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Mycobacterium tuberculosis infection may protect against allergy in a tuberculosis endemic area

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Clinical and Experimental Allergy

Summary

Background Epidemiological studies have shown an inverse relation of mycobacterial infection and the frequency of allergic diseases and asthma. Recent evidence suggests that allergic inflammation may be inhibited in the presence of chronic and persistent infections, such as that by *Mycobacterium tuberculosis* (MTB). The relation of tuberculin skin test (TST) size, an accepted marker of MTB infection and the frequency of allergic disease symptoms has not been reported from an area where MTB infection is endemic.

Objective To investigate the association of TST and allergic disease symptoms, in children living in a tuberculosis (TB) endemic area.

Methods In this cross-sectional study, 841 children aged 6–14 years from randomly selected household addresses in two poor communities of Cape Town, South Africa, were investigated with TST and standardized International Study on Asthma and Allergies in Childhood-based questionnaire on allergic disease symptoms.

Results Children with positive TST (≥ 10 mm) were significantly less likely to have allergic disease symptoms, in particular allergic rhinitis (AR) (adjusted odds ratio 0.43; 95% confidence interval 0.24–0.79) than those with negative TST. This association remained significant after adjusting for possible confounders and correcting for the effect of clustering (> 1 child per household address) in the sample. There was a significant inverse linear trend in the relation of TST size in millimetre and the frequency of allergic disease symptoms, in particular AR ($P < 0.001$).

Conclusions These results of inverse association of strong TST reaction and allergic disease symptoms in children from a TB endemic area are in support of the hypotheses that allergic inflammation may be inhibited by chronic infections, such as MTB.

Keywords allergic disease symptoms, childhood, inverse association, *mycobacterium tuberculosis* infection, tuberculin skin test

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Introduction

The immune response against *Mycobacterium tuberculosis* (MTB) has potential protective effect on the development of atopic disease and asthma [1, 2]. This is of particular relevance given the interest in the use of mycobacterial products as a potential vaccine against atopic disease. MTB infection induces a strong T-helper type 1 (Th1) immune response, with production of IFN- γ [3, 4]. The expression of Th2 skewed immunity against antigens

resulting in the production of cytokines that promote IgE production and eosinophilia is recognized as the primary cause of allergic inflammation in atopic individuals [5].

An important marker of Th1-mediated immunity is the development of delayed-type hypersensitivity (DTH), which can be evaluated by the tuberculin skin test (TST) [1, 6]. TST reactivity becomes apparent in 3–6 weeks after initial MTB infection and may remain positive for the lifetime of the individual [7]. The size of TST induration has been directly correlated with serum levels of IFN- γ ,

implying that a large TST size may reflect strong Th1 immunity [6].

Decline in infection with mycobacteria may be an underlying factor in the rising prevalence of allergic diseases in developed countries [1, 2]. Although some research groups have reported an inverse association of a positive TST and atopic disease, the linear relationship between the size of TST and allergic disease symptoms has not been investigated. In addition most previous studies were carried out in populations with low incidence of MTB infection [2, 8, 9]. It is not clear how TST reactivity and tuberculosis (TB) impact on the development of atopy in developing countries, where MTB infection is endemic and allergy common. This study was conducted in a third-world community with a very high incidence of MTB infection, where allergic disease symptoms are also common [10–13]. We tested the association of TST reactivity or size of TST and the frequency of allergic disease symptoms in the paediatric population.

Methods

Study area

The study area is an established epidemiological field-site comprising of two urban communities in metropolitan Cape Town, South Africa, with a population of 36 334 in 2001, predominantly of mixed ethnicity (previously categorized as 'coloured') [10]. The population density is high (average of 6–14 persons per household). The people live in poor socioeconomic conditions, although all households have running water and electricity. The TB notification rate was 341 per 100 000 for new smear-positive TB and 612 per 100 000 for bacteriological confirmed TB in 2002. Childhood TB cases comprise up to 39% of total TB case load [11]. The prevalence of asthma in children in Cape Town is 13.3%, allergic rhinoconjunctivitis 16% and eczema 9% [13]. The vaccination policy in the area requires all children to receive a single dose of *M. bovis* BCG immunization (Tokyo BCG strain) during the first week of life.

Between July and December 2002 a 15% sample of household addresses was randomly selected. Trained community workers enumerated the people at each address and children aged 6–14 years were invited to participate in the study. Written informed consent for each child was obtained from a parent or legal guardian before enrolment in the study.

A TST was performed, an allergy questionnaire completed and the presence (or absence) of a BCG scar recorded for each child. Children with known immune compromising diseases or active symptomatic TB were excluded. Children less than 6 years of age were not included in order to reduce diagnostic bias, in particular the problem of transient wheeze because of recurrent respiratory tract viral infections in this age category. The

proportion of HIV-1-infected persons in the area is among the lowest in South Africa [12]. However, children with questionnaire-reported positive HIV test were excluded, because of the possible effect on T cell immunity.

Parents completed a questionnaire for each child, under supervision of a trained community worker. Questions on allergic disease symptoms were based on a standardized, validated Phase-I International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire translated into the local language (Afrikaans). Questions were asked on previous and recent (≤ 12 months) symptoms of asthma, allergic rhinitis (AR) and eczema. Other questions were on neonatal BCG immunization, previous TB disease, parental allergic history, number of siblings, environmental tobacco smoke (ETS) exposure in the household, maternal education and household income.

TST was carried out by experienced research nurses by administering two tuberculin units of purified protein derivative (PPD) RT 23 (Statens, Serum Institut, Copenhagen, Denmark) intradermally on the volar aspect of the left arm. The largest transverse diameter of induration was recorded after 2–3 days. Based on the American Thoracic Society guidelines, a positive TST was defined as an induration of 10 mm or more [14].

Children with symptoms and/or chest radiograph suggestive of active TB disease were referred for further diagnosis and treatment in accordance with the National TB programme. They were excluded from the analysis.

Definitions

AR, asthma and eczema refer to questionnaire-reported symptoms. 'Any allergic symptom' in this paper refers to the presence of any reported allergic disease symptom (AR, asthma or eczema).

Statistical analysis

Univariate and linear-trend analyses of the relation of TST reactivity and allergic disease symptoms were performed using the χ^2 -test (SPSS version 11.0). Regression analyses were performed using a random-effects logistic regression (LR) model (STATA 8.0). In this model allergic disease symptoms were used as the dependent variable and TST reactivity as the independent variable, and correction was made for potential confounders: demographic (age and sex) genetic (parental allergic history), socioeconomic variables (household income and number of siblings) and ETS exposure in the household. A total of 506 household addresses were included in the study, with an average of 1.6 children per household. Each child was coded and linked to the specific household. With the random-effects LR model statistical correction was made for the fact that more than one child came from the same household (clustering).

The study was approved by the Ethics Review Board of the Faculty of Health Sciences of Stellenbosch University (2002/042).

Results

Of 978 enumerated children 6–14 years of age, a TST and questionnaire were completed in 841 (86%) children, which form the study population. The median age was 10.3 years (interquartile range (IQR) 8.2–12.5) and 51% were male. Four children identified with active TB disease were excluded from the analyses. None of the children reported positive test result nor had symptoms suggestive of HIV disease.

The total number of children with positive TST (≥ 10 mm) was 327 (38.9%) and negative TST (< 10 mm) 514 (61.1%). There was no measurable TST induration (TST = 0 mm) in 491 (58.4%) children. In 350 children (41.6%) with a measurable induration, the TST sizes were as follows: 1–4 mm in five (1.4%), 5–9 mm in 18 (5.1%), 10–14 mm in 62 (17.7%) and ≥ 15 mm in 265 (75.8%) children. As shown in Fig. 1 the TST distribution in the children was unimodal, with a median TST size of 17.6 mm (IQR 15.0–20.2) in those with TST induration. Of all children irrespective of TST reaction, the median TST size did not differ between children with allergic disease symptoms (median TST 0.0 mm; range 0.0–27.0) and those without (0.0 mm; range 0.0–30.5), of those with any TST reaction ≥ 1 mm, the median TST size did not differ between children with allergic disease symptoms (17.1 mm; range 4.0–27.0) and those without (17.8 mm; 1.0–30.5) and of those with strong positive TST reaction ≥ 10 mm, the median TST size also did not differ between children with allergic disease symptoms (17.5 mm; range 10.0–27.0) and those without (18.0 mm; range 0–30.5). The prevalence's of reported allergic disease symptoms were asthma in 101 (12%) children, AR in 98 (11.7%) and eczema in 76 (9%).

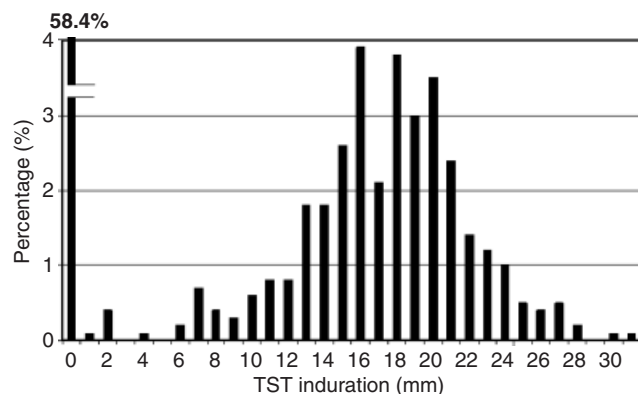


Fig. 1. Frequency distribution of tuberculin skin test (TST) reaction in children aged 6–14 years after 2 TU of *Mycobacterium tuberculosis* PPD RT 23 (N = 841).

The prevalence of allergic disease symptoms did not differ between children who received neonatal BCG immunization or with BCG scar and those without.

Table 1 show the baseline characteristics of children with positive and negative TST. Children with positive TST were older (10.9 years), were more likely to be female, had higher frequency of previous TB disease, and came from poorer households than those with negative TST. Children with positive TST did not differ from those with negative TST with respect to neonatal BCG immunization rate, BCG scar, parental allergic history and number of siblings or maternal education.

As shown in Fig. 2, children with positive TST had lower frequency of AR and eczema than those with negative TST. As shown in Table 2, children with positive TST had significantly lower crude and adjusted risk of AR and eczema than those with negative TST. They also showed a trend to have lower risk of asthma.

To test for possible 'dose-response' effect, we evaluated the linear relation of different TST cut-off sizes (5, 10, 15 or 20 mm) and the frequency of allergic disease symptoms. The risk of AR decreased significantly with increasing TST cut-off size (from odds ratio (OR)_{adj} 0.53; 95% confidence interval (CI) 0.30–0.94 at 5 mm to OR_{adj} 0.33; 95% CI 0.10–1.00 at 20 mm), for asthma the risk decreased (OR_{adj} 0.76; 0.38–1.51 and OR_{adj} 0.31; 0.08–1.24, respectively), although not significantly and for eczema the risk increased with increasing TST cut-off size (OR_{adj} 0.48; 0.25–0.93 and OR_{adj} 0.99; 0.37–2.69, respectively). As illustrated in Fig. 3 there was a significant linear inverse association of TST size in millimetre and reported allergic disease symptoms in the children, particularly AR.

Discussion

In this community-based study from a TB endemic area, we found that children with positive TST had significantly lower risk of allergic disease symptoms, particularly AR, than those with negative TST. In addition, we observed a significant inverse linear association of the size of TST and both the frequency and risk of allergic disease symptoms, particularly AR. These results support previous findings in children [1]. Moreover, an inverse linear association of TST size and the frequency of allergic disease symptoms especially AR in children is being shown for the first time.

Recent evidence suggests that MTB infection, a strong Th1 stimulator, may inhibit Th2-associated allergic inflammation [1, 2]. The size of the TST has been correlated with the serum level of IFN- γ [6], implying that a large TST size reflects strong Th1 activity, which may antagonize Th2 activity [1]. The large median TST induration and typical pattern of the TST distribution in the children implies more of natural MTB infection than of BCG or non-tuberculous mycobacteria infection, which generally provoke a weaker TST induration [7, 14]. The demonstration of an inverse

Table 1. Baseline characteristics of children with negative (< 10 mm) and positive (≥ 10 mm) TST ($N = 841$)

	Total	Negative TST (< 10 mm)	Positive TST (≥ 10 mm)	Crude OR (95% CI)	Adjusted OR (95% CI)
Subjects n (%)	841 (100)	514 (61.1)	327 (38.9)		
Age (years)					
6–9	385	275 (71.4)	128 (33.2)	1.0	1.0
10–14	456	257 (56.4)	199 (43.6)	1.56 (1.17–2.06)	1.62 (1.09–2.42)
Gender					
Male	428	274 (64.0)	154 (36.0)	1.0	1.0
Female	413	240 (58.1)	173 (41.9)	1.28 (0.97–1.69)	1.50 (1.01–2.23)
BCG immunization					
No	36	24 (66.7)	12 (33.3)	1.0	1.0
Yes	805	490 (60.9)	315 (39.1)	1.29 (0.63–2.61)	1.03 (0.39–2.75)
BCG-scar*					
No	289	173 (59.9)	116 (40.1)	1.0	1.0
Yes	476	292 (61.3)	184 (38.7)	0.94 (0.70–1.27)	1.03 (0.68–1.58)
Previous TB disease*					
No	743	480 (64.6)	263 (35.7)	1.0	1.0
Yes	96	33 (34.4)	63 (65.6)	3.48 (2.23–5.45)	4.22 (2.25–7.92)
Parental allergic history					
No	525	311 (59.2)	214 (40.8)	1.0	1.0
Yes	316	203 (64.2)	113 (35.8)	0.81 (0.60–1.08)	0.69 (0.43–1.12)
Number of siblings*					
< 3	583	352 (60.4)	231 (39.6)	1.0	1.0
≥ 3	231	142 (61.5)	89 (38.5)	0.96 (0.70–1.31)	0.76 (0.47–1.22)
Maternal education (years)*					
< 7	435	243 (55.8)	192 (44.2)	1.0	1.0
≥ 7	392	261 (66.6)	131 (33.4)	0.64 (0.48–0.84)	0.68 (0.43–1.08)
Average household income (SAR) [†]					
< 800	514	362 (70.4)	152 (29.6)	1.0	1.0
≥ 800	327	273 (83.5)	54 (16.5)	0.47 (0.33–0.67)	0.42 (0.24–0.73)

Adjusted OR were calculated with the random effects logistic regression model (STATA 8.0) using TST reactivity as the dependent variable and the other variables in the table as the independent variable. In addition, correction was made for clustering (> 1 child per household) in the sampling unit (see 'Methods').

*Not all data were available in all children. [†]Average income of 800 SAR was used to differentiate low income households because it is the official minimum monthly salary in the country (1 US dollar = 6.5 SAR).

TST, tuberculin skin test; OR, odds ratio; CI, confidence interval; TB, tuberculosis; SAR, South African Rand.

linear association of the size of TST and allergic disease symptoms suggests a 'dose-response' effect, which may be evident in the presence of strong Th1 activity, caused by MTB [15]. This 'dose-response' association suggests causal relationship, according to the epidemiological criteria of causal relation proposed by Liu and Murphy [16]. In the light of novel explanatory models of the hygiene hypothesis it has been postulated that expression of allergic inflammation may be inhibited in persons exposed to chronic infections such as that caused by MTB, through the stimulation of regulatory T cells (Tregs) and anti-inflammatory networks [15, 17, 18]. In animal models, Tregs, induced by killed mycobacteria inhibited allergen-induced airway inflammation, via the anti-inflammatory cytokines, IL-10 and TGF- β [18]. Some researchers have suggested that decreased or defective cell-mediated immunity in atopic children leading to impaired DTH reactivity, may explain the inverse association of TST size and allergic

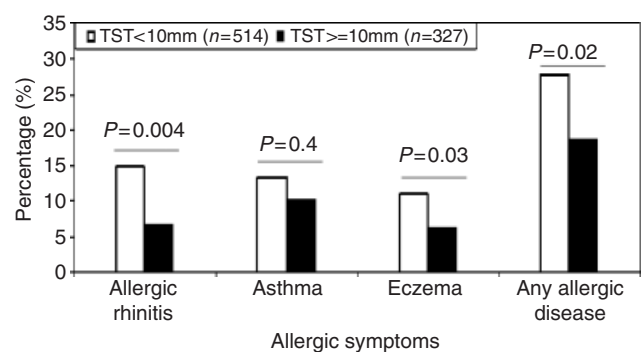


Fig. 2. Frequency of allergic disease symptoms in children with positive (≥ 10 mm) and negative (< 10 mm) tuberculin skin test reaction ($N = 841$) (P -values after adjusting for possible confounding variables and clustering in the sampling unit).

disease [8, 19]. We could not exclude that children with allergic disease symptoms or predisposed to allergic disease,

Table 2. Crude and adjusted risk of different allergic symptoms in children with positive (≥ 10 mm) and negative (< 10 mm) tuberculin skin test (TST), together with confounding variables included

Variable	Allergic rhinitis			Asthma			Eczema		
	n/N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	n/N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	n/N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
TST size (mm)									
< 10	76/514 (14.8)	1.0	1.0	68/511 (13.3)	1.0	1.0	56/510 (11.0)	1.0	1.0
≥ 10	22/327 (6.7)	0.42 (0.25–0.68)	0.43 (0.24–0.79)	33/325 (10.2)	0.74 (0.47–1.15)	0.72 (0.35–1.45)	20/324 (6.2)	0.53 (0.31–0.91)	0.50 (0.26–0.99)
Age (years)									
6–9	39/384 (9.9)	1.0	1.0	56/383 (14.6)	1.0	1.0	36/383 (9.4)	1.0	1.0
10–14	60/456 (13.2)	1.38 (0.90–2.12)	1.80 (1.06–3.08)	45/453 (9.9)	0.64 (0.42–0.98)	0.52 (0.27–0.98)	40/451 (8.9)	0.94 (0.59–1.51)	1.00 (0.59–1.61)
Gender									
Male	54/427 (12.6)	1.0	1.0	61/425 (14.4)	1.0	1.0	36/425 (8.5)	1.0	1.0
Female	45/413 (10.7)	0.82 (0.54–1.26)	0.87 (0.52–1.47)	40/411 (9.7)	0.64 (0.42–0.98)	0.52 (0.26–1.01)	40/409 (9.8)	1.17 (0.73–1.88)	1.35 (0.83–2.76)
Parental allergic history									
No	48/613 (7.8)	1.0	1.0	55/611 (9.0)	1.0	1.0	44/608 (7.2)	1.0	1.0
Yes	50/227 (22.0)	3.32 (2.16–5.11)	3.57 (2.01–6.34)	46/225 (20.4)	2.60 (1.70–3.98)	4.16 (1.84–9.41)	32/226 (14.2)	2.11 (1.30–3.43)	2.58 (1.34–4.96)
Average household income (SAR)									
< 800	56/634 (8.8)	1.0	1.0	71/631 (11.3)	1.0	1.0	57/629 (9.1)	1.0	1.0
≥ 800	42/206 (20.4)	2.64 (1.70–4.01)	2.21 (1.20–4.07)	30/205 (14.6)	1.35 (0.85–2.14)	1.33 (0.57–3.08)	19/205 (9.3)	1.03 (0.59–1.77)	0.75 (0.43–1.56)
Number of siblings									
< 3	79/582 (13.6)	1.0	1.0	77/579 (13.3)	1.0	1.0	54/578 (9.3)	1.0	1.0
≥ 3	17/231 (7.4)	0.51 (0.29–0.88)	0.53 (0.27–1.06)	18/230 (7.8)	0.55 (0.32–0.95)	0.56 (0.24–1.29)	18/230 (7.8)	0.82 (0.47–1.44)	0.74 (0.36–1.53)
ETS exposure in the household									
No	44/337 (13.1)	1.0	1.0	34/336 (10.1)	1.0	1.0	33/334 (9.9)	1.0	1.0
Yes	53/499 (10.6)	0.79 (0.52–1.21)	0.96 (0.55–1.67)	66/496 (13.3)	1.36 (0.88–2.12)	1.72 (0.80–3.69)	42/496 (8.5)	0.84 (0.52–1.36)	0.82 (0.43–1.56)

*Adjusted odds ratio (OR): calculated with the random-effects logistic regression (LR) model, using allergic symptom as the dependent variable and TST size together with all the other possible confounding variables included in the table as independent variable. In addition, correction was made for clustering (> 1 child per household) in the sampling unit (see 'Methods'). SAR, South African Rand (1 US Dollar = 6.5 SAR). Average income of 800 SAR was used to differentiate low-income households because it is the official minimum monthly salary in the country. ETS, environmental tobacco smoke exposure is defined as questionnaire-reported exposure to tobacco smoke at home by an adult living in the same household as the child.

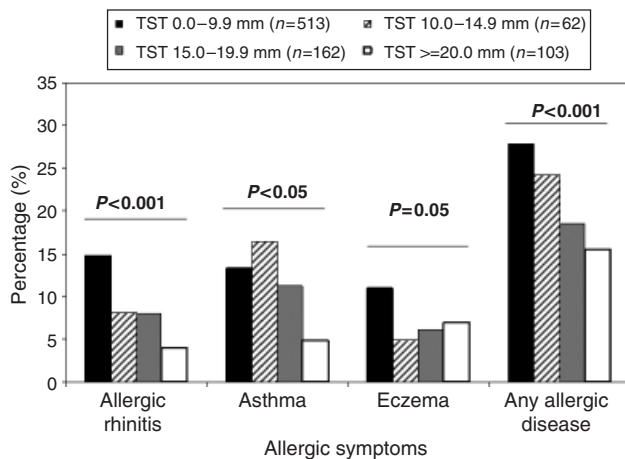


Fig. 3. Linear inverse relation of tuberculin skin test reaction size and frequency of allergic disease symptoms in 841 children (P -value for trend).

tend to mount less intense Th1-type responses to MTB infection. However, the evidence against this argument in our study is that although there was a significant difference in the prevalence of allergic disease symptoms in children with positive TST compared with those with negative TST, the median TST size did not differ between children with and without allergic disease symptoms, irrespective of the TST size. This seems to indicate that both these groups mount a comparable and adequate Th1 response. Although there was a trend towards reduced risk of positive TST reactivity in children of allergic parents, this difference was not statistically significant.

In our study the strongest effect was observed in children with AR. This is in support of previous findings in Japanese children and may be explained by the fact that AR has a stronger correlation with atopy, than asthma or eczema [1, 20, 21]. Epidemiological differences have been described between different allergic diseases [20]. For instance, one review showed that only 25–63% of asthmatic symptoms in children might be of atopic origin [21]. The weaker inverse linear association of TST size and eczema may partly be explained by the high prevalence of other skin disorders in poor children, such as non-atopic dermatitis, or infections with *Sarcoptes scabiei*, which healthworkers may confuse with eczema. Alternatively, eczema may have a different immune mechanism as suggested by its more complex natural history [22].

Although it has been reported that BCG immunization in the first week of life may be protective against the development of atopic sensitization, the same results could not be reproduced in Sweden or Greenland [23–25]. In the present study we did not find less allergic disease symptoms in children who received BCG vaccination in the first week of life. The fact that TST reactivity was not measured in all the previous studies makes it difficult to compare results. The difference in observation

may also partly be explained by the heterogeneity in the efficacy of BCG immunization observed in different populations [26]. Moreover, different studies have shown the BCG effect in children to wane within 5 years of administration [27, 28], which may partly explain why no BCG effect on allergic symptom prevalence was observed in our study population. This seems to imply that BCG vaccination, in some settings, may not be a good alternative for mycobacterium-based immunization in the prevention of allergic disease.

The discrepancy found between neonatal BCG immunization and the presence of BCG-scar confirms previous observations that not all children with documented BCG immunization develop a scar [27]. That children with positive TST were slightly older is a reflection of the high annual risk of TB infection in the communities. The lower household income in the positive TST group supports previous findings in the area that childhood TB correlates inversely with household income [11]. However, this variable did not influence the association of TST reactivity and allergic disease symptoms in the regression analysis model. That children from households with higher average income had a higher frequency of some allergic disease symptoms is in support of epidemiological reports from developed countries, which found higher prevalence of allergic disease symptoms among children from more socio-economically affluent families [20].

The large number of children with positive TST in this study area made it possible to investigate linear relations. Limitations of this study, next to those inherent to its cross-sectional design, are the use of questionnaire-based definition of allergic disease symptoms and the lack of evaluation of the possible confounding effect of co-infection with intestinal parasites. Limitation of questionnaire-based definition of allergic disease symptom was reduced by using the standardized validated ISAAC questionnaire. A more objective measure of atopy, such as skin prick testing would have further strengthened the study design.

In conclusion, our data show an inverse association of strong TST reaction and allergic disease symptoms, especially AR, in children living in a TB endemic area. This data is in support of new insights in the explanation of the hygiene hypothesis, of possible inhibition of allergic inflammation in the presence of chronic and persistent infections, such as MTB, probably through the stimulation of Tregs and production of anti-inflammatory networks. More detailed studies in similar settings are needed to confirm the present findings, considering the possibility of the future use of mycobacterial products as a potential vaccine against atopic disease.

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Competing interest statement of the authors:

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References

- Shirakawa T, Enomoto T, Shimazu S, Hopkin J. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; **275**:77–9.
- Von Mutius E, Pearce N, Beasley R *et al*. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis and atopic dermatitis. *Thorax* 2000; **55**:449–53.
- Cooper A, Roberts A, Rhoades E, Callahan J, Getzy D, Orme I. The role of interleukin-12 in acquired immunity to *Mycobacterium tuberculosis* infection. *Immunology* 1995; **84**:423–32.
- Orme I, Andersen P, Boom W. T cell response to *Mycobacterium tuberculosis*. *J Infect Dis* 1993; **167**:1481–97.
- Romagnani S. Regulation of the development of type 2 T-cells in allergy. *Curr Opin Immunol* 1994; **6**:838–46.
- Black GF, Fine PEM, Warndorff DK *et al*. Relationship between IFN- γ and skin test responsiveness to *Mycobacterium tuberculosis* PPD in healthy, non-BCG-vaccinated young adults in Northern Malawi. *Int J Tuberc Lung Dis* 2001; **7**:664–72.
- Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis* 2003; **3**:624–32.
- Strannegård I, Larsson L, Wennergren G, Strannegård Ö. Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria. *Allergy* 1998; **53**:249–54.
- Von Hertzen L, Klaukka T, Mattila H, Hahtela T. *Mycobacterium tuberculosis* infection and the subsequent development of asthma and allergic conditions. *J Allergy Clin Immunol* 1999; **104**:1211–4.
- Statistical Support and Informatics. Statistics South Africa: Western Cape. Census 2001, 2001.
- Van Rie A, Beyers N, Gie RP, Kunneke M, Zietsman L, Donald PR. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. *Arch Dis Child* 1999; **80**:433–7.
- Verver S, Warren RM, Munch Z *et al*. Proportion of tuberculosis transmission that takes place in a high-incidence area. *Lancet* 2004; **363**:212–4.
- ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **351**:1225–32.
- Committee of Infectious Disease. Screening for tuberculosis in infants and children. *Pediatrics* 1994; **93**:131–4.
- Matricardi PM, Yazdanbakhsh M. Mycobacteria and atopy, 6 years later: a fascinating, still unfinished, business. *Clin Exp Allergy* 2003; **33**:717–20.
- Liu AH, Murphy JR. Hygiene hypothesis: fact or fiction. *J Allergy Clin Immunol* 2003; **111**:471–8.
- Romagnani S. Immunologic influences on allergy and T_H1/T_H2 balance. *J Allergy Clin Immunol* 2004; **113**:395–400.
- Zuany-Amorim C, Sawicka E, Manlius C *et al*. Suppression of airway eosinophilia by killed *Mycobacterium vaccae*-induced allergen-specific regulatory T-cells. *Nat Med* 2002; **8**:625–9.
- Reinhold U, Wehrmann W, Kukel S, Kreysel H. Evidence that defective interferon-gamma production in atopic dermatitis patients is due to intrinsic abnormalities. *Clin Exp Immunol* 1990; **79**:374–9.
- Strachan DP. Family size, infection and atopy: the first decade of the “hygiene hypothesis”. *Thorax* 2000; **55** (Suppl. 1):S2–10.
- Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; **54**:268–72.
- Saarinien UM, Kajosaari M. Breastfeeding as prophylaxis against atopic diseases: prospective follow-up until 17 years old. *Lancet* 1995; **346**:1065–9.
- Aaby P, Shaheen SO, Heyes CB *et al*. Early BCG vaccination and the reduction in atopy in Guinea-Bissau. *Clin Exp Allergy* 1999; **30**:644–50.
- Alm J, Lilja G, Pershagen G, Scheynius A. Early BCG vaccination and development of atopy. *Lancet* 1997; **350**:400–3.
- Krause TG, Hviid A, Koch A *et al*. *JAMA* 2003; **289**:1012–5.
- Fine PEM. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; **346**:1339–45.
- Lienhardt C, Sillah J, Fielding K *et al*. Risk factors for tuberculosis infection in children with contact with infectious tuberculosis cases in The Gambia, West Africa. *Pediatrics* 2003; **111**:e608–14.
- Grüber C, Kulig M, Bergmann R, Guggenmoos-Holzmann I, Wahn Uthe MAS-90 Study Group. Delayed hypersensitivity to tuberculin, total immunoglobulin E, specific sensitization, and atopic manifestation in longitudinally followed early Bacille-Calmette-Guérin-vaccinated and nonvaccinated children. *Pediatrics* 2001; **107**:e36.