

Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis

Mary F. Linehan, PhD,^a Ulugbek Nurmatov, PhD,^b Timothy L. Frank, MD,^a Robert M. Niven, MD,^a David N. Baxter, PhD,^c and Aziz Sheikh, MD^{b,d} *Manchester and Edinburgh, United Kingdom, and Boston, Mass*

Background: The Manchester Community Asthma Study (MANCAS) found a protective effect against the risk of wheeze at age 6 to 11 years for children given neonatal BCG vaccination. Our subsequent systematic review and meta-analysis suggested that BCG vaccination did not protect against allergic sensitization but might have exerted a protective effect against nonatopic asthma.

Objectives: We sought to assess whether the protective effect of BCG vaccination on wheeze observed in the MANCAS cohort was maintained at age 13 to 17 years and to incorporate the findings from this final MANCAS analysis into an updated systematic review and meta-analysis.

Methods: BCG vaccination status was determined from health records and respiratory outcomes from questionnaire responses.

We updated the systematic review and used fixed-effects and random-effects modeling to undertake meta-analyses.

Results: There were 1608 participants in the final MANCAS analysis. The 12-month prevalence of wheeze was 15.1%. There was no difference in prevalence between those who were and were not BCG vaccinated (15.8% vs 14.3%; relative risk, 1.05; 95% CI, 0.94-1.19). The updated meta-analysis incorporated 4 new studies: this showed that the protective effect of BCG vaccination against the development of asthma identified in our previous meta-analysis was attenuated (odds ratio, 0.95; 95% CI, 0.89-1.00). No protective effect of BCG was seen for sensitization, eczema/atopic dermatitis, rhinoconjunctivitis, or allergy in general.

Conclusions: Taken together, the final results of the MANCAS cohort and the updated systematic review and meta-analysis provide clearer evidence that any protective effect of BCG vaccination on childhood asthma is likely to be transient. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

Key words: Wheeze, asthma, atopy, allergy, BCG, children, systematic review, meta-analysis

From ^athe University of Manchester, Manchester Academic Health Science Centre, University Hospital South Manchester NHS Foundation Trust, NIHR South Manchester Respiratory and Allergy Clinical Research Facility; ^bthe Allergy and Respiratory Research Group, Centre for Population Health Sciences, University of Edinburgh; ^cthe University of Manchester, Manchester Academic Health Science Centre, Clinical Epidemiology and Public Health Unit, Manchester; and ^dthe Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston.

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Corresponding author: Mary F. Linehan, PhD, GP Research Unit, 2nd Floor, Education and Research Centre, Wythenshawe Hospital, Manchester M23 9LT, United Kingdom.

E-mail: mary.linehan@manchester.ac.uk.

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Asthma is a chronic childhood disease with many different phenotypes.¹ Atopic asthma is principally an immunologic disease with T_H2-biased immune pathways that is believed to occur as a consequence of a failure of the immature immune system to adapt its cytokine response to a T_H1-dominant environment.

BCG is a potent immune modulator capable of deviating the immune system toward T_H1 dominance, thereby potentially reducing the likelihood of allergic diseases, such as atopic asthma. This potential of BCG vaccination to protect against atopy, asthma, or both has been investigated in many studies,²⁻¹⁹ with conflicting results. Our earlier study (the Manchester Community Asthma Study [MANCAS]) investigating the effect of neonatal BCG vaccine found a clinically important lower risk of wheeze for children age 6 to 11 years.¹¹ The study came about because of an error in dosage of BCG vaccine administered to 857 neonates in St Mary's Hospital, Manchester, United Kingdom, in 1994. These infants were given approximately 5 times the upper limit of the recommended BCG vaccine dose.²⁰ Once the error was discovered, the hospital suspended its policy of routine BCG vaccination for infants. This change in policy resulted in the creation of 3 separate groups, which provided a unique opportunity to study the relationship between BCG vaccination and atopic diseases: (1) children born when BCG vaccine was routinely administered, (2) children born when BCG vaccine was not routinely available, and (3) children

Abbreviations used

ISAAC: International Study of Asthma and Allergies in Childhood
 MANCAS: Manchester Community Asthma Study
 OR: Odds ratio
 PCT: Primary Care Trust
 RR: Relative risk
 SPT: Skin prick test

born after the policy of routine neonatal BCG vaccination was reinstated. Children eligible for vaccination when the higher than recommended dose of BCG vaccine was used were excluded from the original study. The main outcomes investigated were as follows: wheeze in the past 12 months, as determined from questionnaire responses, and atopic status, determined by skin prick test (SPT) responses to common aeroallergens. MANCAS found a reduced risk of wheeze in children given a standard dose of neonatal BCG vaccination (relative risk [RR], 0.73; 95% CI, 0.62-0.88).

We subsequently undertook a systematic review and meta-analysis investigating the relationship between BCG vaccination and atopic allergic disorders.²¹ Most of the evidence uncovered was epidemiologic in nature but nonetheless suggested that BCG vaccination was associated with a protective effect against the development of asthma (odds ratio [OR], 0.73; 95% CI, 0.56-0.95). However, there was no associated protection in the risk of sensitization, as judged by specific IgE test results (OR, 1.31; 95% CI, 1.07-1.60) or SPT responses (OR, 0.87; 95% CI, 0.67-1.13), with this indicating that any possible benefits in relation to asthma outcomes were likely to be in relation to nonatopic asthma phenotypes, which have a relatively good prognosis in childhood.²²

In this final follow-up to the MANCAS cohort, we sought to investigate whether the benefits in relation to wheeze and related outcomes were maintained during adolescence (age 13-17 years), and this time we included the group eligible for vaccination when the higher than recommended dose of BCG vaccine was in use to explore the possibility of a dose-response relationship. To contextualize these data in light of recent international evidence, we also updated our earlier meta-analysis.²¹

METHODS**Overview of methods**

The details of MANCAS and our systematic review and meta-analysis have been previously reported in the *Journal of Allergy and Clinical Immunology*.^{11,21,23} For the present analysis, we conducted a 2-phase program of work in which we first collected additional follow-up data from MANCAS (hereafter referred to as MANCAS 2) and then reran our earlier searches to identify additional recent studies to synthesize the findings from MANCAS 2 into an updated systematic review.

Ethical approval was obtained from the Manchester Local Research Ethics Committee, Manchester, United Kingdom.

Phase 1: MANCAS 2

MANCAS 2 was a retrospective cohort study carried out in 2009-2010 in which vaccination status was determined from health authority records and follow-up data on respiratory/allergy symptoms were collected by using a postal questionnaire (incorporating questions from the International Study of Asthma and Allergies in Childhood [ISAAC] instrument).²⁴

The MANCAS 2 cohort included the children eligible for inclusion in the first phase of MANCAS and also the children eligible for vaccination when the

higher than recommended dose of BCG vaccine was in use, regardless of whether they had actually received the vaccine. In essence, all children born in St Mary's Hospital between July 1, 1993, and March 31, 1997, and still residing or attending schools in Manchester were eligible for inclusion unless they were considered "vulnerable" (ie, on an at-risk register) or were living with a short-term caregiver. Eligible children were identified from the Primary Care Trust (PCT) database, and the PCT then sent a letter of invitation to the child's parent or parents/caregiver or caregivers. The invitation letter advised that return of the questionnaire in the prepaid envelope to the study team would constitute consent to participate in the study and thereby allow the study team to access medical data held by the PCT. Reminders were sent to nonresponders after 4 and 8 weeks. The addresses of nonresponders were checked, and a further letter/questionnaire was sent to nonresponders for whom an alternative address was identified.

Vaccination status for BCG and all other immunizations was determined for responders from the PCT immunization records database.¹¹ The PCT database documented BCG vaccination before 12 weeks of age as neonatal BCG and after 12 weeks of age as simply BCG vaccination but did not document the dose or strain of BCG. However, the Evans BCG vaccine was the official BCG vaccine in use in the United Kingdom at the time, and the recommended dose was 0.05 mL for infants less than 3 months old and 0.1 mL for those older than 3 months.²⁵

Questionnaire responses were entered onto a database by the principal researcher (M.F.L.), who did not have access to immunization records during the data collection phase. At the end of the data collection period, questionnaire responses were linked to immunization records, with data identified only by a study number. The main outcomes of interest were wheeze in the past 12 months and hay fever/eczema status.

Statistical methods for MANCAS 2

Analyses were performed with SPSS for Windows software (version 16; SPSS, Chicago, Ill). Univariate analyses (χ^2 tests, as appropriate) were carried out to examine relationships between BCG vaccination and wheeze and hay fever/eczema. RRs were calculated to estimate the effect of BCG vaccination, with values of less than 1 indicating a protective effect of BCG vaccination, whereas a value of greater than 1 was considered to suggest an increased risk. ORs were calculated to compare the difference in risk between those who were not given any BCG vaccination and those given a recommended dose of BCG during the neonatal period, a recommended dose of BCG after the neonatal period, and a higher than recommended dose of BCG. The 95% CI around each of these RRs and ORs was also calculated, and the summary measures of risk were only considered significant if the 95% CI did not include the value of 1.00. The effect of age on the protective ability of BCG vaccination was examined by applying the McNemar test to a 2 × 2 contingency table of the subgroup of responders to both phases of MANCAS, who had all received neonatal BCG vaccination.

Phase 2: Updated systematic review and meta-analysis

We updated our systematic review by using the same search strategy (see the [Methods](#) section in this article's Online Repository at www.jacionline.org) and critical appraisal technique used in our earlier systematic review.²¹ We report here only on those outcomes for which additional data were available: (1) asthma, (2) sensitization, (3) eczema/atopic dermatitis, (4) rhinoconjunctivitis, and (5) allergy in general.

Because the main cohort remained essentially the same for both phases of MANCAS, it was necessary to ensure that data were not included twice for the same respondent. The databases were cross-checked and those who responded to both phases were identified to prevent double entry for individual respondents. Responders were then stratified into 3 separate groups: (1) those who responded only to the first phase of MANCAS, (2) those who responded to both phases, and (3) those who responded only to MANCAS 2. Because the most recent information provided by each responder was considered the most appropriate data to use, responders were then recategorized into 2 groups: those who responded only to the first phase of MANCAS and those who responded to both phases and to MANCAS 2 ([Table 1](#)). This allowed data from

TABLE I. Responders to one phase of MANCAS only and to both phases of MANCAS

Responded to first phase of MANCAS only	1613	Total available for revised asthma and allergy in general outcomes	1613
Responded to both phases	801	Total available for revised asthma and allergy in general outcomes	1608
Responded to MANCAS 2 only	807		

the first phase of MANCAS to be replaced with data from MANCAS 2 in the updated meta-analysis, where appropriate.

Both phases of MANCAS asked the following question: “Has your child had hay fever or eczema?” Because this did not differentiate between allergic and nonallergic reactions and because it combined both hay fever and eczema in one outcome, the data from this question could not be included in either the eczema/atopic dermatitis outcome or the rhinoconjunctivitis outcome; therefore this was included in the “Allergy in general” category in the updated meta-analysis.

Statistical methods for updated meta-analysis

Data were analyzed by using the same statistical methods as our original meta-analysis.²¹ Subgroup analyses were considered appropriate only if the new studies included data on family history or area of birth. Publication bias was assessed graphically for the new studies by using funnel plots, and where possible, sensitivity analyses were revised for outcomes at high risk of bias.

RESULTS

Phase 1: MANCAS 2

There were 6338 potentially eligible children, from whom 1608 (25.4%) responses were received. There were 769 female and 839 male subjects aged 13 to 17 years. The overall prevalence of wheeze in the last 12 months was 15.1%. There was no statistically significant difference in prevalence between those who did and did not receive BCG vaccination (15.8% vs 14.3%; RR, 1.05; 95% CI, 0.94-1.19), and this remained nonsignificant when BCG vaccination status was stratified by neonatal BCG, postnatal BCG, and high-dose BCG (Table II).

The overall prevalence of hay fever/eczema was 45.1%; there was no statistically significant difference in prevalence between those who did and did not receive BCG vaccination (44.4% vs 46.0%; RR, 0.97; 95% CI, 0.89-1.06), and this also remained nonsignificant when vaccination status was stratified by neonatal BCG, postnatal BCG, and high-dose BCG (Table II).

When the effect of age was examined, there was no evidence of a change in the ability of BCG to protect against the development of wheeze ($n = 368$, $P = .21$).

Phase 2: Updated systematic review and meta-analysis

Fig 1 describes the updated study selection process, with details of the additional studies identified for inclusion in the updated meta-analysis.

In addition to the unpublished MANCAS 2 data, 3 further studies²⁶⁻²⁸ published after the cutoff date for inclusion in our previous meta-analysis were identified that met the eligibility criteria. Details of the studies included in the updated meta-analysis are outlined in Table III.^{2-19,26-29}

Asthma. The updated systematic review for asthma included a total of 17 studies, but suitable data for meta-analysis were available from 16 of these studies (see Table E1 in this article’s

Online Repository at www.jacionline.org). The meta-analysis estimated an overall OR of 0.95 (95% CI, 0.89-1.00) for the risk of asthma in those who were BCG vaccinated compared with those who were not (see Fig E1, A in this article’s Online Repository at www.jacionline.org). The funnel plot was not suggestive of publication bias (see Fig E1, B). The sensitivity analysis for higher-quality studies was repeated to allow for the additional data from MANCAS 2 and estimated an overall OR of 0.90 (95% CI, 0.78-1.03; see Fig E1, C).

Sensitization to common allergens. Six studies investigated sensitization by increased specific IgE levels (see Table E2 in this article’s Online Repository at www.jacionline.org). The estimated overall OR was 1.05 (95% CI, 0.65-1.69) for the risk of sensitization in those who were vaccinated compared with those who were not, but there was evidence of heterogeneity ($I^2 = 88\%$, see Fig E2, A in this article’s Online Repository at www.jacionline.org). The funnel plot was suggestive of publication bias (see Fig E2, B). Nine studies investigated SPT response to identify sensitization, with data available from 7 of these studies (see Table E3 in this article’s Online Repository at www.jacionline.org). The estimated overall OR was 0.93 (95% CI, 0.83-1.04) for the risk of sensitization in those who were BCG vaccinated compared with those who were not (see Fig E3, A in this article’s Online Repository at www.jacionline.org). The funnel plot was not suggestive of publication bias (see Fig E3, B).

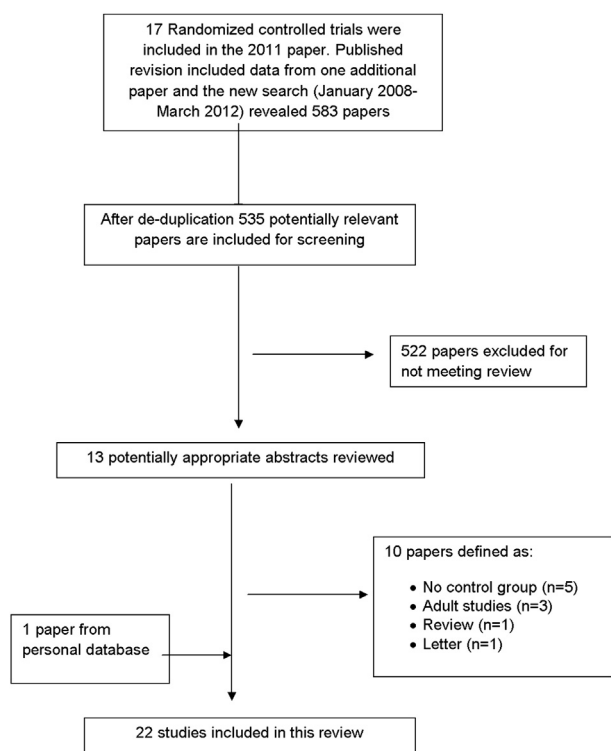
Eczema/atopic dermatitis. Twelve studies investigated BCG vaccination and eczema/atopic dermatitis, with suitable data available from 11 of the studies for inclusion in the updated meta-analysis (see Table E4 in this article’s Online Repository at www.jacionline.org). The overall OR was calculated as 0.85 (95% CI, 0.68-1.08) for the risk of eczema/atopic dermatitis in those who were BCG vaccinated compared with those who were not, but there was evidence of heterogeneity ($I^2 = 86\%$, see Fig E4, A in this article’s Online Repository at www.jacionline.org). The funnel plot was suggestive of publication bias (see Fig E4, B).

Rhinoconjunctivitis. The updated systematic review included 13 studies that investigated BCG vaccination and rhinoconjunctivitis, with pooling of data possible for 11 of these studies (see Table E5 in this article’s Online Repository at www.jacionline.org). The data used were from the most important outcome reported in individual studies, with lifetime prevalence of rhinoconjunctivitis considered the most important outcome. The overall estimated OR was 1.06 (95% CI, 0.91-1.23) for the risk of rhinoconjunctivitis in those who were BCG vaccinated compared with those who were not, but there was some evidence of heterogeneity ($I^2 = 59\%$, see Fig E5, A in this article’s Online Repository at www.jacionline.org). The funnel plot was not suggestive of publication bias (see Fig E5, B).

Allergy in general. The updated meta-analysis for allergy in general included 4 studies (see Table E6 in this article’s Online Repository at www.jacionline.org). The overall estimated OR

TABLE II. Prevalence of wheeze and hay fever/eczema in MANCAS 2 stratified by BCG vaccination status

	Not BCG vaccinated	Routine neonatal BCG vaccination	Postneonatal routine BCG vaccination	High-dose BCG vaccination	Total
Wheeze, yes (n = 237)	14.3% (99/694)	15.6% (98/630)	15.7% (26/166)	18.7% (14/75)	15.1% (237/1565)
Wheeze, no (n = 1328)	85.7% (595/694)	84.4% (532/630)	84.3% (140/166)	81.3% (61/75)	84.9% (1328/1565)
$\chi^2_3 = 1.26, P = .74$ 43 Cases missing data re: wheeze					
	Reference group	OR, 1.11; 95% CI, 0.81-1.52	OR, 1.12; 95% CI, 0.68-1.83	OR, 1.38; 95% CI, 0.71-2.65	
Hay fever/eczema, yes (n = 716)	46.0% (325/706)	43.5% (277/637)	46.4% (78/168)	47.4% (36/76)	45.1% (716/1587)
Hay fever/eczema, no (n = 871)	54.0% (381/706)	56.5% (360/637)	53.6% (90/168)	52.6% (40/76)	54.9% (871/1587)
$\chi^2_3 = 1.20, P = .75$ 21 Cases missing data re: hay fever/eczema					
	Reference group	OR, 0.90; 95% CI, 0.72-1.13	OR, 1.02; 95% CI, 0.72-1.44	OR, 1.06; 95% CI, 0.64-1.74	

**FIG 1.** Updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

was 0.94 (95% CI, 0.83-1.07) for the risk of allergy in general in those who were BCG vaccinated compared with those who were not (see Fig E6, A in this article's Online Repository at www.jacionline.org). The funnel plot was not suggestive of publication bias (see Fig E6, B). A sensitivity analysis for higher-quality studies was carried out and estimated an overall OR of 0.96 (95% CI, 0.84-1.10; see Fig E6, C).

No new subgroup analyses were conducted for high-risk children or for children from a non-Western population for any of the outcomes examined because we failed to identify additional relevant data.

DISCUSSION

The final results from MANCAS 2 found that the earlier protective effect associated with neonatal BCG vaccination at age 6 to 11 years was no longer present at age 13 to 17 years, suggesting that any benefits are likely to be transient. In the updated meta-analysis incorporating data from MANCAS 2 and from 3 recent studies,²⁶⁻²⁸ the protective effect against the development of asthma was no longer evident, and we again failed to show any evidence of protection against allergic sensitization. Taken together, these data provide further evidence that any benefits associated with BCG vaccination on asthma outcomes are likely to be transient and unlikely to be mediated through reducing the risk of atopy.

Strengths and limitations

MANCAS/MANCAS 2 were able to investigate the relationship between BCG vaccination and risk of asthma symptoms and allergy in a unique cohort born in a hospital in which the BCG vaccination policy changed twice within a relatively short period of time. The cohort was followed up over a 7-year period, and the present analysis investigated the prevalence of wheeze and allergy in BCG-vaccinated and nonvaccinated adolescents. We used questionnaire data to identify the prevalence of symptoms and immunization records to establish vaccination status. The questionnaire used was derived from the validated ISAAC questionnaire.²⁴ No significant associations between BCG vaccination and wheeze or allergy were identified. Consequently, a dose-response relationship between BCG vaccination and asthma/allergy symptoms could not be investigated.

There were some limitations in our use of an ISAAC-based questionnaire. Differences in interpretation of the word *wheeze* and the difficulties in defining asthma have been well documented in the medical literature, as highlighted by Cane et al³⁰ and Netuveli et al.³¹ However, our study was concentrated in one geographic area only, and because the children were born in the area, it is likely that respondents were familiar with the area and with local dialects and language for at least 14 years.

TABLE III. Characteristics of studies included in the systematic review and meta-analysis

Reference (year of publication)	Design	Population studied	No. of patients	Age at receipt of BCG vaccination	Outcomes	Quality assessment	Adjusted effect sizes
Aaby et al, ² 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, 0-3072 d)	SPT	C	Yes
Alm et al, ³ 1997	Retrospective cohort study	Cohort and control subjects: atopic heredity, Stockholm	Cases: n = 216 Control subjects: n = 358	Mean, 17 d (range, 0- 180 d)	SPT Specific IgE Eczema/atopic dermatitis Asthma Rhinitis/ conjunctivitis Food allergy Allergy in general	B	No
Annus et al, ⁴ 2004	Cross-sectional study	Estonian schoolchildren	Cases: n = 717	Divided into ≤1 mo, 1 mo to 1 y, and ≥1 y	SPT Eczema/atopic dermatitis Asthma Rhinitis	C	No
Bremner et al, ⁵ 2005	Case-control study	Cases and control subjects derived from GP database; cases had ≥1 diagnosis of hay fever	Cases: n = 7,098 Control subjects: n = 7,098	Before age 2 y	Rhinitis	C	Yes
da Cunha et al, ⁶ 2004	Cross-sectional study	Sources 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/atopic dermatitis Asthma Rhinitis	C	Yes
Flohr et al, ²⁸ 2011	Cross-sectional study	Children participating in ISAAC Phase 2	Cases: n = 23,901	Divided into ≤1 y and <1 y	SPT Eczema/atopic dermatitis Asthma Rhinitis	C	Yes
García-Marcos et al, ⁷ 2005	Retrospective cohort study	Children from health care centers in Bilbao, Asturias, and San Sebastian, Spain	Cases: n = 6,762 Control subjects: n = 2,828	Newborns (no exact age reported)	Eczema/atopic dermatitis Asthma Rhinitis	B	Yes
Grüber et al, ⁸ 2001	Prospective cohort study	Health care centers from 5 different cities in (West) Germany	Cases: n = 92 Control subjects: n = 682	Before age of 1 y	SPT Specific IgE Eczema/atopic dermatitis Asthma Rhinitis	C	No
Grüber et al, ⁹ 2002	Retrospective cohort study	Children who were beginning school in 1994	Cases: n = 20,383 Control subjects: n = 18,425	Neonatal (no exact age reported)	Eczema/atopic dermatitis Asthma Rhinitis	B	Yes

(Continued)

TABLE III. (Continued)

Reference (year of publication)	Design	Population studied	No. of patients	Age at receipt of BCG vaccination	Outcomes	Quality assessment	Adjusted effect sizes
Grüber et al, ²⁶ 2008	Retrospective cohort study	Infants screened for inclusion in randomized clinical trial	N = 2,173	11.5-25.5 mo	Specific IgE	C	Not in published article but obtained from the author
Krause et al, ¹⁰ 2003	Cross-sectional study	All children in certain age groups, Greenland	Cases: n = 1,065 Control subjects: n = 510	Within a few days of birth	Specific IgE	B	Yes
Linehan et al, ^{11,29} 2006/2007	Retrospective cohort study	Children in PCT database; Northwest England	Cases: n = 834 Control subjects: n = 775	Within the first 12 wk of life in most cases but with some delayed vaccination	SPT Asthma Hay fever/ eczema	B	Yes
Linehan et al, unpublished data, MANCAS 2	Retrospective cohort study	Adolescents in PCT database, Northwest England	Cases: n = 871 Control subjects: n = 694	Within the first 12 wk of life in most cases	Asthma Hay fever/ eczema	B	Yes
Marks et al, ¹² 2003	Retrospective cohort study	Children born 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/atopic dermatitis Asthma Rhinitis	B	Yes
Miyake et al, ¹³ 2008	Cross-sectional study	Okinawa, Japan	Cases: n = 5,717	Infancy	Eczema/atopic dermatitis Asthma Rhinitis	B	Yes
Möhrenschlager et al, ¹⁴ 2007	Cross-sectional study	Children on admission to school in Augsburg, Germany	Cases: n = 1,496	—	SPT Eczema/atopic dermatitis Asthma Rhinitis	C	Yes
Mommers et al, ¹⁵ 2004*	Case-control study	The 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, ¹⁶ 2002	Cross-sectional study	Children from secondary school in Haringey, North London	Cases: n = 308	—	Asthma	C	No
Soysal et al, ²⁷ 2008	Retrospective cohort study	Children with recent household contact to adult given a diagnosis of sputum smear-positive pulmonary TB at one of 7 government-funded TB clinics in Istanbul	Cases: n = 290 Control subjects: n = 71		SPT Asthma Rhinitis Atopic dermatitis	C	No

(Continued)

TABLE III. (Continued)

Reference (year of publication)	Design	Population studied	No. of patients	Age at receipt of BCG vaccination	Outcomes	Quality assessment	Adjusted effect sizes
Steenhuis et al, ¹⁷ 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 age 6 wk	Specific IgE Eczema/atopic dermatitis Asthma Rhinitis	B	Yes
Strannegård et al, ¹⁸ 1998	Cross-sectional study	Children attending schools in 3 cities in Sweden	Cases: n = 6,497	Before age 1 y	Allergy in general	C	No
Wickens et al, ¹⁹ 2001	Case-control study	New Zealand	Cases (asthma): n = 220 Control subjects (no asthma): n = 231		Asthma	C	No

GP, General practitioner; TB, tuberculosis.

*Data used for asthma analysis were from a personal communication with the author and not from the published article.

A further possible limitation was that our MANCAS 2 questionnaire was directed to parents rather than the children themselves. Parents were encouraged to discuss the study with their child and to obtain their child's agreement before participating in the study. This is likely to have increased the possibility of both the child and parent completing the questionnaire together, a factor noted by Braun-Fahrlander et al³² to increase conformity between parental and adolescent responses. A more recent study reported no significant differences between parent and adolescent responses to an ISAAC-based asthma questionnaire in a longitudinal asthma and allergy study.³³

The low response rate in MANCAS 2 means there is some imprecision in interpretation of the results. On the basis of the number of respondents, the study had 80% power to detect differences in prevalence of 5% or more between the no BCG and the combined normal/high-dose BCG group and 80% power to detect differences in prevalence of 11% or more between the normal and high-dose BCG groups. There is also the risk of bias that always needs to be considered when faced with losses to follow-up.

A key strength of this work is our formal attempt at synthesizing and interpreting these data with those from the wider international literature through formally updating our systematic review and meta-analysis. However, as with our first systematic review and meta-analysis, most of the evidence uncovered comes from epidemiologic rather than experimental studies. The new studies included in the updated work are observational studies and, as such, do not enhance the quality of studies included in the meta-analysis. Therefore the risk of bias remains a limitation of this work. Sensitivity analyses were carried out to minimize the risk of bias, where possible.

Interpreting findings within the context of the international literature

The contrasting results from MANCAS and MANCAS 2 are reflected in the results generally reported for studies

investigating BCG vaccination and asthma or atopy and included in the meta-analysis. However, most of the other studies have been carried out in different populations of children in different regions of the world by different research teams. A recent study in Brazil³⁴ did not find any association between BCG revaccination 7 to 10 years after neonatal vaccination and asthma symptoms or atopic asthma in adolescents participating in an ISAAC study. However, the prevalence of asthma is high in Brazil,^{34,35} despite a universal neonatal BCG vaccination policy, supporting the hypothesis that environmental and genetic factors also influence vulnerability to asthma and atopic symptoms.

MANCAS and MANCAS 2 used the same population in the same area, and the research team remained essentially the same throughout both studies. If the significant result seen in the first MANCAS study was truly a *bona fide* finding, then why was this not replicated in this final round of data collection? The most likely explanation is that because the entire cohort had reached adolescence by the time MANCAS 2 was carried out, the protective effect of BCG vaccination was lost during transition from childhood to adolescence. The fact that there was no effect of BCG vaccination on atopy suggests that there was no effect on the development of atopic asthma, which is known to have a poor prognosis.²²

Any protective effect of BCG vaccination on asthma outcomes is likely to be relatively short-lived, with this being lost in adolescence. BCG vaccination does not protect against the development of allergic sensitization or other allergic disorders.

We thank Julie A. Morris, Head of Medical Statistics, University Hospital of South Manchester, for her guidance and advice on the statistical analysis of the MANCAS data. We would also like to thank the authors of the Mommers et al (2004) and Grüber et al (2008) studies for providing unpublished data for us to use in the meta-analyses. Finally, we would like to express our gratitude to the 3 anonymous peer reviewers for their constructive suggestions on earlier drafts of this manuscript.

Key messages

- The previously found protective effect of BCG vaccination on wheeze in primary school-aged children in the MANCAS cohort was lost in adolescence.
- The original meta-analysis identified an OR of 0.73 (95% CI, 0.56-0.95) for the association between BCG vaccination and asthma. In the updated meta-analysis the OR was 0.95 (95% CI, 0.89-1.00), and this effect was lost when lower-quality studies were excluded (OR, 0.90; 95% CI, 0.78-1.03).
- The updated systematic review and meta-analysis has again confirmed that there was no protective effect of BCG vaccination against allergic sensitization, eczema, rhinoconjunctivitis, or allergy in general.
- Overall, the evidence from our updated asthma meta-analysis indicates that any protective effect of BCG vaccination on the risk of asthma symptoms is likely to be transient.

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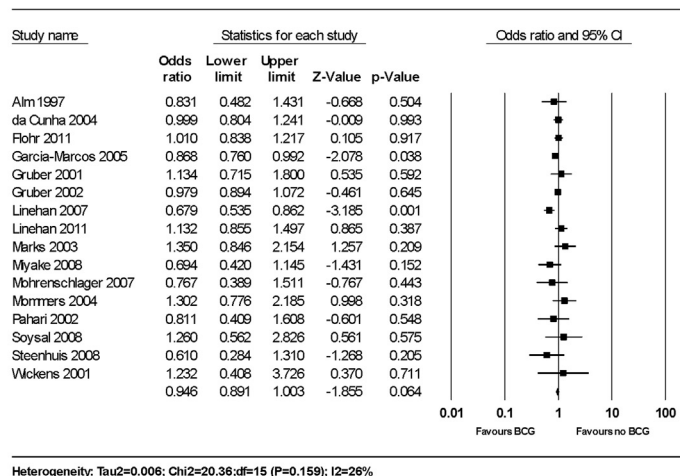
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METHODS

Search strategy

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- This search resulted in 91 studies (previously 74).

A**B**

Funnel Plot of Standard Error by Log odds ratio

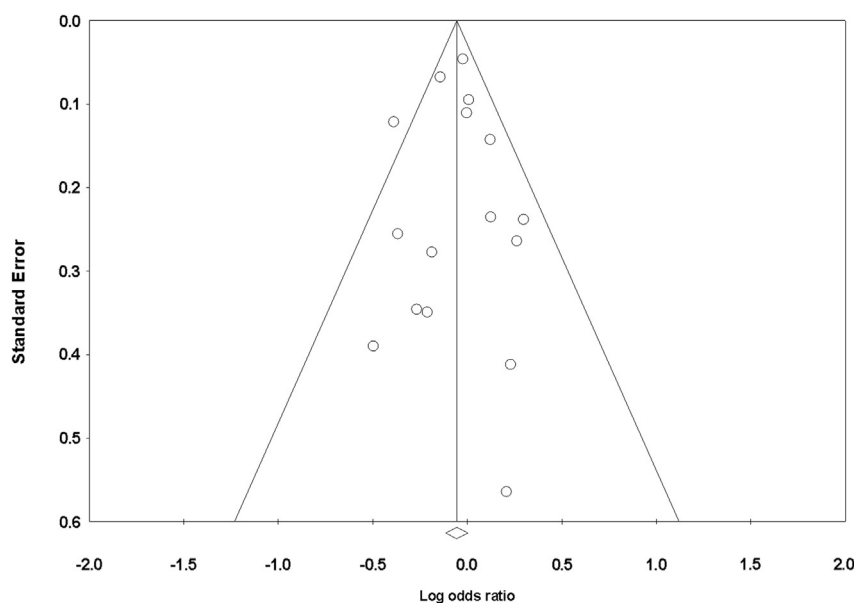
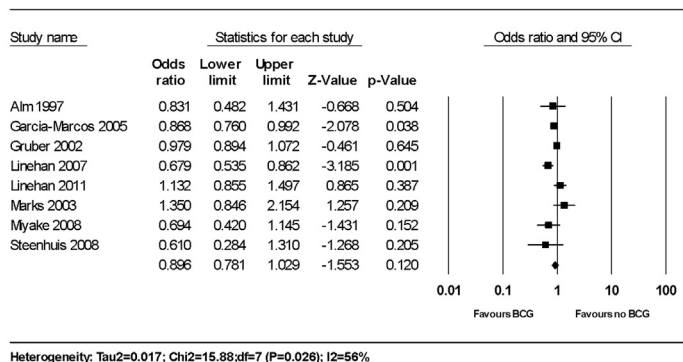
**C**

FIG E1. A, Forest plot (fixed-effects model) showing ORs and 95% CIs for the association between BCG vaccination and asthma. **B,** Funnel plot for the association between BCG vaccination and asthma. **C,** Forest plot (random-effects model) showing ORs and 95% CIs for the association between BCG vaccination and asthma in category B studies.

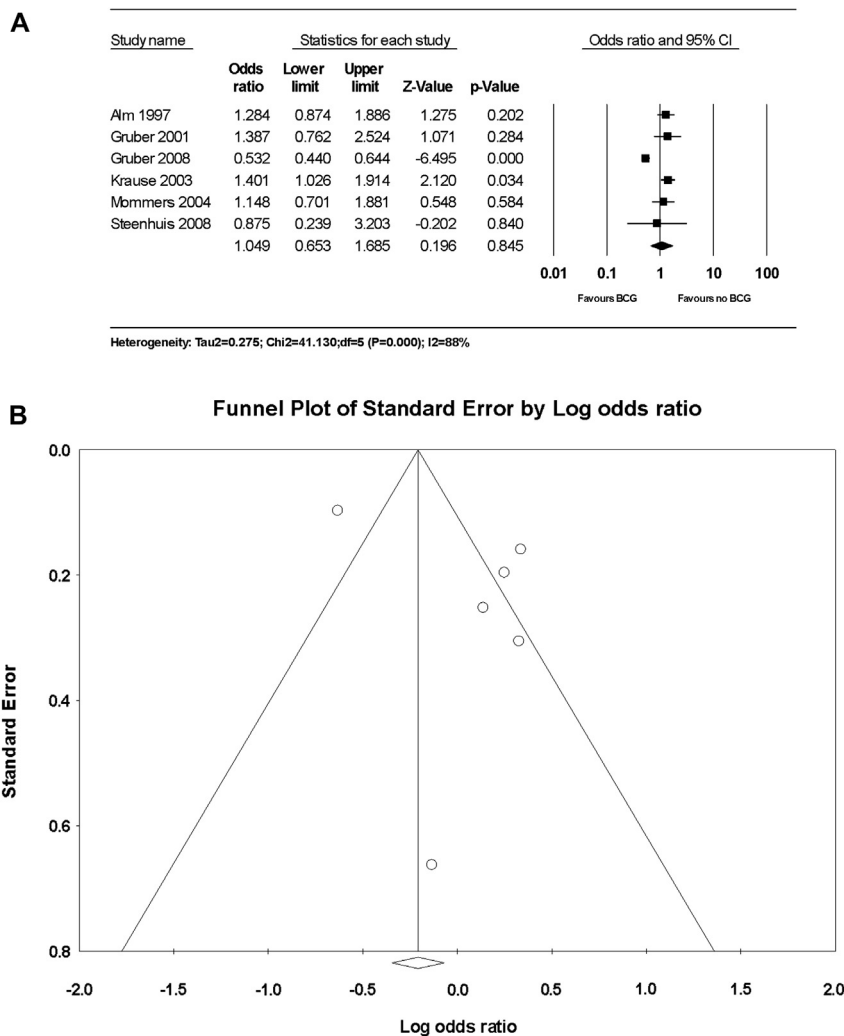


FIG E2. A, Forest plot (random-effects model) showing ORs and 95% CIs for the association between BCG vaccination and sensitization measured by using specific IgE level. **B,** Funnel plot for the association between BCG vaccination and a positive specific IgE level.

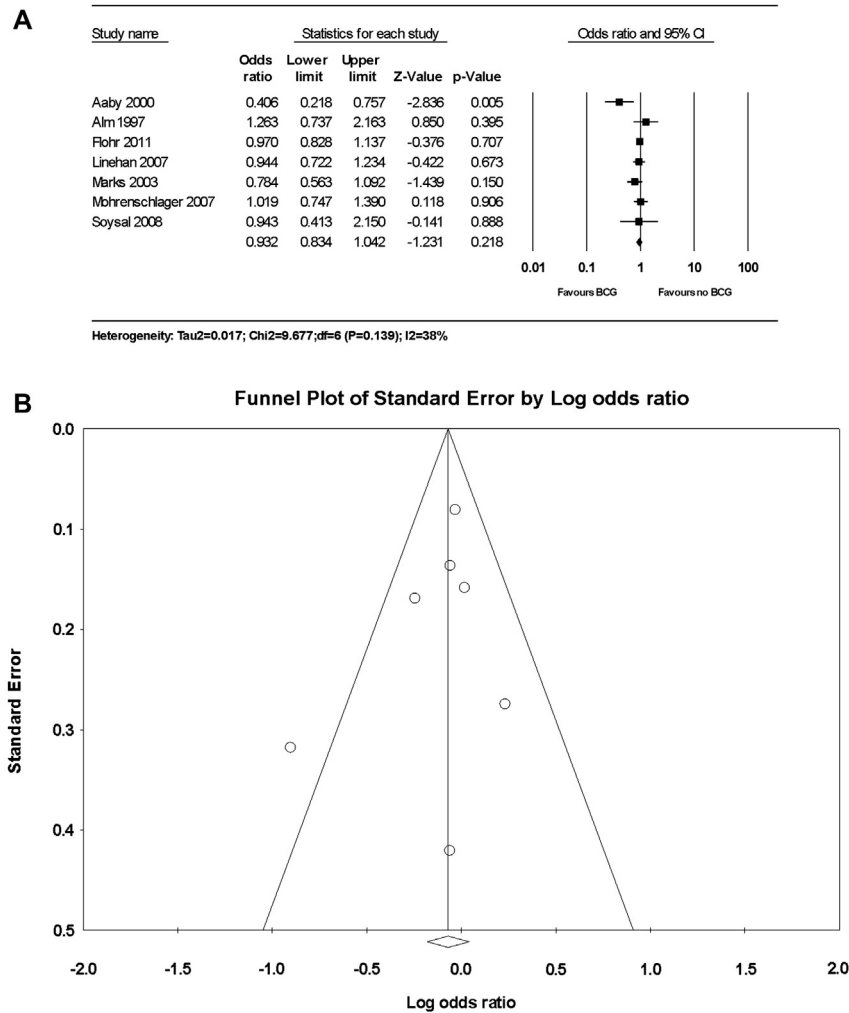


FIG E3. A, Forest plot (fixed-effects model) showing ORs and 95% CIs for the association between BCG vaccination and a positive SPT response. **B**, Funnel plot for the association between BCG vaccination and a positive SPT response.

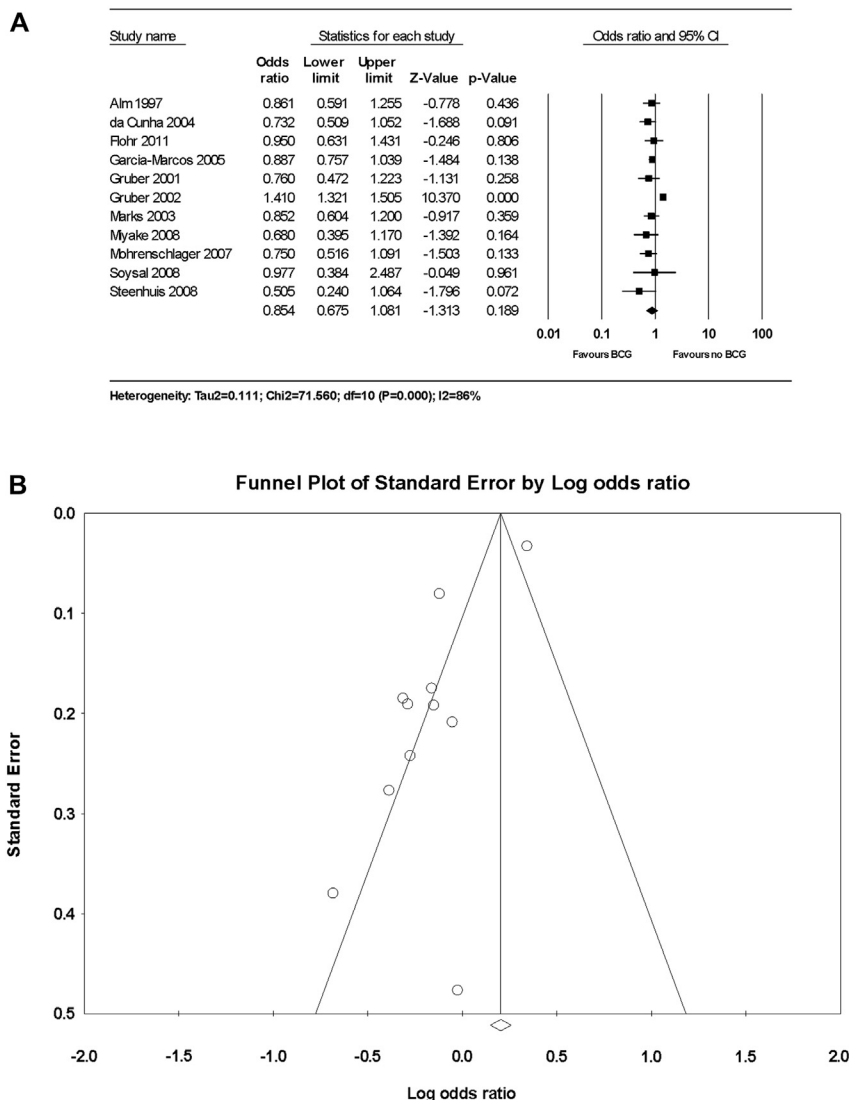


FIG E4. A, Forest plot (random-effects model) showing ORs and 95% CIs for the association between BCG and atopic dermatitis/eczema. **B,** Funnel plot for the association between BCG vaccination and eczema/atopic dermatitis.

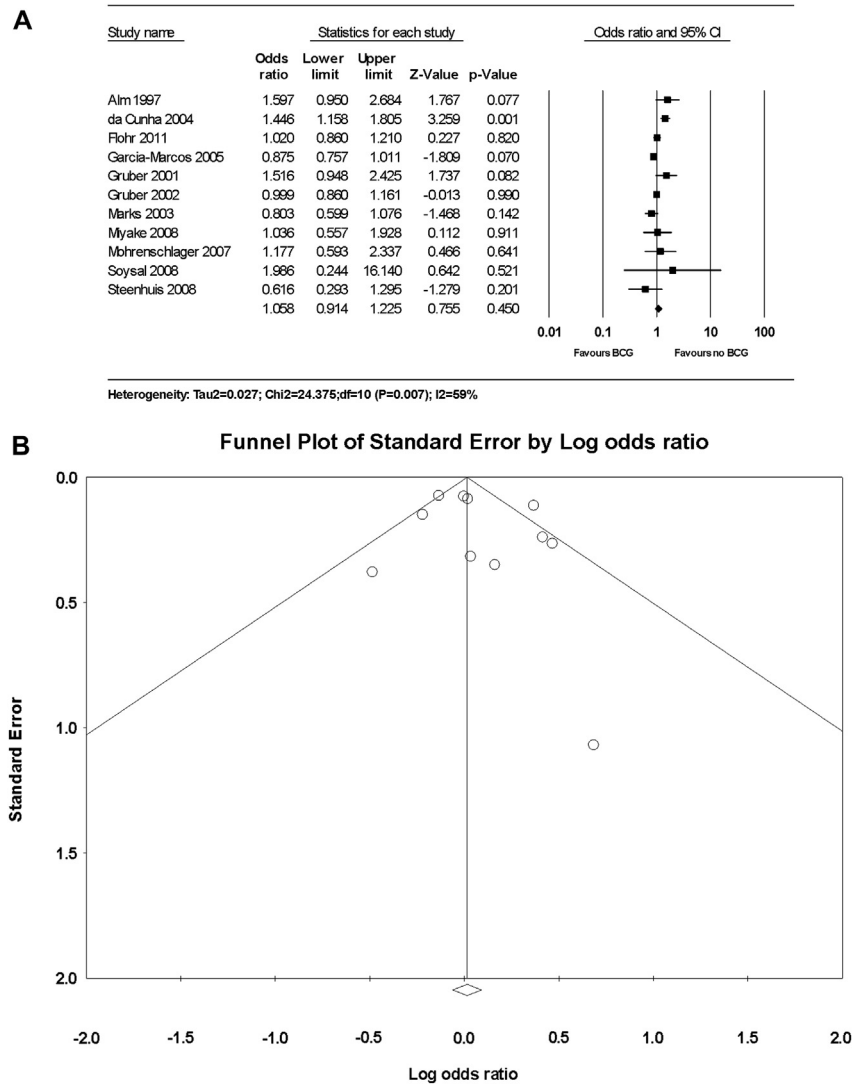


FIG E5. A, Forest plot (random-effects model) showing ORs and 95% CIs for the association between BCG and allergic rhinoconjunctivitis. **B,** Funnel plot for the association between BCG vaccination and rhinoconjunctivitis.

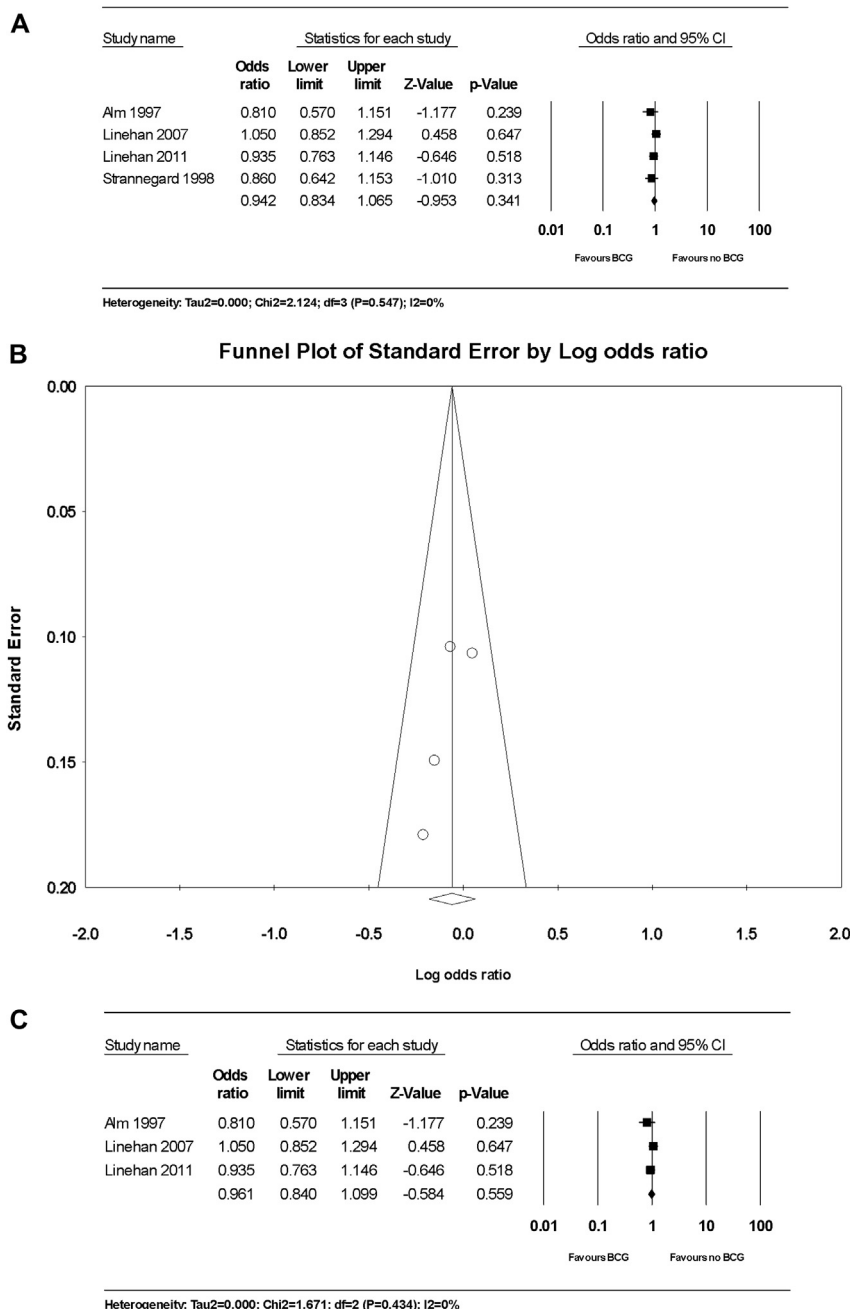


FIG E6. A, Forest plot (fixed-effects model) showing ORs and 95% CIs for the association between BCG vaccination and allergy in general. **B,** Funnel plot for the association between BCG vaccination and allergy in general. **C,** Forest plot (fixed-effects model) showing ORs and 95% CIs for the association between BCG vaccination and allergy in general in category B studies.

TABLE E1. Characteristics of studies investigating the relationship between BCG vaccination and asthma

Reference	Design	Population	Outcome	OR	95% CI
Alm et al, ³ 1997	Cohort	Sweden	Lifetime wheezing	0.83	0.48-1.43
Annus et al, ⁴ 2004	Cross-sectional	Estonia	Lifetime asthma	No suitable summary data available	
da Cunha et al, ⁶ 2004	Cross-sectional	Brazil	Lifetime asthma	1.00	0.80-1.24
Flohr et al, ²⁸ 2011	Cross-sectional	Worldwide	Wheezing, 12-mo prevalence	1.01	0.84-1.22
García-Marcos et al, ⁷ 2005	Cohort	Spain	Wheezing, 12-mo prevalence	0.87	0.76-0.99
Grüber et al, ⁸ 2001	Cohort	Germany	Recurrent wheezing	1.13	0.72-1.80
Grüber et al, ⁹ 2002	Cohort	Germany	Lifetime asthma	0.98	0.89-1.07
Linehan et al, ¹¹ 2007	Cohort	United Kingdom	Wheezing, 12-mo prevalence	0.68	0.54-0.86
Linehan et al, unpublished data, MANCAS 2	Cohort	United Kingdom	Wheezing, 12-mo prevalence	1.13	0.86-1.50
Marks et al, ¹² 2003	Cohort	Australian Asian	Lifetime asthma	1.35	0.85-2.15
Miyake et al, ¹³ 2008	Cross-sectional	Japan	Wheezing, 12-mo prevalence	0.69	0.42-1.15
Möhrenschlager, et al, ¹⁴ 2007	Cross-sectional	Germany	Lifetime asthma	0.77	0.39-1.51
Mommers et al, ¹⁵ 2004*	Case-control	Germany and The Netherlands	Wheezing, 12-mo prevalence	1.30	0.78-2.19
Pahari et al, ¹⁶ 2002	Cross-sectional	United Kingdom	Lifetime asthma	0.81	0.41-1.61
Soysal et al, ²⁷ 2008	Cohort	Turkey	Doctor-diagnosed asthma	1.26	0.56-2.83
Steenhuis et al, ¹⁷ 2008	RCT	The Netherlands	Lifetime asthma	0.61	0.28-1.31
Wickens et al, ¹⁹ 2001	Case-control	New Zealand	Current asthma	1.23	0.41-3.73

RCT, Randomized controlled trial.

*Data used for asthma analysis were from personal communication with the author and not from the published article.

TABLE E2. Characteristics of studies investigating the relationship between BCG vaccination and sensitization by specific IgE level

Reference	Design	Population	Outcome	OR	95% CI
Alm et al, ³ 1997	Cohort	Sweden	IgE	1.28	0.87-1.89
Grüber et al, ⁸ 2001	Cohort	Germany	IgE	1.39	0.76-2.52
Grüber et al, ²⁶ 2008*	Cohort	10 European countries	IgE	0.53	0.44-0.64
		South Africa			
		Australia			
Krause et al, ¹⁰ 2003	Cross-sectional	Greenland	IgE	1.40	1.03-1.91
Mommers et al, ¹⁵ 2004	Case-control	Germany and The Netherlands	IgE	1.15	0.70-1.88
Steenhuis et al, ¹⁷ 2008	RCT	The Netherlands	IgE	0.88	0.24-3.20

RCT, Randomized controlled trial.

*Data used were from personal communication with the author and not from the published article.

TABLE E3. Characteristics of studies investigating the relationship between BCG vaccination and sensitization by positive SPT response

Reference	Design	Population	Outcome	OR	95% CI
Aaby et al, ² 2000	Cohort	Africa	SPT	0.41	0.22-0.76
Alm et al, ³ 1997	Cohort	Sweden	SPT	1.26	0.74-2.16
Annus et al, ⁴ 2004	Cross-sectional	Estonia	SPT	No suitable summary data available	
Flohr et al, ²⁸ 2011	Cross-sectional	Worldwide	SPT	0.97	0.83-1.14
Grüber et al, ⁸ 2001	Cohort	Germany	SPT	No summary data presented	
Linehan thesis, ²⁹ 2006	Cohort	United Kingdom	SPT	0.94	0.72-1.23
Marks et al, ¹² 2003	Cohort	Australian Asian	SPT	0.78	0.56-1.09
Möhrenschlager et al, ¹⁴ 2007	Cross-sectional	Germany	SPT	1.02	0.75-1.39
Soysal et al, ²⁷ 2008	Cohort	Turkey	SPT	0.94	0.41-2.15

TABLE E4. Characteristics of studies investigating the relationship between BCG vaccination and eczema/atopic dermatitis

Reference	Design	Population	Outcome	OR	95% CI
Alm et al, ³ 1997	Cohort	Sweden	Atopic dermatitis	0.86	0.59-1.26
Annus et al, ⁴ 2004	Cross-sectional	Estonia	Atopic dermatitis	No suitable summary data available	
da Cunha et al, ⁶ 2004	Cross-sectional	Brazil	Atopic dermatitis	0.73	0.51-1.05
Flohr et al, ²⁸ 2011	Cross-sectional	Worldwide	Atopic dermatitis	0.95	0.63-1.43
García-Marcos, et al, ⁷ 2005	Cohort	Spain	Atopic dermatitis	0.89	0.76-1.04
Grüber et al, ⁸ 2001	Cohort	Germany	Atopic dermatitis	0.76	0.47-1.22
Grüber et al, ⁹ 2002	Cohort	Germany	Atopic dermatitis	1.41	1.32-1.51
Marks et al, ¹² 2003	Cohort	Australian Asian	Atopic dermatitis	0.85	0.60-1.20
Miyake et al, ¹³ 2008	Cross-sectional	Japan	Rash, 12-mo prevalence	0.68	0.40-1.17
Möhrenschlager et al, ¹⁴ 2007	Cross-sectional	Germany	Atopic dermatitis	0.75	0.52-1.09
Soysal et al, ²⁷ 2008	Cohort	Turkey	Atopic dermatitis	0.98	0.38-2.49
Steenhuis et al, ¹⁷ 2008	RCT	The Netherlands	Atopic dermatitis	0.51	0.24-1.06

RCT, Randomized controlled trial.

TABLE E5. Characteristics of studies investigating the relationship between BCG vaccination and rhinoconjunctivitis

Reference	Design	Population	Outcome	OR	95% CI
Alm et al, ³ 1997	Cohort	Sweden	Allergic rhinitis or conjunctivitis	1.60	0.95-2.68
Annus et al, ⁴ 2004	Cross-sectional	Estonia	Lifetime rhinitis	No suitable summary data available	
Bremner et al, ⁵ 2005	Case-control	United Kingdom	Hay fever	No suitable summary data available	
da Cunha et al, ⁶ 2004	Cross-sectional	Brazil	Current allergy with sneezing	1.45	1.16-1.81
Flohr et al, ²⁸ 2011	Cross-sectional	Worldwide	Hay fever, 12-mo prevalence	1.02	0.86-1.21
García-Marcos et al, ⁷ 2005	Cohort	Spain	Rhinitis, 12-mo prevalence	0.88	0.76-1.01
Grüber et al, ⁸ 2001	Cohort	Germany	Allergic rhinitis	1.52	0.95-2.43
Grüber et al, ⁹ 2002	Cohort	Germany	Hay fever	1.00	0.86-1.16
Marks et al, ¹² 2003	Cohort	Australian Asian	Hay fever	0.80	0.60-1.08
Miyake et al, ¹³ 2008	Cross-sectional	Japan	Allergic rhinitis, 12-mo prevalence	1.04	0.56-1.93
Möhrenschlager et al, ¹⁴ 2007	Cross-sectional	Germany	Hay fever	1.18	0.59-2.34
Soysal et al, ²⁷ 2008	Cohort	Turkey	Allergic rhinitis	1.99	0.24-16.14
Steenhuis et al, ¹⁷	RCT	The Netherlands	Allergic rhinitis, 12-mo prevalence	0.62	0.29-1.30

RCT, Randomized controlled trial.

TABLE E6. Characteristics of studies investigating the relationship between BCG vaccination and allergy in general

Reference	Design	Population	Outcome	OR	95% CI
Alm et al, ³ 1997	Cohort	Sweden	Allergic rhinitis or conjunctivitis	0.81	0.57-1.15
Linehan et al, ¹¹ 2007	Cohort	United Kingdom	Hay fever/eczema	1.05	0.85-1.29
Linehan et al, unpublished data, MANCAS 2	Cohort	United Kingdom	Hay fever/eczema	0.94	0.76-1.15
Strannegård et al, ¹⁸ 1998	Case-control study	Sweden	Allergy in general	0.86	0.64-1.15