ORIGINAL ARTICLE

Tuberculosis, bacillus Calmette–Guérin vaccination, and allergic disease: Findings from the International Study of Asthma and Allergies in Childhood Phase Two

Carsten Flohr[1], Gabriele Nagel[2], Gudrun Weinmayr[2], Andrea Kleiner[2], Hywel C. Williams[3], Nadia Aït-Khaled[4], David P. Strachan[5] & the ISAAC Phase Two Study Group*

[1]Department of Paediatric Allergy & Dermatology, St John's Institute of Dermatology, St Thomas' Hospital and King's College London, London, UK; [2]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany; [3]Centre for Evidence Based Dermatology, University of Nottingham, Nottingham, UK; [4]International Union Against Tuberculosis and Lung Disease (The Union), Cheraga, Algeria; [5]Division of Community Health Sciences, St. George's University of London, London, UK

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Correspondence
Carsten Flohr, Department of Paediatric Allergy & Dermatology, St John's Institute of Dermatology, St Thomas' Hospital and King's College London, London, UK.
Tel.: +44 (0) 20 7188 7188, ext. 51601
Fax: +44 (0) 20 7188 9782
E-mail: carsten.flohr@kcl.ac.uk

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*ISAAC Phase Two Study Group members are presented in Appendix.

Abstract

Some have suggested a protective effect of tuberculosis (TB) infection on allergic disease risk, but few studies have examined the association between the two. We therefore investigated whether TB disease and bacillus Calmette–Guérin (BCG) vaccination in early life protect against allergic disease. Information on allergic disease symptoms, past TB disease, and BCG vaccination as well as potential confounding factors was gathered by parental questionnaire from a randomly selected subset of 23,901 8- to 12-yr-old schoolchildren in 20 centers in both developed and developing countries. Children were also physically examined for flexural eczema and underwent skin prick testing. Pooled odds ratio (OR) estimates and corresponding 95% confidence intervals (CIs) across study centers were calculated, using random effects meta-analysis models. There were 245 (1.0%) reported cases of TB disease, and 66.3% (15,857) of all children received the BCG vaccine. Asthma, hay fever, and flexural eczema symptoms in the past year as well as flexural eczema on skin examination were all positively linked to a history of TB (adjusted pooled OR 'wheeze in the past year' = 2.27, 95% CI 1.52–3.41; adjusted pooled OR 'hay fever symptoms in the past year' = 2.23, 1.22–4.09; adjusted pooled OR 'flexural eczema symptoms in the past year' = 3.21, 2.01–5.12; adjusted pooled OR 'flexural eczema on skin examination' = 4.04, 1.71–9.56). Even higher risk estimates were seen for severe asthma and eczema symptoms [adjusted OR = 4.02 (2.17–7.47) and adjusted OR = 6.31 (2.19–18.17), respectively]. There was no significant association between past TB and skin prick test positivity (adjusted pooled OR = 1.32, 0.87–2.02). BCG vaccination during the first year of life was also not associated with any of the allergy outcomes. We found a uniform positive association between TB and all allergic disease outcomes, including eczema on skin examination. As this was a cross-sectional study, it is unclear whether this positive association is attributable to a causal relationship, and further longitudinal studies are required.

The past few decades have seen a dramatic rise in allergic diseases in industrialized countries, accompanied by a decline in exposure to previously prevalent infectious diseases, such as helminth parasites and childhood viral and bacterial infections (1–3). In this context, some have suggested that *Mycobacterium tuberculosis* infection might have a direct protective effect on the risk of allergic disease.

Initial support for a protective effect of mycobacterial infection on allergic disease and allergic sensitization came from a study among Japanese children in a population with a universal program of tuberculin testing and bacillus Calmette–Guérin (BCG) vaccination, showing strong inverse associations between delayed hypersensitivity to *M. tuberculosis* and clinical allergic disease (4). Two further cross-sectional

studies from Japan and South Africa found a similar reduction in symptoms of allergic disease in children with positive tuberculin responses (5, 6). However, all subsequent studies on tuberculin responses have not confirmed these findings (7–20). A recent systematic review also examined the association between BCG vaccination and atopic conditions and found no convincing protective effect on allergic sensitization, eczema, or hay fever, but could not rule out a potential small risk reduction for asthma (21–25). There has been one randomized controlled trial using BCG vaccination after birth as a potential method to prevent asthma, but this did not show a significant protective effect (OR = 0.61, 0.28–1.31) (26).

The lack of a convincing association between BCG vaccination and allergic diseases is surprising, as murine models strongly suggest that BCG infection can suppress allergic sensitization and allergen-induced airway eosinophilia and hyper-reactivity, partly due to the induction of regulatory T cells (27–29). Nevertheless, therapeutic interventions with BCG and non-pathogenic mycobacteria in humans with established allergic disease have been disappointing (30).

To date, there has been little work on the association between tuberculosis (TB) and allergic disease. Two of three ecological studies suggested an inverse relationship between TB notification rates and allergic disease prevalences at the population level (31–33). Furthermore, a large case–control study among Finnish adults suggested that TB disease during childhood may protect against allergic disease in women. However, the opposite trend was observed for men (34), and there have so far not been any population-based studies among children on the potential association between TB and allergic disease.

We therefore studied the association between BCG vaccination, TB, and allergic disease among schoolchildren who took part in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. In accordance with the World Allergy Organization nomenclature, we use the term 'eczema' throughout (syn. 'atopic eczema', 'atopic dermatitis') (35). We refer to TB disease as 'TB' and latent TB as 'TB infection'.

Methods

The rationale and methods of ISAAC Phase Two have been described elsewhere in detail (36). In brief and with reference to this paper, ISAAC Phase Two was conducted among schoolchildren aged 8–12 yr to evaluate the prevalence of and risk factors for allergic disease between and within populations. Study centers were required to randomly select at least 10 schools from a sampling frame of schools in a defined geographical areas, and children ($n \geq 1000$ per centre) attending classes with a majority of 9- to 11-yr-olds were invited to participate.

Following written consent, data were collected through parental questionnaires on symptoms of asthma, rhinitis, and eczema, identical to those used for children aged 6–7 yr in ISAAC Phase One (37). The questions relating to asthma symptoms were the following: 'Has your child ever had wheezing or whistling in the chest at any time in the past?' (yes/no = 'asthma symptoms ever'), and 'Has your child had wheezing or whistling in the chest in the last 12 months?' (yes/no = 'asthma symptoms past year'). In case of asthma symptoms in the past year, parents were also asked about symptom severity: 'How many attacks of wheezing has your child had in the last 12 months?' (none/1–3/4–12/more than 12), 'In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?' (never/less than one night per week/one or more nights per week), and 'In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?' (yes/no). Anybody with either four or more wheezing episodes in the past 12 months, sleep disturbance for at least one night per week, or speech limitation was classified as having 'severe wheeze in the past year'.

For rhinitis, participants' parents were asked the following: 'Has your child ever had a problem with sneezing or a runny or blocked nose, when he/she did not have a cold or flu?' (yes/no = 'rhinitis symptoms ever'), and 'In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?' (yes/no = 'rhinitis symptoms in the past year').

The eczema-related questions were as follows: 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' (yes/no = 'eczema symptoms ever'), 'Has your child had this itchy rash at any time in the past 12 months?' (yes/no = 'eczema symptoms past year'), and 'Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?' (yes/no = 'flexural eczema past year'). If applicable, parents were additionally asked at what age this itchy rash first occurred (< 2 yr/age 2–4 yr/age 5 or more). Eczema severity was assessed by asking 'Has this rash cleared completely at any time during the past 12 months?' ('persistent flexural eczema past year') and 'In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?' (never in the past 12 months/less than one night per week/one or more nights per week). Any child with either persistent eczema symptoms or sleep disturbance for one or more nights a week was classified as having 'severe flexural eczema symptoms in the past year'. Finally, parents were asked whether their child had ever had eczema ('eczema ever').

For TB and BCG vaccination, parents were asked 'Has your child ever had any of the following diseases? … Tuberculosis?' (yes/no) and 'Has your child been vaccinated against tuberculosis/BCG?' (yes/no). If the answer was 'yes', parents were additionally asked about the child's age in years at time of TB disease and vaccination. Unless specifically stated, we use the term 'TB' for TB disease, i.e., TB with clinical symptoms as ascertained by the ISAAC questionnaire, as opposed to 'TB infection', which is the term commonly used for latent TB.

Children were also physically examined for flexural eczema in the following five body areas: (i) around the eyes, (ii) the neck, (iii) in front of the elbows, (iv) behind the knees, and

(v) in front of the ankles. Participants were categorized as having flexural eczema if they had a typical erythematous flexural rash with surface change (e.g., fine scaling, vesicles, oozing, crusting, or lichenification) (http://www.nottingham.ac.uk/dermatology/eczema/contents.html, last accessed 16 November 2011). All fieldworkers were first trained and then formally tested in the recognition of flexural eczema, using a manual and photographic images specifically developed for this purpose (33, 34). Children also received skin prick testing to the following six common aeroallergens: *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, cat hair, *Alternaria tenuis*, mixed tree, and grass pollen as well as histamine (10 mg/ml) and normal saline control solutions (all ALK, Hørsholm, Denmark). Study centers were allowed to add allergens of local relevance. Additional allergens were tested in 15 centers and included cockroach, dog, horse, olive, *Parietaria officinalis*, mixed weeds, local tree mix, mixed molds, and *Cladosporium*. A drop of each allergen and both control solutions were placed onto the volar aspect of the left forearm and pierced vertically using 1-mm ALK lancets. Reactions were recorded after 15 min and considered positive if the mean wheal diameter was at least 3 mm greater than the saline control (32). Atopy was defined as having at least one positive skin prick test to any of the allergens tested.

Following local data entry, the data were sent to the ISAAC Phase Two Co-ordinating Centre at the University of Ulm (Germany) for consistency checks and statistical analysis. Crude odds ratios for past TB and BCG vaccination (exposure) and all allergic disease outcomes were calculated with corresponding 95% confidence intervals. If centers had studied stratified subsamples [i.e., approximately 100 children with and 100 children without wheeze in the past year (32)], prevalence rates and ORs were calculated applying appropriate sampling weights (38, 39). Combined odds ratio estimates across study centers were calculated using random effects meta-analysis models (40). As confounders, we considered age, sex, the number of all siblings, current bedroom sharing as an indicator of crowding and living conditions and thus surrogate marker of socioeconomic status, a history of parental allergic disease, and maternal education. We also explored the effect of symptom severity and age of eczema onset. The statistical analyses were performed with SAS statistical software version 9.1 (SAS Institute Ltd., Cary, NC, USA). All study centers obtained local ethics committee approval. We followed the STROBE guidelines on reporting of epidemiological studies throughout (41).

Results

Data were collected in 20 centers with a total number of 23,901 schoolchildren aged 8–12 yr. 50.5% were girls. BCG vaccination coverage ranged between 16.5% in West Sussex (UK) and 99.7% in Uruguaiana (Brazil). Overall, there were 245 (1.0%) reported cases of TB disease, and 66.3% (15,857) of all children received the BCG vaccine. The lowest TB prevalences were reported in Pichincha (Ecuador) and Riga (Latvia) with 0% and 0.1%, respectively, and the highest in Mumbai (India) with 3.5%. For further details on TB, BCG vaccination, and allergic disease prevalence values, see summary Table 1.

BCG vaccination and allergic disease risk

Overall, there was no association between BCG vaccination under 1 yr of age and any of the allergic disease outcomes in both crude and adjusted analysis, and stratification by atopy status did not appreciably change these risk estimates (Table 2). The situation was largely similar if the BCG vaccination was given after the first year of life, except for a positive association between flexural eczema on skin examination and late BCG vaccination (adjusted OR = 1.82, 95% CI 1.14–2.91), which was even stronger in the non-atopic subgroup (adjusted OR = 2.94, 1.61–5.37; Table 2). Symptom severity and age of eczema onset did not affect these risk estimates.

TB and allergic disease risk

As for past TB, there was a universal positive association with all allergic disease outcomes, with adjusted odds ratios ranging between 2.23 and 4.04 (Table 2). Risk estimates were even higher for 'severe wheeze in the past year' (adj OR = 4.02, 2.17–7.47) and 'severe flexural eczema symptoms in the past year' (adj OR = 6.31, 2.19–18.17; Table 2). Except for flexural eczema on skin examination, associations were stronger in non-atopic children compared to those with at least one positive skin prick test, although skin prick test positivity itself was not associated with past TB (adjusted OR = 1.32; 0.87–2.02; Table 2). Restricting the analysis only to children who also had a BCG vaccination or, separately, eczema onset after 2 yr of age did not appreciably change the risk estimates.

Discussion

We found no protection of BCG vaccination on asthma, rhinitis, or eczema and some evidence to support a positive association between TB and allergic disease. This effect was even stronger in children with severe asthma and eczema symptoms as well as flexural eczema on skin examination. The effect persisted after adjustment for confounding factors and was equally present in developing and developed countries.

Like us, a recent systematic review found no significant association between early BCG vaccination and eczema and hay fever, although a small reduction in asthma risk could not be ruled out (20–25). Even if two of three ecological studies suggested an inverse relationship between TB notification rates and allergic disease prevalences, such studies do not allow to examine associations at the individual level or adjustment for environmental confounders (30–32). Interestingly, the only other study that looked at TB disease also suggested a positive association between TB during childhood and later asthma, albeit only in men, and the opposite was found in women, if TB had occurred by age 16. This was a population-based case–control study among Finnish adults, comprising 1162 individuals who had been reported to the

Table 1 Summary table showing number of participating children in each study center as well as the corresponding frequencies of allergic disease outcomes, bacillus Calmette–Guérin (BCG) vaccination, and tuberculosis (TB) disease

			Wheeze past year		Rhinoconjunctivitis past year		Flexural eczema past year		Flexural eczema on skin examination		BCG vaccination		TB disease	
Country	Centre	N	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Albania	Tirana	771	4.4	3.1–5.6	6.7	5.2–8.2	5.8	4.4–7.3	2.4	1.5–3.4	53.3	49.8–56.7	1.8	1.0–2.7
Brazil	Uruguaiana	1968	25.6	23.7–27.6	21.0	19.2–22.8	11.5	10.1–13.0	–	–	99.7	99.5–100.0	0.3	0.0–0.5
China	Guangzhou	2119	3.2	2.6–3.8	7.0	6.1–7.8	1.3	0.9–1.7	0.7	0.2–1.3	94.7	93.8–95.6	0.2	0.0–0.3
China	Hong Kong	2173	5.5	4.7–6.3	12.4	11.2–13.5	2.9	2.3–3.5	3.5	2.5–4.5	91.8	90.7–92.9	0.7	0.4–1.1
Ecuador	Pichincha	870	0.8	0.2–1.4	1.5	0.7–2.2	1.8	0.9–2.7	4.5	3.1–5.8	88.1	86.0–90.3	0.0	–
Georgia	Tbilisi	481	9.2	7.4–11.1	7.0	5.4–8.6	6.2	4.6–7.8	14.0	8.2–19.7	90.2	88.2–92.2	2.6	1.2–3.9
Greece	Athens	985	5.6	4.2–7.1	4.8	3.5–6.2	7.4	5.8–9.1	1.3	0.6–2.0	76.0	73.4–78.7	1.1	0.5–1.8
Greece	Thessaloniki	1009	8.4	6.7–10.1	7.0	5.5–8.6	5.1	3.8–6.5	1.4	0.7–2.1	90.1	88.2–91.9	0.9	0.3–1.5
India	Mumbai	1647	6.1	4.9–7.3	4.9	3.9–6.0	4.4	3.4–5.3	1.1	0.6–1.6	87.9	86.3–89.5	3.5	2.6–4.4
Iceland	Reykjavik	944	9.2	7.3–11.0	11.2	9.2–13.3	22.2	19.5–24.8	8.8	6.6–11.1	26.5	23.7–29.3	0.5	0.1–1.0
Latvia	Riga	736	6.9	5.3–8.6	8.5	6.7–10.4	9.5	7.5–11.4	6.4	4.2–8.5	96.0	94.6–97.3	0.1	0.0–0.4
New Zealand	Hawkes Bay	1223	21.9	19.7–24.1	22.3	20.0–24.5	13.8	11.9–15.7	8.2	6.7–9.7	24.2	21.8–26.6	0.6	0.2–1.0
Norway	Tromsø	3714	14.0	12.9–15.2	12.6	11.5–13.7	20.8	19.5–22.1	10.5	8.2–12.9	25.2	23.8–26.6	0.2	0.0–0.3
Palestine	Ramallah	284	8.8	7.6–9.9	6.9	5.9–8.0	7.5	6.4–8.6	2.8	0.5–5.2	67.6	61.9–73.3	1.4	0.0–2.8
Spain	Almeria	635	15.5	13.4–17.7	24.5	22.0–27.1	10.0	8.2–11.7	1.9	1.1–2.7	27.9	24.6–31.2	2.0	1.1–2.9
Spain	Cartagena	665	11.9	10.2–13.6	15.4	13.5–17.4	7.1	5.7–8.4	0.9	0.4–1.5	54.1	50.5–57.6	1.1	0.5–1.7
Spain	Madrid	522	11.6	9.6–13.7	18.7	16.2–21.2	13.1	10.9–15.2	3.2	1.8–4.5	48.5	44.6–52.4	0.9	0.2–1.6
Spain	Valencia	718	9.1	7.6–10.7	12.6	10.8–14.3	8.7	7.1–10.2	3.7	2.6–4.7	34.0	30.6–37.3	0.5	0.1–0.9
Turkey	Ankara	1797	10.9	9.8–12.0	11.8	10.6–13.0	5.4	4.5–6.2	1.4	1.0–1.9	96.3	95.6–97.0	2.9	2.1–3.7
UK	West Sussex	640	16.2	13.9–18.4	16.2	13.9–18.4	14.6	12.5–16.8	6.7	5.1–8.3	16.5	13.7–19.4	0.3	0.0–0.6

Table 2 Pooled odds ratio (OR) estimates for the association between past tuberculosis (TB), bacillus Calmette–Guérin (BCG) vaccination, and allergy outcomes

	All children		Atopics*		Non-atopics*	
Outcome	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
BCG vaccination ≤1 yr‡						
Wheeze past year	1.00 (0.85–1.17)	1.01 (0.84–1.22)	1.10 (0.82–1.48)	1.20 (0.86–1.67)	1.06 (0.80–1.40)	1.09 (0.80–1.47)
Severe wheeze past year	0.97 (0.72–1.31)	1.04 (0.76–1.42)	1.08 (0.64–1.84)	1.13 (0.64–1.97)	1.24 (0.64–2.41)	1.00 (0.58–1.72)
Hay fever symptoms past year	1.08 (0.93–1.25)	1.02 (0.86–1.21)	1.32 (0.99–1.75)	1.24 (0.90–1.70)	0.94 (0.71–1.25)	0.88 (0.64–1.21)
Flexural eczema symptoms past year	1.10 (0.82–1.47)	1.08 (0.83–1.42)	1.14 (0.73–1.80)	1.10 (0.65–1.85)	1.07 (0.76–1.53)	0.97 (0.68–1.38)
Severe flexural eczema symptoms past year	1.29 (0.92–1.81)	1.26 (0.87–1.83)	1.89 (0.95–3.75)	1.71 (0.54–5.41)	1.16 (0.65–2.09)	1.19 (0.63–2.25)
Flexural eczema on skin examination	1.08 (0.74–1.58)	0.95 (0.63–1.43)	1.98 (0.76–5.15)	1.53 (0.59–3.94)	1.15 (0.63–2.12)	1.04 (0.56–1.94)
Skin prick test positivity	1.01 (0.87–1.17)	0.97 (0.83–1.14)	–	–	–	–
BCG vaccination >1 yr‡						
Wheeze past year	1.17 (0.95–1.46)	1.08 (0.85–1.37)	1.37 (0.94–2.00)	1.07 (0.69–1.65)	**1.37 (1.00–1.87)**	1.30 (0.92–1.85)
Severe wheeze past year	1.53 (1.05–2.22)	1.33 (0.89–1.99)	**2.06 (1.14–3.71)**	1.61 (0.82–3.15)	2.01 (0.99–4.10)	1.54 (0.65–3.64)
Hay fever symptoms past year	0.91 (0.75–1.09)	0.93 (0.75–1.15)	0.89 (0.62–1.27)	0.81 (0.55–1.20)	1.02 (0.75–1.40)	1.04 (0.74–1.47)
Flexural eczema symptoms past year	1.01 (0.79–1.29)	1.04 (0.80–1.35)	0.88 (0.51–1.52)	0.92 (0.51–1.67)	1.06 (0.77–1.47)	1.10 (0.78–1.56)
Severe flexural eczema symptoms past year	1.09 (0.72–1.65)	1.16 (0.74–1.82)	1.32 (0.38–4.56)	1.81 (0.56–5.80)	1.44 (0.81–2.55)	1.41 (0.77–2.58)
Flexural eczema on skin examination	**1.77 (1.10–2.83)**	**1.82 (1.14–2.91)**	1.40 (0.56–3.45)	1.16 (0.50–2.68)	**2.76 (1.57–4.84)**	**2.94 (1.61–5.37)**
Skin prick test positivity	1.06 (0.90–1.25)	1.14 (0.87–1.50)	–	–	–	–
Past TB disease‡						
Wheeze past year	**2.24 (1.56–3.21)**	**2.27 (1.52–3.41)**	2.08 (0.92–4.72)	2.57 (0.97–6.82)	**2.63 (1.62–4.28)**	**2.65 (1.57–4.49)**
Severe wheeze past year	**3.25 (1.85–5.73)**	**4.02 (2.17–7.47)**	2.90 (0.53–15.75)	4.98 (0.94–26.46)	**4.42 (1.96–9.97)**	**3.76 (1.22–11.02)**
Hay fever symptoms past year	**2.46 (1.65–3.66)**	**2.23 (1.22–4.09)**	1.41 (0.57–3.45)	1.24 (0.36–4.32)	**4.04 (2.52–6.46)**	**4.38 (2.51–7.65)**
Flexural eczema symptoms past year	**2.91 (1.91–4.44)**	**3.21 (2.01–5.12)**	3.02 (0.60–15.14)	2.88 (0.51–16.27)	**3.47 (2.12–5.67)**	**4.02 (2.35–6.86)**
Severe flexural eczema symptoms past year	**4.47 (2.09–9.59)**	**6.31 (2.19–18.17)**	No centers left in analysis	No centers left in analysis	**4.75 (2.11–10.71)**	**5.98 (2.38–15.03)**
Flexural eczema on skin examination	**4.25 (1.89–9.59)**	**4.04 (1.71–9.56)**	**6.21 (1.14–33.91)**	**6.75 (1.06–42.80)**	**6.02 (2.17–16.71)**	**6.88 (2.35–20.12)**
Skin prick test positivity	1.16 (0.81–1.65)	1.32 (0.87–2.02)	–	–	–	–

*There was no significant interaction between past TB/BCG vaccination and skin prick test positivity on allergy outcomes (except for hay fever symptoms and TB), rendering stratification by atopic status largely unnecessary. †ORs were adjusted for age, sex, bedroom sharing (as a marker of socio-economic status and crowding), and number of siblings. ‡The TB/BCG vaccination–related risk estimates were additionally adjusted for either BCG vaccination or TB.

Finnish National TB Registry aged 20 yr or younger. There was an equal number of age- and sex-matched controls taken from the Population Registry of the Social Insurance Institution in Finland (33). Participants were followed for a mean of 30 yr. The paper's main focus was asthma (diagnosis purely based on the use of asthma medication). Other allergic diseases were not separately reported, and no distinction between atopic and non-atopic asthma was made. This is an important omission, as it is becoming increasingly clear that atopic and non-atopic asthma represent two distinct phenotypes. While we stratified our sample by allergic sensitization, there was no suggestion that the effect of BCG vaccination and TB was significantly different in sensitized vs. non-atopic individuals.

Apart from skin prick testing, a clear strength of our study is that ISAAC Phase Two provides a very large population-based data set, and lack of statistical power is therefore not a likely explanation for the absence of a protective effect of BCG vaccination and TB on allergic disease outcomes. ISAAC Phase Two uses standardized validated methods in all study centers and rigid quality control for ascertaining the physical signs of flexural eczema and determination of skin sensitization. This ensures direct comparability of results between centers and allows statistical pooling of risk estimates across study populations.

A disadvantage of our data set is the lack of objective data related to the exposures of interest. For instance, the ISAAC Phase Two field protocol did not include physical examination for a BCG scar. While our question about past TB is likely to have captured significant clinical disease, much commoner subclinical cases (latent TB infection) would have occurred unnoticed. Performing tuberculin skin tests or interferon-gamma release assays was not feasible given the substantial size of this study.

As with any other cross-sectional study, there are also a number of unavoidable design-related shortcomings. Information on exposures and questionnaire-derived outcomes was gathered retrospectively, relying on parental recall. It is possible that parents of a child with respiratory allergy might have been more likely to incorrectly attribute respiratory symptoms in early life to TB or that parents of children with asthma, hay fever, or eczema were more likely to remember or think that their child had had TB, which might account for some of the positive associations seen, in particular with wheeze. However, this would not explain the positive and strong association with flexural eczema on skin examination. Non-differential inaccurate recall can also not explain the positive associations found in this study, but if present could imply that the true associations between TB, BCG, and allergic diseases are even stronger.

It is worth considering whether clinical, rather than the much commoner latent mycobacterial infection, could promote allergic tissue inflammation or *vice versa*. As discussed above, the argument for a protective effect of immune responses generated against both the BCG vaccine and *M. tuberculosis* has centered around the over-expression of Th1 cells and their cytokines and the potential long-lasting effect this might have, steering the immune system away from Th2-driven tissue inflammation, such as asthma or eczema. There is certainly animal research to suggest that the BCG vaccine is able to suppress allergic tissue inflammation (27–29). However, the adaptive immunity to TB appears more complex and not fully understood, as it also involves Th2 and Th17 cells, as well as modulation through regulatory T cells (42). While regulatory T cells mainly produce anti-inflammatory cytokines, such as IL-10 and transforming growth factor-beta, Th2 and Th17 cell over-expression is also involved in the patho-etiology of asthma, hay fever, and eczema, potentially providing an explanation why past TB disease could increase the risk and severity of allergic diseases. Equally, allergic tissue inflammation might make established TB worse or render individuals more susceptible to infection.

As this was a cross-sectional study, we were not able to examine the temporal relationship between TB and allergic disease and further longitudinal studies are required. For instance, it would be important to examine the impact of perinatal mycobacterial exposure on allergic disease risk in later life, as there is evidence for a protective effect of helminth parasite infection during pregnancy on the development of eczema in the offspring (43–45).

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Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix

The ISAAC Phase Two Study Group consists of: ISAAC Phase Two Coordinating and Data Centre (Institute of Epidemiology, University of Ulm, Germany): G. Büchele, J. Genuneit, A. Kleiner, G. Nagel, G. Weinmayr.

Principal Investigators and Scientific Team

Tirana, Albania: A. Priftanji, A. Shkurti, J. Simenati, E. Grabocka, K. Shyti, S. Agolli, A. Gurakuqi. *Uruguaiana, Brazil*: R.T. Stein, M. Urrutia de Pereira, M.H. Jones, P.M. Pitrez. *Pichincha province, Ecuador*: P.J Cooper, M. Chico. *Bejing, China*: Y.Z. Chen. *Guangzhou, China:* N.S. Zhong. *HongKong, China:* C. Lai, G. Wong. *Tallinn, Estland:* M.-A. Riikjärv, T. Annus. *Créteil, France:* I. Annesi-Maesano. *Tbilisi, Georgia:* M. Gotua, M. Rukhadze, T. Abramidze, I. Kvachadze, L. Karsanidze, M. Kiladze, N. Dolidze. *Dresden, Germany*: W. Leupold, U. Keil, E. von Mutius, S.K. Weiland (deceased). *Munich, Germany*: E. von Mutius, U. Keil, S. Weiland (deceased). *Kintampo, Ghana*: P.Arthur (deceased), E. Addo-Yobo. *Athens, Greece:* C. Gratziou, C. Priftis, A. Papadopoulou, C. Katsardis. *Thessaloniki, Greece:* J. Tsanakas, E. Hatziagorou, F. Kirvassilis. *Reykjavik, Iceland*: M. Clausen. *Mumbai, India*: J.R. Shah, R.S. Mathur, R.P. Khubchandani, S. Mantri. *Rome, Italy*: F. Forastiere, R. Di Domenicantonio, M. De Sario, S. Sammarro, R. Pistelli, M.G. Serra, G. Corbo, C.A. Perucci. *Riga, Latvia:* V. Svabe, D. Sebre, G. Casno, I. Novikova, L. Bagrade. *Utrecht, the Netherlands*: B. Brunekreef, D. Schram, G. Doekes, P.H.N. Jansen-van Vliet, N.A.H. Janssen, F.J.H. Aarts, G. de Meer. *Hawkes Bay, New Zealand*: J. Crane, K. Wickens, D. Barry. *Tromsø, Norway*: W. Nystad, R. Bolle, E. Lund. *Ramallah, Palestine*: N. El-Sharif, B. Nemery, F. Barghuthy, S. Abu Huij, M. Qlebo. *Almeria, Spain*: J. Batlles Garrido, T. Rubi Ruiz, A. Bonillo Perales,Y. Gonzalez Jiménez, J. Aguirre Rodriguez, J. Momblan de Cabo, A. Losilla Maldonado, M. Daza Torres. *Cartagena, Spain*: L. Garcia-Marcos, A. Martinez Torres, J.J. Guillén Pérez, A. Piñana López, S. Castejon Robles. *Madrid, Spain*: G. Garcia Hernandez, A. Martinez Gimeno, A.L. Moro Rodríguez, C. Luna Paredes, I. Gonzalez Gil. *Valencia, Spain:* M.M. Morales Suarez-Varela, A. Llopis González, A. Escribano Montaner, M. Tallon Guerola. *Linköping, Sweden:* L. Bråbäck, M. Kjellman, L. Nilsson, X-M. Mai. *Östersund, Sweden:* L. Bråbäck, A. Sandin. *Ankara, Turkey*: Y. Saraçlar, S. Kuyucu, A. Tuncer, C. Saçkesen, V. Sumbuloğlu, P. Geyik, C. Kocabaş. *West Sussex, UK*: D. Strachan, B. Kaur.

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