see Fig E3, A, in this article's Online Repository at www.jacionline.org). The funnel plot suggested that publication bias was unlikely (see Fig E3, B).

To investigate the sources of the heterogeneity, we conducted subgroup analyses by pooling data from the studies of high-risk children; this resulted in an OR of 0.95 (95% CI, 0.60-1.50) for the positive SPT outcome and an OR of 1.24 (95% CI, 0.86-1.80) for the positive specific IgE outcome (see Fig E4 in this article's Online Repository at www.jacionline.org).

Eczema/atopic dermatitis

Nine studies investigated the relationship between BCG vaccination and atopic dermatitis or eczema (see Table E4 in this article's Online Repository at www.jacionline.org).^{18,19,21-24,27-29,32}

Analysis showed an overall OR of 0.84 (95% CI, 0.64-1.09) in the risk of eczema/atopic dermatitis (Fig 4); there was significant heterogeneity ($I^2 = 89\%$). The funnel plot was suggestive of publication bias (see Fig E5 in this article's Online Repository at www.jacionline.org). Sensitivity analysis found that the OR was unchanged when excluding studies judged to be at high risk of bias (OR, 0.89; 95% CI, 0.65-1.21; see Fig E6 in this article's Online Repository at www.jacionline.org).

Subgroup analysis was conducted to investigate the source of heterogeneity; analysis of children judged to be at high risk

of allergic disorders found a similar effect size (OR, 0.81; 95% CI, 0.64-1.03; see Fig E7, A, in this article's Online Repository at www.jacionline.org). The effect size was also similar when the analysis was confined to studies conducted in non-Western populations (OR, 0.78; 95% CI, 0.62-0.97; see Fig E7, B).

Asthma

Thirteen studies investigated the effect of BCG on the risk of asthma (see Table E5 in this article's Online Repository at www.jacionline.org).^{18,19,21-24,26-32}

Because studies often used a range of asthma-related outcome measures, we used the most important reported outcome for meta-analysis. Our preferred order of importance was as follows: lifetime asthma, 12-month prevalence of asthma, lifetime wheezing, and 12-month prevalence of wheezing. We estimated an overall OR of 0.73 (95% CI, 0.56-0.95; Fig 5), but there was evidence of heterogeneity ($I^2 = 91\%$). The funnel plot showed evidence suggestive of publication bias (see Fig E8 in this article's Online Repository at www.jacionline.org). Sensitivity analysis, focusing only on the higher-quality studies, reduced the estimated effect size (OR, 0.87; 95% CI, 0.76-1.00; see Fig E9 in this article's Online Repository at www.jacionline.org).

To investigate the heterogeneity, we conducted subgroup analyses of children at high risk based on family history and also children of non-Western origin. The subgroup analysis of children at genetically high risk showed no significant effect (OR, 0.94; 95% CI, 0.60-1.48; see Fig E10, A, in this article's Online Repository at www.jacionline.org), but this pooled estimate should be interpreted with caution because only 3 studies were included, and these showed evidence of significant heterogeneity; the 95% CIs are furthermore wide. The subgroup analysis of children from non-Western backgrounds did not show a significant protective effect of BCG vaccination on the development of

TABLE I. Characteristics of included studies

Reference (year of publication)	Design	Population studied	Nos. of patients	Age receiving BCG vaccination	Outcomes	Quality assessment	Adjusted effect sizes
Aaby et al ¹⁷ (2000)	Retrospective cohort study	Cohort and control subjects: children who had measles in 1991 from Bissau	Cases: n = 347 Control subjects: n = 53	Median: 12 d (range, 0-3,072)	SPT	C	Yes
Alm et al ¹⁸ (1997)	Retrospective cohort study	Cohort and control subjects: atopic heredity, Stockholm	Cases: n = 216 Control subjects: n = 358	Mean: 17 d (range, 0-180)	SPT Specific IgE Eczema Asthma Rhinitis Allergy in general	B	No
Annus et al ¹⁹ (2004)	Cross-sectional study	Estonian schoolchildren	Cases: n = 717	Divided into: ≤1 mo 1 mo to 1 y ≥1 y	SPT Eczema Asthma Rhinitis	C	No
Bremner et al ²⁰ (2005)	Case-control study	Cases and control subjects derived from GP database; cases had at least 1 diagnosis of hay fever	Cases: n = 7,098 Control subjects: n = 7,098	Before the age of 2 y	Rhinitis	C	Yes
da Cunha et al ²¹ (2004)	Cross-sectional study	Source of cases: children of schools enrolled in trial of effectiveness of BCG vaccination in city of Salvador	Cases: n = 1,089	Neonatal BCG (no exact age reported)	Eczema Asthma Rhinitis	C	Yes
Garcia-Marcos et al ²² (2005)	Retrospective cohort study	Children from health care centers in Bilbao, Asturias, and San Sebastian in Spain	Cases: n = 6,762 Control subjects: n = 2,828	Newborns (no exact age reported)	Eczema Asthma Rhinitis	B	Yes
Gruber et al ²³ (2001)	Prospective cohort study	Health care centers from 5 different cities in (West) Germany	Cases: n = 92 Control subjects: n = 682	Before the age of 1 y	SPT Specific IgE Eczema Asthma Rhinitis	C	No
Gruber et al ²⁴ (2002)	Retrospective cohort study	Children who were beginning school in 1994, recruitment in analysis for school maturity	Cases: n = 20,383 Control subjects: n = 18,425	Neonatal (no exact age reported)	Eczema Asthma Rhinitis	B	Yes
Krause et al ²⁵ (2003)	Cross-sectional study	All children in certain age groups, Greenland	Cases: n = 1,065 Control subjects: n = 510	Within a few days after birth	Specific IgE	B	Yes
Linehan et al ^{26,34} (2007)	Retrospective cohort study	Children in a Primary Care Trust database in the northwest of England	Cases: n = 1,332 Control subjects: n = 1,076	Within the first 12 wk of life in most cases but with some getting delayed vaccination	SPT Asthma	B	Yes
Marks et al ²⁷ (2003)	Retrospective cohort study	Place of birth of children: in 2 different health care centers in Sydney, Australia	Cases: n = 309 Control subjects: n = 442	Within the first 8 wk of life	SPT Eczema Asthma Rhinitis	B	Yes

(Continued)

TABLE I. (Continued)

Reference (year of publication)	Design	Population studied	Nos. of patients	Age receiving BCG vaccination	Outcomes	Quality assessment	Adjusted effect sizes
Miyake et al ²⁸ (2008)	Cross-sectional	Okinawa, Japan	Cases: n = 5,717	Infancy	Eczema Asthma Rhinitis	B	Yes
Mohrenschlager et al ²⁹ (2007)	Cross-sectional study	Children on admission to school in Augsburg, Germany	Cases: n = 1,496	—	SPT Eczema Asthma Rhinitis	C	Yes
Mommers et al ³⁰ (2004)	Case-control study	Netherlands and Germany, from healthcare database, control subjects random	Cases: n = 279 Control subjects: n = 293	Neonatal	Specific IgE Asthma	C	Yes
Pahari et al ³¹ (2002)	Cross-sectional study	Children from secondary school in Haringey, North London; all children attending were recruited	Cases: n = 308	—	Asthma	C	No
Steenhuis et al ³² (2008)	Randomized, prospective, single-blind study	High-risk children born in hospitals in the north and central area of The Netherlands	BCG: n = 62 Placebo: n = 59	At the age of 6 wk	Specific IgE Eczema Asthma Rhinitis	B	Yes
Strannegard et al ³³ (1998)	Cross-sectional study	Children attending schools in 3 cities in Sweden	Cases: n = 6,497	Before the age of 1 y	Allergy in general	C	No

GP, General practitioner.

asthma, with an overall OR of 0.99 (95% CI, 0.74-1.33; see Fig E10, B).

Rhinoconjunctivitis

Eleven studies investigated the relationship between BCG vaccination and rhinoconjunctivitis, although only 10 studies yielded relevant data (see Table E6 in this article's Online Repository at www.jacionline.org).^{18-24,27-29,32} It was possible to pool the results of 9 of these studies.

We pooled the results of all studies using the most important outcome reported in individual studies, preferentially considering the lifetime prevalence of rhinoconjunctivitis outcome as most important. This resulted in an overall OR of 1.07 (95% CI, 0.89-1.28; Fig 6). The funnel plot was suggestive of publication bias (see Fig E11 in this article's Online Repository at www.jacionline.org). Sensitivity analysis included only the studies of moderate-to-high quality; the overall OR was 0.93 (95% CI, 0.85-1.02; see Fig E12 in this article's Online Repository at www.jacionline.org).

There was significant heterogeneity, and this was investigated through subgroup analyses of assessing the relationship between BCG vaccination and allergic rhinitis in the group of children of non-Western origin. This analysis estimated an overall OR of 1.08 (95% CI, 0.70-1.67; see Fig E13 in this article's Online Repository at www.jacionline.org). There were insufficient data to allow meaningful subgroup analysis for children deemed to be genetically at high risk.

Allergy in general

Two studies investigated the relationship between BCG vaccination and allergy in general.^{18,33} These studies both investigated different symptoms suggestive of atopic disorders, such as history of asthma, wheezing, atopic dermatitis, and allergic rhinitis, based on clinical outcomes through questionnaires, but they put all of the results together to calculate 1 outcome: overall risk of atopic allergic disease. Neither study showed a protective effect of BCG vaccination on the development of atopic allergic disease in general (see Table E7 in this article's Online Repository at www.jacionline.org). When pooling both studies, this resulted in an overall OR of 0.84 (95% CI, 0.67-1.05).

Food allergy, urticaria, angioedema, and anaphylaxis

There was 1 study investigating the relationship between BCG vaccination and urticaria.¹⁸ This study did not show a significant effect.

There were 2 studies investigating the outcome of food allergy.^{18,32} The first study investigated the outcome of acute onset of suggestive symptoms after exposure to food on more than 1 occasion. The second study investigated the outcome of symptoms of feeding induced vomiting. We did not pool the results of these studies because their outcomes were judged to be too heterogeneous on clinical grounds. Neither study showed a significant protective effect of BCG vaccination on the development of food

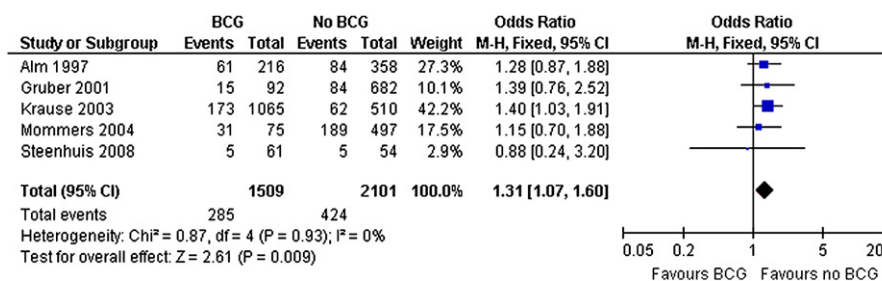


FIG 2. Fixed-effects model forest plot showing ORs and 95% CIs for the association between BCG vaccination and sensitization measured by using specific IgE levels. See Table I for reference citations. *M-H*, Mantel-Haenszel.

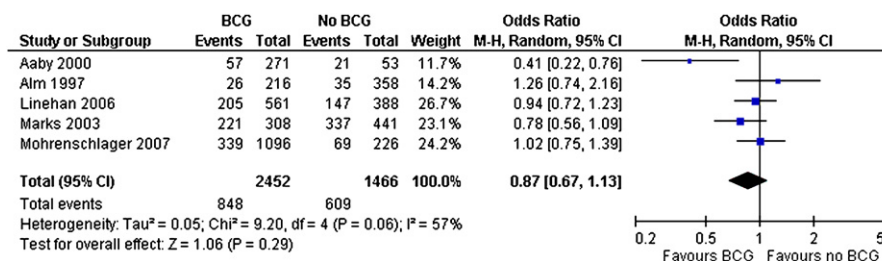


FIG 3. Random-effects model forest plot showing ORs and 95% CIs for the association between BCG vaccination and a positive SPT response. *M-H*, Mantel-Haenszel.

allergy. There were no studies investigating the outcomes of angioedema or anaphylaxis.

DISCUSSION

Our systematic review and meta-analysis has uncovered a wealth of epidemiologic evidence but a paucity of evidence from experimental studies investigating the relationship between BCG vaccination and the risk of allergic sensitization and disease. The overall body of evidence, although voluminous, is therefore methodologically weak. The available evidence suggests that BCG vaccination is unlikely to be effective in preventing allergic sensitization or eczema but might possibly offer some benefits against the development of asthma. Based on this analysis, it might be appropriate to investigate this possible protective role of BCG vaccination in the general population by using more robust study designs, particularly RCTs.

The findings that risk of sensitization is not influenced by BCG vaccination, however, suggests that the mechanism through which any such benefits are being mediated is unclear, making the possibility of study bias, residual confounding, and publication bias important alternative explanations for this finding.

Strengths and limitations of this work

The main strengths of this study lie in the effort to find all eligible articles through a detailed search strategy, including a search for unpublished and ongoing work, and the independent evaluation and quality assessment of potentially eligible and included studies. Our willingness to extend our inclusion criteria to also include epidemiologic studies and RCTs that were not

double-blind was also, with hindsight, appropriate because we would otherwise have returned a near-empty review, ignoring the broader, less rigorous, but nonetheless still useful evidence on this subject.

Another strength of our work was that the exposure was restricted solely to BCG vaccination. Shirakawa et al³⁵ looked at the association between tuberculin response and atopic disorders. His findings of an inverse relationship between tuberculin response and markers of atopic disease did not actually identify whether tuberculin response was associated with atopic disease or was due to genetic factors that might influence expression of the immune response. In this respect our study, in which the only exposure examined was BCG vaccination, was clear and concise in what it was measuring.

Although previous reviews have investigated the association between BCG and some atopic outcomes, our study, which looked at the effect on a range of clinically relevant outcomes, is the most comprehensive to date. For example, El-Zein et al³⁶ focused solely on asthma as an outcome; their study also differs from ours in that it included tuberculin response and scar diameter as markers of mycobacterial exposure. Although Balicer et al¹³ used only the more reliable measure of actual BCG vaccination as an exposure, they too were only interested in asthma outcomes. The broader review by Obihara et al³⁷ investigated the relationship between mycobacterial infection and atopy, but the limited analyses undertaken hinder the ability to draw any clear conclusions from their work.

Another strength of our approach was our decision to investigate the sources of heterogeneity on the basis both of familial risk and likely endemic exposure to helminths and mycobacteria through subgroup analyses. Ideally, we would have liked to explore these questions in more detail (eg, considering maternal

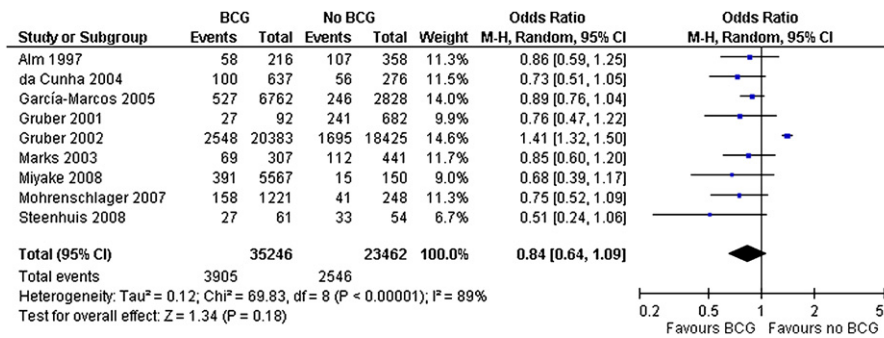


FIG 4. Random-effects model forest plot showing ORs and 95% CIs for the association between BCG vaccination and atopic dermatitis/eczema. *M-H*, Mantel-Haenszel.

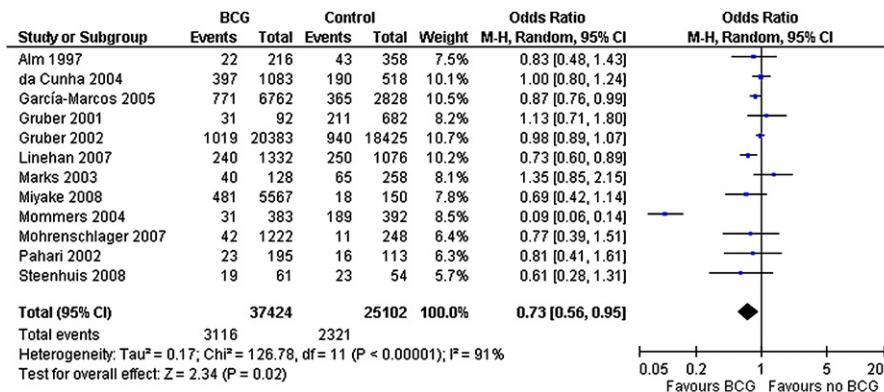


FIG 5. Random-effects model forest plot showing ORs and 95% CIs for the association between BCG vaccination and asthma. *M-H*, Mantel-Haenszel.

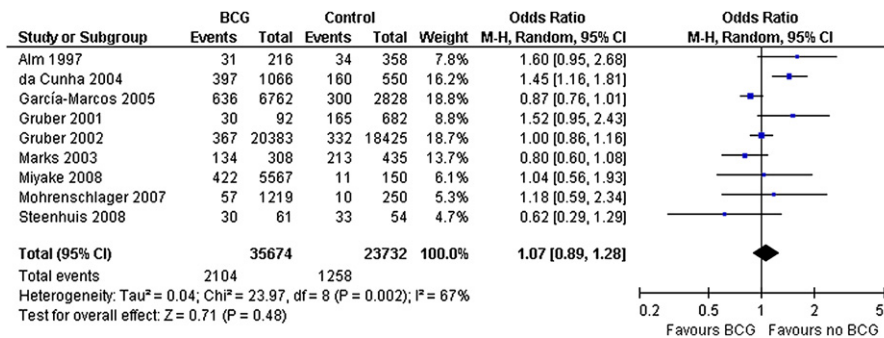


FIG 6. Random-effects model forest plot showing ORs and 95% CIs for the association between BCG vaccination and allergic rhinoconjunctivitis. *M-H*, Mantel-Haenszel.

and paternal history of allergic disease separately and more detailed measures of exposure to helminths, mycobacteria, or both), but we were restricted by the available data.

The main limitation of this review is that all but 1 of the studies identified and included are observational. The quality of the included studies is therefore predictably not high; this is because results of epidemiologic studies can be influenced by confounders and other forms of bias. To minimize the risk of drawing erroneous conclusions, we, where possible, also conducted sensitivity analyses, excluding studies thought to be at highest risk of bias.

Implications for policy, practice, and research

Our findings indicate that any possible beneficial effect of BCG vaccination in preventing the development of asthma is likely to be relatively modest. It is therefore not possible on the basis of this review to recommend that BCG vaccination for the prevention of asthma be incorporated into national vaccination programs. Such BCG vaccination programs might, however, be instituted on the basis of other considerations relating to the prevention of tuberculosis, leprosy, or both.

Asthma can be caused by allergic and nonallergic mechanisms, and given the failure to show evidence of protection against

sensitization, it is likely that if this is a real effect, it is unlikely to be related to atopic mechanisms. Although biases of various kinds could explain the observed relationship with asthma, we believe that to provide clarity on this issue, consideration needs to be given to undertaking an RCT formally investigating the role of BCG vaccination for the prevention of asthma. The available data suggest that any trial should investigate administration within the first few months of life to maximize the chances of benefits. Such a trial would need to be long enough to allow asthma to be reliably assessed (ie, until at least 5 years of age), should involve the undertaking of relevant mechanistic work, and should also assess for evidence of cost-effectiveness and safety. Given the likely modest effect size, the study would of necessity need to be large and be conducted in all subjects, irrespective of likely risk of allergic disease based on family history. The modest effect size and suggestions of publication bias, however, suggest that any effects we found are likely to be artifactual, but given the now very high prevalence of asthma in many parts of the world, if real, this might nonetheless prove important at a population level.

We thank all of the experts and the manufacturers of the BCG vaccine for their assistance in identifying eligible studies. We also thank Dr Allison Worth for reviewing data extraction and quality assessment procedures and her helpful comments on an earlier draft of this article.

Clinical implications: Preschool BCG vaccination was not found to reduce the risk of allergic sensitization, atopic eczema, or allergic rhinoconjunctivitis. However, its possible role in reducing the risk of some cases of childhood asthma warrants further investigation.

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APPENDIX E1. SEARCH STRATEGY

1. BCG Vaccine/
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5. tuberculin response.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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10. atop*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11. or/7-10
12. Asthma/
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14. night cough*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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17. hyper-responsiveness wheez*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18. wheez*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
19. allergic alveolitis.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
20. Respiratory Sounds/
21. or/12-20
22. Food Hypersensitivity/
23. food edg3 allerg*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
24. food hypersensitivit*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
25. or/22-24
26. Dermatitis, Atopic/
27. Eczema/
28. Neurodermatitis/
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32. besnier* prurigo.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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34. pruritus.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
35. itching.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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41. Rhinitis, Allergic, Seasonal/
42. Rhinitis, Allergic, Perennial/
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49. Conjunctivitis/
50. Conjunctivitis, Allergic/
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53. rhinoconjunctivit*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
54. or/40-53
55. Anaphylaxis/
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57. anaphylactoid react*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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66. RAST.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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68. Radioallergosorbent Test/
69. Immunoglobulin E/
70. specific IgE.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
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72. Epidemiologic Studies/
73. Cohort Studies/
74. Case-Control Studies/
75. cohort stud*.mp.
76. case-control stud*.mp.
77. etiology.mp.
78. trial.mp.
79. Clinical Trial/
80. clinical trial.mp.
81. Controlled Clinical Trial/
82. controlled clinical trial.mp.
83. Randomized Controlled Trial/
84. randomi?ed controlled trial.mp.
85. or/72-84
86. 25 or 11 or 63 or 39 or 21 or 71 or 54
87. 6 and 85 and 86

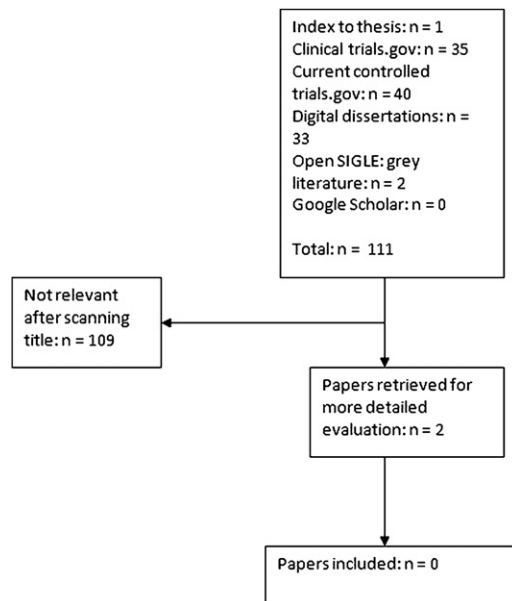


FIG E1. Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) diagram of unpublished studies.

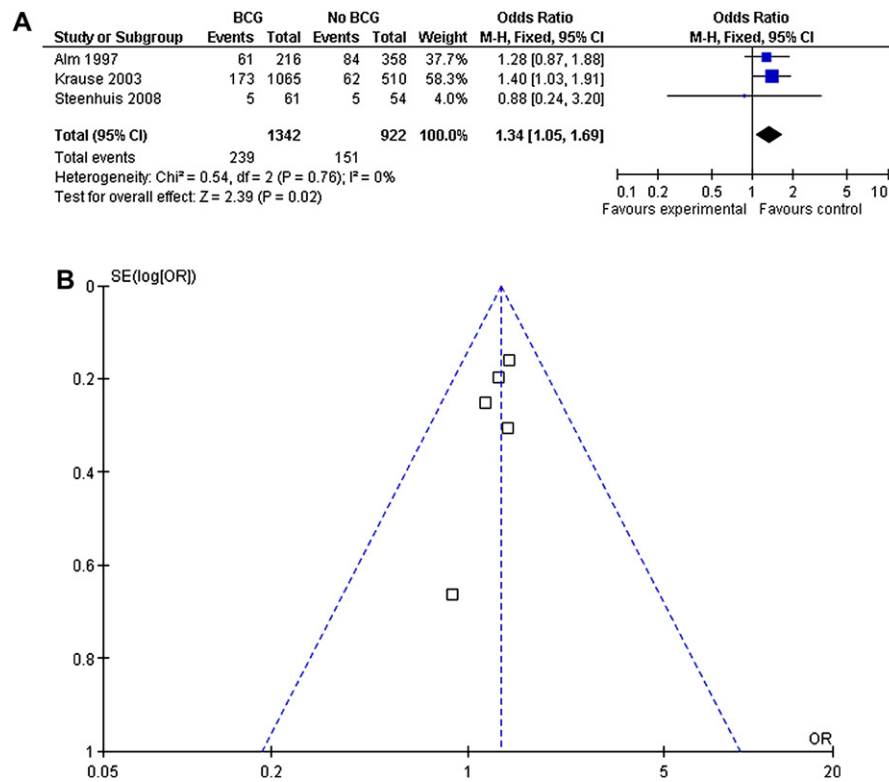


FIG E2. **A**, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and sensitization measured by specific IgE levels in category B studies (see the Methods section for more details; fixed-effects model). **B**, Funnel plot for the association between BCG vaccination and a positive specific IgE level. See Table I for reference citations. *M-H*, Mantel-Haenszel.

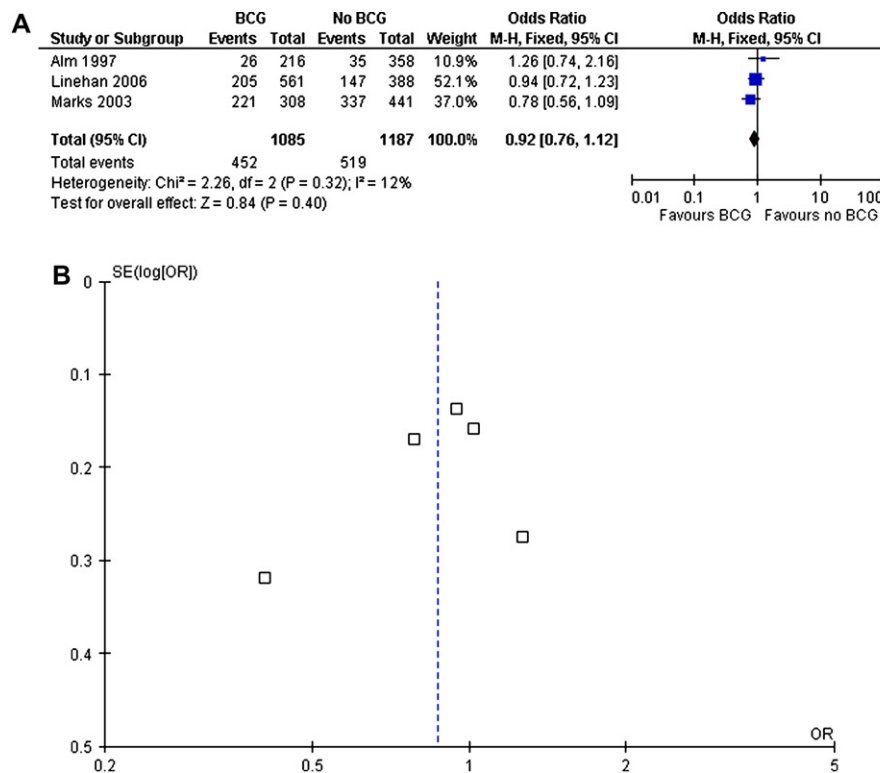


FIG E3. **A**, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and sensitization measured by SPT response in category B studies (see the Methods section for more details; fixed-effects model). **B**, Funnel plot for the association between BCG vaccination and an SPT response. See Table I for reference citations. *M-H*, Mantel-Haenszel.

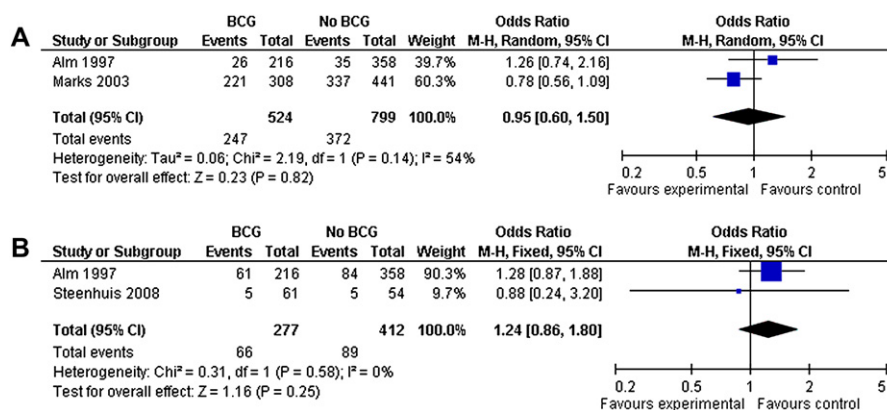


FIG E4. A, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and sensitization measured by SPT response in subgroups of children at high risk of atopic disorders (random-effects model). **B**, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and sensitization measured by a positive specific IgE level in subgroups children at high risk of atopic disorders (fixed-effects model). See Table I for reference citations. *M-H*, Mantel-Haenszel.

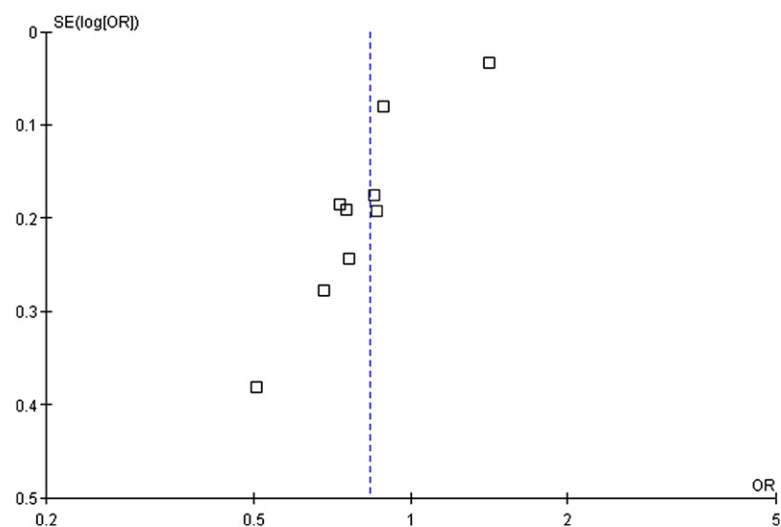


FIG E5. Funnel plot for the association between BCG vaccination and atopic dermatitis.

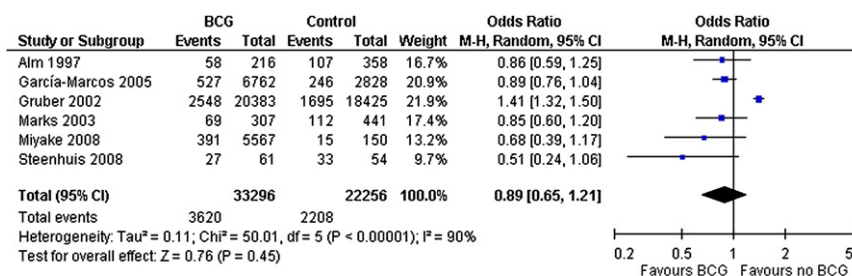


FIG E6. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and atopic dermatitis in category B studies (see the Methods section for more details; random-effects model). See Table I for reference citations. *M-H*, Mantel-Haenszel.

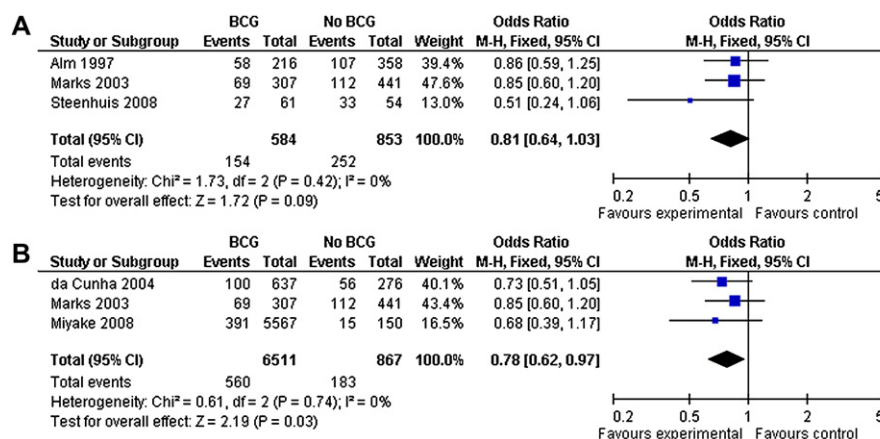


FIG E7. A, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and atopic dermatitis in children at higher risk (fixed-effects model). **B,** Forest plot showing ORs and 95% CIs for the association between BCG vaccination and atopic dermatitis in children with a non-Western origin (fixed-effects model). See Table I for reference citations. *M-H*, Mantel-Haenszel.

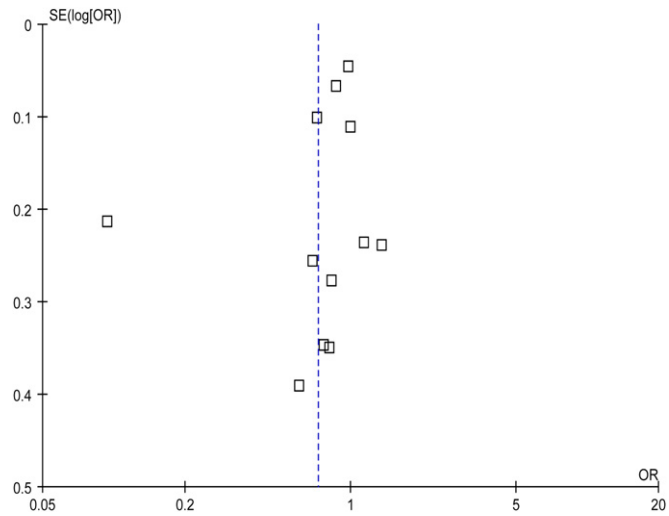


FIG E8. Funnel plot for the association between BCG vaccination and asthma.

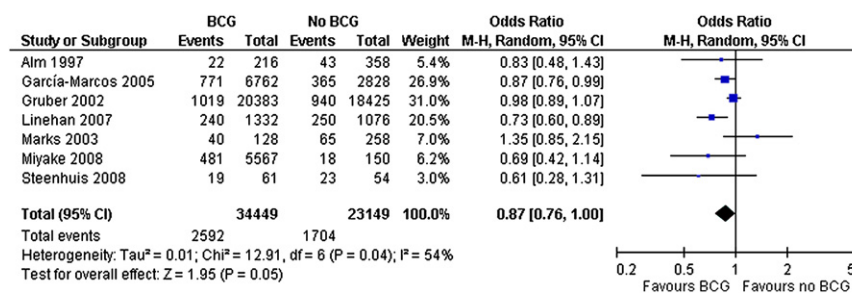


FIG E9. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and asthma in category B studies (see the Methods section for more details; random-effects model). See Table I for reference citations. *M-H*, Mantel-Haenszel.

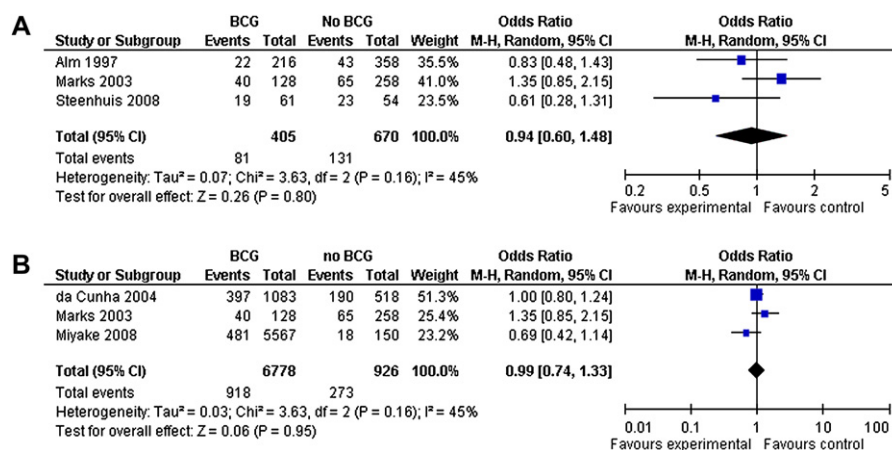


FIG E10. A, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and asthma in the subgroup of children at high risk (random-effects model). **B**, Forest plot showing ORs and 95% CIs for the association between BCG vaccination and asthma in the subgroup of children from a non-Western origin (random-effects model). See Table I for reference citations. *M-H*, Mantel-Haenszel.

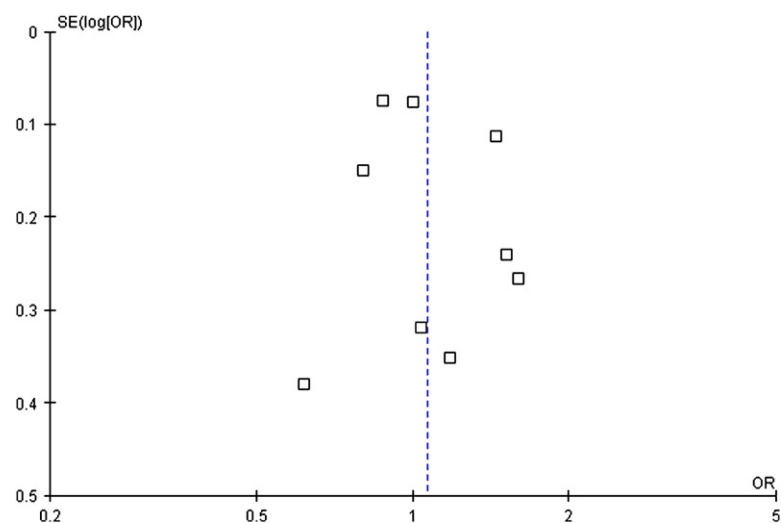


FIG E11. Funnel plot for the association between BCG vaccination and rhinitis.

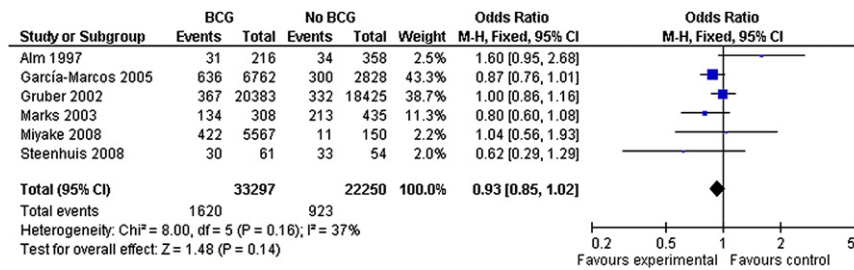


FIG E12. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and prevalence of rhinitis in category B studies (see the Methods section for more details; fixed-effects model). See [Table I](#) for reference citations. *M-H*, Mantel-Haenszel.

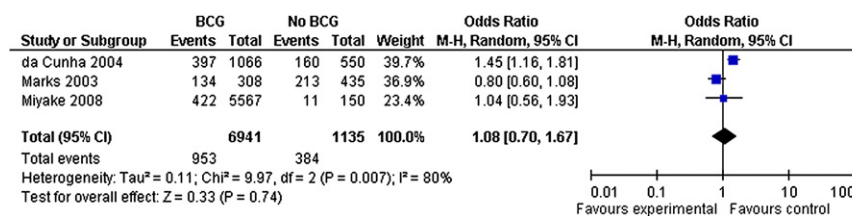


FIG E13. Forest plot showing ORs and 95% CIs for the association between BCG vaccination and prevalence of rhinitis in the group of children from a non-Western origin (random-effects model). See [Table I](#) for reference citations. *M-H*, Mantel-Haenszel.

TABLE E1. ORs, 95% CIs, and outcomes of studies investigating the relationship between BCG vaccination and sensitization by positive specific IgE levels

Reference	Design	Population	Outcome	OR	95% CI
Alm et al ¹⁸ (1997)	Cohort	Sweden	Positive IgE level	1.28	0.87-1.88
Gruber et al ²³ (2001)	Cohort	Germany	Positive IgE level	1.39	0.76-2.52
Krause et al ²⁵ (2003)	Cross-sectional	Greenland	Positive IgE level	1.40	1.03-1.91
Mommers et al ³⁰ (2004)	Case-control	Germany and The Netherlands	Positive IgE level	1.15	0.70-1.88
Steenhuis et al ³² (2008)	RCT	The Netherlands	Positive IgE level	0.88	0.24-3.20

TABLE E2. Cutoff points for measures of specific IgE sensitization for allergens, as described in studies

Reference	Cutoff point	Allergens tested
Alm et al ¹⁸ (1997)	Not stated	Eleven common inhalant allergens (Phadiatop) and 6 food allergens (fx5)
Gruber et al ²³ (2001)	An infant was considered sensitized if the IgE antibody titer of ≥ 1 of the 9 allergens tested was >0.35 kU/L.	Birch, grass, mite dl, cat, dog, egg, milk, wheat, soy
Krause et al ²⁵ (2003)	Not stated	Venous blood samples were analyzed for total IgE levels with the UniCAP total IgE test (Pharmacia, Copenhagen, Denmark) and for specific IgE with the Phadiatop test (Pharmacia), which is a qualitative (yes/no) assay testing for the 8 most common inhalant allergens (grass, birch, mugwort, dog, cat, horse, <i>Cladosporium herbarum</i> , house dust mite) in 1 pool. Children with a positive specific IgE test result were considered atopic.
Mommers et al ³⁰ (2004)	Measures were regarded as positive at >0.35 kU/L.	Levels of specific IgE against <i>Dermatophagoides pteronyssinus</i> , <i>Dermatophagoides farinae</i> , <i>Cladosporium herbarum</i> , <i>Aspergillus fumigatus</i> , <i>Alternaria tenuis</i> , chicken egg, cow's milk, cat and dog epithelium, and a mix of grasses were measured by using the Pharmacia CAP System (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden).
Steenhuis et al ³² (2008)	Not stated	IgE was determined with a Phadiatop assay against the 6 most prevalent allergens.

TABLE E3. ORs, 95% CIs, and outcomes of studies investigating the relationship between BCG vaccination and sensitization by positive SPT response

Reference	Design	Population	Outcome	OR	95% CI
Aaby et al ¹⁷ (2000)	Cohort	Africa	SPT	0.41	0.22-0.76
Alm et al ¹⁸ (1997)	Cohort	Sweden	SPT	1.26	0.74-2.16
Annus et al ¹⁹ (2004)	Cross-sectional	Estonia	SPT	No suitable summary data available	
Gruber et al ²³ (2001)	Cohort	Germany	SPT	No summary data presented	
Linehan thesis ³⁴ (2006)	Cohort	United Kingdom	SPT	0.94	0.72-1.23
Marks et al ²⁷ (2003)	Cohort	Australian Asian	SPT	0.78	0.56-1.09
Mohrenschlager et al ²⁹ (2007)	Cross-sectional	Germany	SPT	1.02	0.75-1.39

TABLE E4. ORs, 95% CIs, and outcomes of studies investigating the relationship between BCG vaccination and atopic dermatitis

Reference	Design	Population	Outcome	OR	95% CI
Alm et al ¹⁸ (1997)	Cohort	Sweden	Atopic dermatitis	0.86	0.59-1.25
Annus et al ¹⁹ (2004)	Cross-sectional	Estonia	Atopic dermatitis	No suitable summary data	
da Cunha et al ²¹ (2004)	Cross-sectional	Brazil	Atopic dermatitis	0.73	0.51-1.05
Garcia-Marcos et al ²² (2005)	Cohort	Spain	Atopic dermatitis	0.89	0.76-1.04
Gruber et al ²³ (2001)	Cohort	Germany	Atopic dermatitis	0.76	0.47-1.22
Gruber et al ²⁴ (2002)	Cohort	Germany	Atopic dermatitis	1.41	1.31-1.50
Marks et al ²⁷ (2003)	Cohort	Australian Asian	Atopic dermatitis	0.85	0.60-1.20
Miyake et al ²⁸ (2008)	Cross-sectional	Japan	Rash (12 months)	0.68	0.39-1.17
Mohrenschlager et al ²⁹ (2007)	Cross-sectional	Germany	Atopic dermatitis	0.75	0.52-1.09
Steenhuis et al ³² (2008)	RCT	Netherlands	Atopic dermatitis	0.51	0.24-1.06

TABLE E5. ORs, 95% CIs, and outcomes of studies investigating the relationship between BCG vaccination and asthma

References	Design	Population	Outcome	OR	95% CI
Alm et al ¹⁸ (1997)	Cohort	Sweden	Lifetime wheezing	0.83	0.48-1.43
Annus et al ¹⁹ (2004)	Cross-sectional	Estonia	Lifetime asthma	No suitable summary data	
da Cunha et al ²¹ (2004)	Cross-sectional	South America	Lifetime asthma	1.00	0.80 - 1.24
Garcia-Marcos et al ²² (2005)	Cohort	Spain	Wheezing 12-mo prevalence	0.87	0.76-0.99
Gruber et al ²³ (2001)	Cohort	Germany	Recurrent wheezing	1.13	0.71-1.80
Gruber et al ²⁴ (2002)	Cohort	Germany	Lifetime asthma	0.98	0.89-1.07
Linehan et al ²⁶ (2007)	Cohort	United Kingdom	Wheezing 12-mo prevalence	0.73	0.60-0.89
Marks et al ²⁷ (2003)	Cohort	Australian Asian	Lifetime asthma	1.35	0.85-2.15
Miyake et al ²⁸ (2008)	Cross-sectional	Japan	Wheezing 12-mo prevalence	0.69	0.42-1.14
Mohrenschlager et al ²⁹ (2007)	Cross-sectional	Germany	Lifetime asthma	0.77	0.39-1.51
Mommers et al ³⁰ (2004)	Case-control	Germany and The Netherlands	Wheezing 12-mo prevalence	0.09	0.06-0.14
Pahari et al ³¹ (2002)	Cross-sectional	United Kingdom	Lifetime asthma	0.81	0.41-1.61
Steenhuis et al ³² (2008)	RCT	The Netherlands	Lifetime asthma	0.61	0.28-1.31

TABLE E6. ORs, 95% CIs, and outcomes of studies investigating the relationship between BCG vaccination and rhinoconjunctivitis

References	Design	Population	Outcome	OR	95% CI
Alm et al ¹⁸ (1997)	Cohort	Sweden	Allergic rhinitis or conjunctivitis	1.60	0.95-2.68
Annus et al ¹⁹ (2004)	Cross-sectional	Estonia	Lifetime rhinitis	No suitable summary data	
Bremner et al ²⁰ (2005)	Case-control	United Kingdom	Hay fever	No suitable summary data	
da Cunha et al ²¹ (2004)	Cross-sectional	South America	Current allergy with sneezing	1.45	1.16-1.81
Garcia-Marcos et al ²² (2005)	Cohort	Spain	Rhinitis prevalence last 12 mo	0.87	0.76-1.01
Gruber et al ²³ (2001)	Cohort	Germany	Allergic rhinitis	1.52	0.95-2.43
Gruber et al ²⁴ (2002)	Cohort	Germany	Hay fever	1.00	0.86-1.16
Marks et al ²⁷ (2003)	Cohort	Australian Asian	Hay fever	0.80	0.60-1.08
Miyake et al ²⁸ (2008)	Cross-sectional	Japan	Allergic rhinitis (12-mo prevalence)	1.04	0.56-1.93
Mohrenschlager et al ²⁹ (2007)	Cross-sectional	Germany	Hay fever	1.18	0.59-2.34
Steenhuis et al ³² (2008)	RCT	The Netherlands	Allergic rhinitis (12-mo prevalence)	0.62	0.29-1.29

TABLE E7. ORs, 95% CIs, and outcomes of studies investigating the relationship between BCG vaccination and allergy in general

References	Design	Population	Outcome	OR	95% CI
Alm et al ¹⁸ (1997)	Cohort	Sweden	Allergy in general	0.81	0.57-1.15
Strannegard et al ³³ (1998)	Cross-sectional study	Sweden	Allergy in general	0.86	0.64-1.15