

Short communication

Absence of relationship between tuberculin reactivity and asthmatic symptoms, level of FEV₁ and bronchial hyperresponsiveness in BCG vaccinated young adults

Background: Some recent studies have suggested that bacillus Calmette-Guérin (BCG) vaccination or mycobacterial infection early in life is inversely related to asthma. We wondered if an increase in tuberculin reactivity was inversely related to commonly used indices of asthma in a population of young adults who were BCG vaccinated at age 14.

Methods: Men and women aged 20–44 years, randomly selected from the general population, were tuberculin tested with the epinephrine-Pirquet method with Norwegian-produced synthetic medium tuberculin ($n=588$). In addition they were interviewed using eight questions on asthma symptoms and medication. Lung function and bronchial responsiveness were also tested.

Results: Altogether 95% of those studied had been BCG vaccinated at age 14 ($n=558$). In the 386 subjects with complete examinations, there was no relationship between a positive tuberculin reaction (≥ 4 mm) and asthma symptoms or use of asthma medication. Furthermore we did not observe any relationship between a positive tuberculin reaction and the level of forced expiratory volume (FEV₁) or a positive bronchial responsiveness test, assessed as the percent of predicted of FEV₁ and PD₂₀ < 2 mg methacholine, respectively. In multiple logistic regression analyses neither respiratory symptoms, level of FEV₁, nor bronchial hyperresponsiveness were related to tuberculin reactivity after adjustment for age, gender and smoking habits.

Conclusions: In this young adult population who were BCG vaccinated at the age of 14 no significant relationship existed between tuberculin reactivity and asthmatic symptoms, level of FEV₁ or bronchial hyperresponsiveness. Our data does not support the hypothesis that BCG immunization is beneficial in reducing asthmatic symptoms and disease in young adults.

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Shirakawa et al. (1) reported an inverse association between tuberculin responses and atopic disorders in Japanese children suggesting that BCG immunization, subclinical exposure to *Mycobacterium tuberculosis* without clinical disease, or host characteristics may influence the lymphocyte balance with decreased atopy as a result. Sarinho et al. (2) found smaller BCG scars in asthmatics than in nonasthmatics in 4-year-old Brazilian children, BCG vaccinated as newborns. Von Mutius et al. (3) recently reported an inverse relationship between national tuberculosis rates (World Health Organisation) and the prevalence of asthmatic symptoms in subjects from Europe, the USA, Canada, Australia and New Zealand. An increase in tuberculosis notification rate by 25 per 100 000 inhabitants was associated with an absolute decrease in the prevalence

of 'wheeze ever' by 4.7%, even after adjusting for the gross national product (GNP) as a measure of level of affluence. For Finnish females who had tuberculosis before the age of 20, von Hertzen et al. (4) reported a significantly lower prevalence of persistent asthma 30 years later (3.7%) compared with controls matched by age and geography (8.3%).

A shift in the Th1/Th2 balance (5, 6, 7) with increase in atopic and related disease is hypothesized to be a result of decline in viral, bacterial or mycobacterial infections (3, 4) and might be counteracted by BCG immunization (1, 2). We studied whether an increase in tuberculin reactivity after BCG vaccination was inversely related to commonly used indices of asthma in a cross-sectional study of a young adult population vaccinated at age 14.

Material and methods

Study design and population

A random sample of 1200 men and women 20–44 years of age, living in the city of Bergen, was invited to participate in the Norwegian part of the European Community Respiratory Health Survey (ECRHS) (8, 9). Nine-hundred and three persons (75%) attended the clinical examination.

Interviewer-led questionnaire

The ECRHS modified version of the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire (9) was used. The interviews were performed by a well-trained nurse and included questions about respiratory symptoms during the last 12 months: namely: wheezing or whistling; breathlessness while wheezing; wheeze without cold; waking with chest tightness; woken by attacks of breathlessness or by attacks of cough; attacks of asthma; current asthma medication.

Lung function

Measurement of forced expiratory volume in one second (FEV₁) was obtained according to the protocol of the ECRHS (9). The European Community for Coal and Steel (ECCS) prediction equations were used (10).

Bronchial responsiveness testing

The ECRHS protocol was used, including methacholine challenge (11) to a maximal cumulative dose of 2 mg methacholine. The methacholine was delivered via a Mefar dosimeter (Mefar, Bovezzo, Italy), FEV₁ recorded 2 min after each inhalation and the test stopped when either a 20% fall in FEV₁ from baseline value had been achieved (positive test) or the final dose given. All respondents whose FEV₁ was at least 70% of predicted and was more than 1.5 L were invited to participate in the methacholine challenge test, unless contraindicated by heart disease, epilepsy, pregnancy, breastfeeding or using a beta-blocker. Subjects were advised to avoid smoking for 1 h, to avoid using β_2 -agonist or anticholinergic inhalers for 4 h, or oral medication with β_2 -agonists, theophylline, or antimuscarinic agents for 8 h before the test. Subjects who reported a respiratory tract infection were re-scheduled (11).

Tuberculin testing and BCG vaccination

The Norwegian reference method of the epinephrine-Pirquet tuberculin test (a modification of von Pirquet's skin scarification method) comprising Norwegian-produced synthetic medium tuberculin (SMT) with adrenaline (epinephrine) was used. The duplicate epinephrine-Pirquet test should be read within 48–72 h as the greatest value perpendicular to the scratch. The larger of the two epinephrine-Pirquet readings was used in this study. The criterion for a positive epinephrine-Pirquet tuberculin test is by convention ≥ 4 mm (12) and has been as reproducible as the Mantoux PPD test (12, 13, 14). Norway shifted from BCG Bergen strain to BCG Copenhagen strain in 1972. BCG vaccination usually takes place at age 14, administered to the pupils by the school-health nurse, usually with an attendance rate of 95–98%.

Statistical analyses

The relationship between a positive epinephrine-Pirquet tuberculin test (≥ 4 mm) and each of the seven respiratory symptoms, and current use of asthma medication, as well as a positive methacholine challenge test, was analysed by Fisher's exact test for two-by-two tables. The relationship between tuberculin reactivity (mm) and baseline FEV₁ was analysed by linear

regression analysis. For each symptom FEV₁ level was compared between those with the symptom and those without using the two-sample *t*-test assuming separate variances. Adjusted odds ratios (OR) and 95% confidence intervals for having a positive epinephrine-Pirquet tuberculin test were estimated by a multiple logistic regression analysis with respect to age, gender, smoking habits, respiratory symptoms, level of FEV₁, bronchial responsiveness and BCG strain. The statistical analyses were done with the statistical computer packages BMDP (BMDP Statistical Solutions, Crosses Green, Cork, Ireland) (15) and MINITAB (Minitab Inc., State College, PA, USA) (16).

Results

Altogether 95% of those tuberculin tested reported to be BCG vaccinated at age 14 ($n=558$). This was documented from records in 278 subjects in addition to the questionnaire data. Of those tuberculin tested and read ($n=588$), 386 subjects had complete data on asthma symptoms and medication, spirometry and methacholine testing of bronchial responsiveness. Their mean age was 34.2 years and 53.7% were men. They were comparable to the complementary group of those invited ($n=814$) with respect to gender ($P=0.50$), while the study subjects were 1.5 years older ($P<0.01$). The prevalence of respiratory symptoms ($P>0.05$) and smoking habits ($P=0.08$) did not differ between those studied ($n=386$) and the complementary group of those attending ($n=517$). Subjects in the complementary group had incomplete data of respiratory symptoms, FEV₁ level, bronchial responsiveness and tuberculin reactivity, and were not included in further analyses.

Table 1 shows that there was no significant relationship between a positive tuberculin test and asthma symptoms or use of asthma medication. No relationship ($P=0.76$) was found between the epinephrine-Pirquet reactivity (in mm) groups and the level of FEV₁ (in percent of predicted value) (Fig. 1). An almost horizontal regression line: $y=5.1209-0.00327 \times \text{FEV}_1\%$ was estimated ($r=-0.013$, $P=0.76$). Nor was a significant difference found in frequency of tuberculin positivity (≥ 4 mm) between those with and without bronchial hyperresponsiveness (Table 1).

We know from previous analyses that tuberculin reactivity is independently predicted by gender, age and smoking habits. We have therefore adjusted for these factors in a multiple logistic regression analysis (Table 2). No relationship persisted between tuberculin reactivity on the one hand, and asthma symptoms, number of symptoms, level of FEV₁ or bronchial hyperresponsiveness on the other. Finally, the BCG strain variable (Copenhagen strain vs. Bergen strain) was not an independent predictor for a positive tuberculin test ($P=0.29$) and was thus not included in the final model.

Table 1. Distribution of tuberculin reactivity in 386 young Norwegian adults according to asthmatic symptoms, medication and bronchial hyperresponsiveness

	Tuberculin negative (< 4 mm) $n=136$		Tuberculin positive (≥ 4 mm) $n=250$		P -value ¹
Respiratory symptoms and asthma medication	n	%	n	%	
No symptoms	113	83.1	201	80.4	0.85
Wheezing or whistling	45	33.1	81	32.4	1.00
Breathlessness while wheezing	25	18.4	42	16.8	0.78
Wheeze without cold	30	22.1	54	21.6	1.00
Waking with chest tightness	20	14.7	34	13.6	0.88
Woken by attack of breathlessness	10	7.4	22	8.8	0.70
Woken by attack of cough	46	33.8	80	32.0	0.83
Attacks of asthma ever	4	2.9	13	5.2	0.44
Current asthma medication	5	3.7	14	5.6	0.47
Reactors to bronchial methacholine challenge ²	24	17.6	37	14.8	0.47

¹Fisher's exact test (two-tailed).²Reactors are subjects with a $\geq 20\%$ in FEV₁ from pretest value after challenge with a maximum cumulative dose of methacholine of 2 mg.

Discussion

We observed no relationship between tuberculin reactivity and any asthma symptoms or asthma medication. Neither did we find any significant association between tuberculin reactivity and FEV₁ level, nor any association with bronchial hyperresponsiveness. The results were consistent in both the univariate and the multivariate analyses.

The mean ages and the proportion of males and females were comparable in the study group ($n=386$)

and the complementary group of those invited ($n=814$). The distribution of smoking habits in those studied did not differ from the rest of those attending ($n=517$). This indicates that those examined were fairly representative of the general population.

We have previously assessed the epinephrine-Pirquet tuberculin test with Norwegian-produced SMT tuberculin (12) and found it to be as reproducible as the Mantoux PPD test (13) and yielding around 10% less subjects with positive reactions compared to the

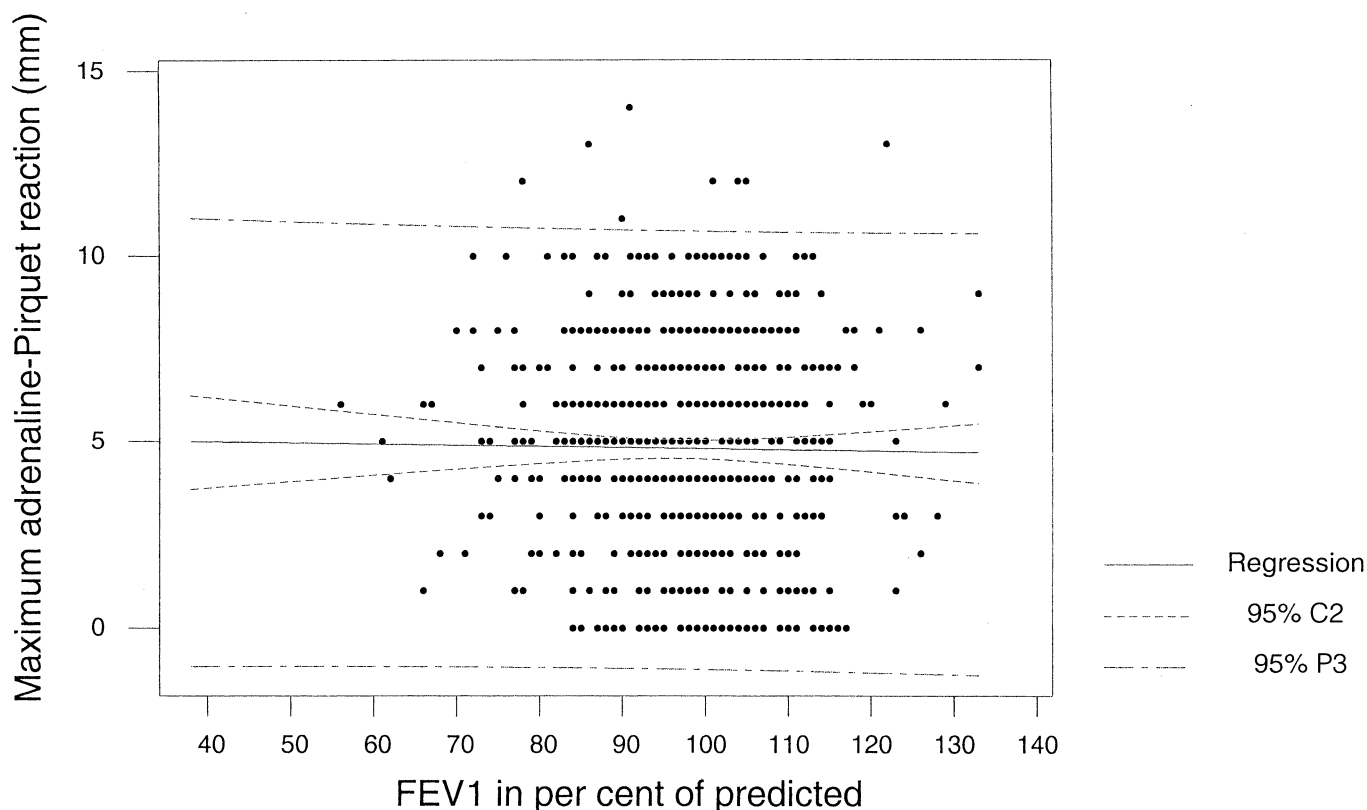


Figure 1. Distribution of epinephrine-Pirquet tuberculin reactions in mm in relation to level of FEV₁ as percent of predicted values (ECCS) in a young BCG-vaccinated Norwegian population ($n=386$).

Table 2. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for having a positive (≥ 4 mm) epinephrine-Pirquet tuberculin test with respiratory symptoms, lung function and bronchial responsiveness in 386 young Norwegian adults based on multiple logistic regression analysis

	<i>n</i>	OR	95% CI	<i>P</i> -value ¹
Age (years)				0.01
21–29	120	1.00		
30–39	158	2.32	1.40–3.84	
40–46	108	4.61	2.48–8.55	
Gender				0.02
Women	185	1.00		
Men	201	1.74	1.11–2.75	
Smoking status				0.06
Non-smoker	156	1.00		
Ex-smoker	78	1.62	0.88–2.99	
Smoker	152	1.79	1.07–2.98	
Respiratory symptoms				0.97
Per increase of one respiratory symptom ²	386	1.00	0.8–1.18	
FEV ₁				0.43
Per 10% loss of predicted	386	0.91	0.73–1.14	
Bronchial responsiveness by methacholine challenge ³				0.94
Non-reactors	333	1.00		
Reactors (<2 mg methacholine)	53	0.97	0.49–1.94	

¹Likelihood ratio test.²Minimum 0; Maximum 7.³Reactors are subjects with a $\geq 20\%$ fall in FEV₁ from pretest value after challenge with a maximum cumulative dose of methacholine of 2 mg.

Mantoux PPD RT23 2 TU (Statens Serum Institute (SSI), Copenhagen, Denmark) test (14). Furthermore, Norway shifted from BCG Bergen strain to BCG Copenhagen strain in January 1972. However, including this variable in the statistical analyses did not alter the relationship between tuberculin reactivity and indices of asthmatic disease in this study.

We found no relationship between tuberculin reactivity and asthma in this young adult population being BCG vaccinated at age 14. No other studies assessing this question have been found. However, there is data on the relationship between BCG vaccination and allergy and atopy, presenting conflicting results (1, 8, 17, 18, 19). A single BCG vaccination or a subclinical tuberculosis infection in childhood or adolescence may be too late, too weak and too short-lasting a stimulus of the cellular immune system to mount a lasting immune response as compared with an established tuberculosis infection. The tuberculin reactivity induced by BCG vaccination seems to wear off in the following 10–15 years, probably also related to the strain of BCG vaccine applied. Furthermore, we have found that tuberculin reactivity seems to be age-related, more so in men than in women and in tobacco smokers than in

nonsmokers (8). An inverse relationship between indices of asthma and tuberculosis disease was observed by von Mutius et al. (3) and von Hertzen et al. (4) in highly developed countries, while our study of tuberculin reactivity induced by BCG vaccination or subclinical tuberculosis infection does not show this relationship.

To assess the benefits of BCG vaccination on the development of atopic as well as asthmatic disorders in later life as an inverse relationship between increased tuberculin reactivity and asthmatic disease, prospective controlled trials from childhood onwards should be carried out.

This manuscript includes the revised EAACI nomenclature for allergy (20).

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