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Neonatal BCG has no effect on allergic sensitization and suspected food allergy until 13 months.

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Abstract

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Title: Neonatal BCG has no effect on allergic sensitization and suspected food allergy until 13 months.

Journal: Pediatr Allergy Immunol

Abstract:

Background: Vaccination with Bacillus Calmette-Guérin (BCG) is used in many countries as protection against tuberculosis. Studies have suggested that BCG may also have non-specific effects, reducing non-tuberculosis mortality, morbidity, and atopic manifestations. In this study we evaluated the effect of neonatal BCG vaccination on allergic sensitization and suspected food allergy at 13 months of age.

Methods: The Danish Calmette Study was conducted from 2012-2015 at three Danish hospitals. Within 7 days of birth, the 4262 newborns of 4184 included mothers were randomized 1:1 to BCG or to a no-intervention control group. Exclusion criteria were gestational age <32 weeks, birth weight <1000 g, known immunodeficiency, or no Danish-speaking parent. Follow-up information was collected through telephone interviews at 3 and 13 months of age. Subgroups of participants were offered blood sampling at 13 months of age.

Results:

By 13 months of age the parents and/or general practitioners of 5.6% (117/2089) of the children in the BCG group and 6.1% (126/2061) of the control group suspected food allergy, resulting in a risk ratio comparing BCG-vaccinated children with control children of 0.91 (95% CI 0.71 to 1.16).

Among 1370 blood samples, sensitization (Phadiatop Infant > 0.35 kUA/l) was found in 55/743 (7.4%) children in the BCG group and 50/627 (8.0%) of the control group (risk ratio 0.94 (0.65 to 1.36)).

Conclusion: In this randomized clinical trial neonatal BCG had no significant effect on suspected food allergy or on sensitization at 13 months of age.

Keywords

BCG; Food Allergy; Heterologous immunity; Infant; Sensitization; Specific IgE; Vaccine

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Abbreviations:

BCG: Bacillus Calmette-Guérin

CI: confidence interval

DSMB: Data and Safety Monitoring Board

IgE: Immunoglobulin E

OR: odds ratio

RCT: randomized controlled trial

RR: risk ratio

Introduction

Vaccination with Bacillus Calmette-Guérin (BCG) is used in many countries as protection against the severe forms of tuberculosis (1). In Denmark BCG was used until the 1980s.

Apart from their disease-specific effects, vaccines may have so-called “non-specific effects”. Studies have shown that BCG reduced mortality more than anticipated based on its effect against tuberculosis (2-5).

BCG has also been suggested to protect against atopy (6). Atopy is “an inherited tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of common environmental proteins” (7). Atopy is diagnosed by measuring specific IgE in peripheral blood and/or doing a skin prick test (8).

A systematic review from 2011 concluded that the combined odds ratio (OR) for BCG-vaccinated children to develop raised specific IgE was 1.34 [1.05-1.69] (9). However, only one of the three included studies was a randomized controlled trial (RCT) (10), the other two being a retrospective cohort study (11) and a cross-sectional study (12).

The Danish Calmette Study was an RCT, which aimed to study non-specific effects of neonatal BCG vaccination in a high-income country (13). The primary trial outcome was early childhood hospitalization, for which no effect of BCG was observed (14). Secondary atopic outcomes were atopic dermatitis, recurrent wheeze, and food allergy / allergic sensitization. Neonatal BCG had no overall effect on atopic dermatitis, but was associated with a 16% [5-26%] reduction in atopic dermatitis in the subgroup of children with atopic predisposition (Thøstesen et al, submitted). No effect of BCG was found on recurrent wheeze (15).

In the present paper, we studied the effect of neonatal BCG on the cumulative incidence of suspected food allergy within the entire cohort of the Danish Calmette Study. In a nested sub study, we evaluated the effect of BCG on allergic sensitization.

Methods

The Danish Calmette Study was conducted 2012-2015. Parents expecting to give birth from October 2012 to November 2013 at one of the three Danish participating hospitals were invited to have their new-born child participate in the study. Exclusion criteria were gestational age <32 week, birth weight <1000 g, known immunodeficiency, or no Danish-speaking parent. Within 7 days of birth, newborns randomized to the BCG group were vaccinated intradermally with 0.05 ml BCG (SSI strain 1331); the

control group received no intervention. Randomization was stratified by maturity (≥ 37 weeks of gestation versus < 37 weeks). Background information was obtained from the inclusion interview, and follow-up consisted of telephone interviews and clinical examinations at 3 and 13 months of age. The methods have been described in details elsewhere (13).

The sensitization sub study

All children included at site A (Kolding, Denmark) were invited to have a venous blood sample of 1.0 ml taken by laboratory staff at 13 months of age. Serum was pipetted in micro tubes and stored at -20°C until transport on dry ice to the analyzing laboratory. To increase sample size and the power of this sub study, blood samples from 304 children participating in the immunological sub study at site B (Hvidovre, Denmark) were obtained in a similar manner (16).

Thermo Fisher Phadia Aps, Allerød, Denmark, analyzed the sensitization blood samples with Phadiatop Infant®, including allergens against milk, egg white, peanut, cat, dog, house dust mite (*Dermatophagoides pteronyssinus*), timothy and birch. All samples were also analyzed for sensitization against hazelnut.

Blinding

Due to the typical skin reaction following a BCG vaccination, the parents could not be blinded, but they were instructed not to reveal the randomization group to the study staff.

Definition of atopic predisposition

A child was considered to have atopic predisposition if a biological parent or a full sibling had (had) one or more of the following atopic diseases, diagnosed by a medical doctor: food allergy, atopic dermatitis, hay fever, or asthma.

Outcomes

Suspected food allergy was defined as the answers “Yes” or “Suspecting” to at least one of the two questions: “Is your child allergic to any foods?” or “Has a doctor said that your child has food allergy?”

A secondary, more specific definition of doctor-diagnosed food allergy required a confirmative answer to the question “Has a doctor said that your child has food allergy?”

Food challenges were not included in the protocol.

Sensitization was defined as Phadiatop Infant® ≥ 0.35 kU/l, which is in concordance with the generally accepted cut-off level for atopy (17). *Post-hoc* it was decided to conduct a supplementary analysis of sensitization towards foods only (specific IgE ≥ 0.35 kU/l against milk, egg white, peanut, or hazelnut), as the questionnaire concerned food allergy and did not include symptoms of inhalant allergy.

Statistical analyses

Prior to unblinding the data, the statistical analysis plan was deposited with the Data and Safety Monitoring Board (DSMB). Analyses were intention-to-treat. Prevalence of suspected food allergy and prevalence of sensitization in the two randomization groups was compared using log binomial regression, resulting in Risk Ratios (RR) with 95% confidence intervals (CI). The exact values of Phadiatop Infant® were compared by a Wilcoxon test.

Subgroup analyses

A previous study of BCG on atopy emphasized children with atopic predisposition (10) and vaccination studies have shown potential differential non-specific effects by sex (18, 19) and maternal immunity (20). It was therefore pre-specified to address the possible effect modification by these factors as well as by factors previously found to be associated with the development of atopic diseases (ethnicity, number of siblings, pets at home, smoking, breast-feeding, and child day-care).

P-values less than 0.05 were considered statistically significant. STATA 14 (StataCorp, College Station, Texas, USA) was used for the analyses.

Sample size

The Danish Calmette Study was powered to detect an effect of BCG on all cause hospitalizations and on atopic dermatitis, aiming at the inclusion of 4300 newborns (13). Anticipating sensitization in 20% of the blood samples (21), with 1272 children (636 BCG-vaccinated and 636 not-BCG-vaccinated children) a protection of 30% could be detected with a power of 80% and an alpha of 0.05.

Ethics

The Danish Calmette Study was approved by the Danish Data Protection Board (2009-41-4141), the Committees on Biomedical Research Ethics (H-3-2010-087) and the Danish Medicines Agency (2612-4356, EudraCT 2010-021979-85, Protocol 2009-323). It was registered at www.ClinicalTrials.gov (NCT01694108), and supervised by the Good Clinical Practice Units and by an independent DSMB. All parents gave verbal and written consent, and separate consent for the blood sampling.

Results

The Danish Calmette Study enrolled 4262 newborns from 4184 families, resulting in a BCG group of 2129 children and a control group of 2133 children (14). Information about food allergy was collected for 4188 children: 2109 from the BCG group (99.1%) and 2079 from the control group (97.5%), forming the food allergy cohort. The 74/4262 children (1.2%) not participating did not differ from participating children regarding background factors. Median age at the 13 month telephone interview was 375 days (10-90 centiles: 370-390 days) in the BCG group, and 375 days (10-90 centiles: 371-392 days) in the control group.

The sensitization cohort consisted of 1370 children (Figure1). Background characteristics are shown in Table I. Median age at the blood sampling was 396 days (10-90 centiles: 380-418 days) and 397 days (10-90 centiles: 380-420 days), respectively.

BCG and suspected food allergy

By 13 months of age, the parents and/or general practitioners of 5.6% (117/2089) of the children in the BCG group and 6.1% (126/2061) of the control group suspected food allergy, resulting in an RR comparing BCG-vaccinated children with control children of 0.91 (95% CI 0.71 to 1.16) (Supplementary Table I).

A doctor-derived diagnosis of food allergy had been given to 0.7% (15/2109) and 0.5% (10/2079), RR 1.48 (0.67 to 3.29). Irrespective of the definition of suspected food allergy, we found no effect of BCG on this outcome (Supplementary Table I). With one exception (non-Danish ethnicity), the effect of BCG on risk of suspected food allergy did not differ between the different subgroups (Table II).

BCG and sensitization

At 13 months of age 1370 blood samples were analyzed for sensitization. 105 (7.7%) children had a Phadiatop Infant® ≥ 0.35 kU/l, 7.4% (55/743) of the BCG group and 8.0% (50/627) of the control group (RR=0.94 (0.65 to 1.36)). The effect of BCG on risk of sensitization did not differ between the different subgroups (Table III).

The Wilcoxon test comparing the exact values of Phadiatop Infant® derived a p-value of 0.75; the median values being 0.8 in both randomization groups. Looking solely at Phadiatop Infant® values ≥ 0.35 , the median values were 0.89 (BCG group) and 0.69 (control group), $p=0.32$.

In the *post-hoc* analysis emphasizing sensitization against foods, 7.8% (58/742) of the BCG group and 8.2% (51/625) of the control group were sensitized to at least one food allergen, resulting in an RR of 0.97 (0.68 to 1.39).

Allergic diseases and sensitization

The *post-hoc* analysis of the correlation between allergic disease, suspicion of food allergy and sensitization against foods is shown in Table IV. 13.9% of children with atopic dermatitis and 6.5% children without atopic dermatitis were sensitized against milk, egg, peanut and/or hazelnut, RR 2.14 [1.48-3.11].

Of the 25 children with doctor-diagnosed food allergy, only 7 had a blood sample drawn (Table IV).

The pre-planned analysis of the correlation between suspicion of food allergy and Phadiatop infant® ≥ 0.35 derived similar results as Table IV (data not shown).

Discussion

Neonatal BCG vaccination was not associated with parents' or doctors' suspicion of food allergy or with allergic sensitization at age 13 months.

Strengths and limitations

Important strengths of our study are the RCT design and the very high follow-up rate at 13 months.

Study staff and laboratory staff was blinded to study allocation.

Limitations were the impossibility of blinding the parents, and the lower than anticipated incidence of sensitization (7.7%, compared with the 20% in the power calculation (21)). Thus, the study was underpowered with regard to the sensitization outcome. Our blood samples were analyzed by another laboratory (Thermo Fisher Scientific) than in the study mentioned in the power calculation (ALK ABELLO) (21). In another Danish report from 2009 11.8% of the children were sensitized at age 12 months (22), which is comparable with our result. Our pre-study anticipated frequency of sensitization seems overestimated.

The fact that oral food challenges were not performed is an important limitation. As this study was part of a large scale study with very different endpoints, oral food challenges could unfortunately not be included in the protocol due to practical and financial reasons. The equal distribution of not only food sensitization but also clinical suspicion to food allergy in the two randomization groups might indicate that also challenge-proven food allergy would be equally represented in the two groups, but only food challenges would have provided certainty.

The interaction for ethnicity in the effect of BCG on suspicion of food allergy was significant (Table II), showing significantly better effect among children with non-Danish ethnicity. It might be a coincidence in a long row of sub-analyses, or it might reflect different genetic susceptibility. The

effect was not mediated through maternal BCG (Table II), and only 33.9% of children with non-Danish ethnicity had BCG-vaccinated mothers.

Correlation between allergic disease and sensitization

Doctor-diagnosed food allergy was correlated with an increased rate of sensitization, as was atopic dermatitis. Surprisingly, sensitization was not higher in predisposed children than in non-predisposed children (Table IV). This might be explained by the quite young age of the children when follow-up ended.

A recently published Swedish study found the presence of specific IgE strongly associated with eczema and from 4 years of age also with asthma and rhinitis. Interestingly, 23% of sensitized children did not develop any allergic disease in childhood (23).

Comparison with other studies

No other studies evaluated the effect of BCG on food allergy.

A Dutch RCT evaluated the effect of BCG vaccination in 6-week-old children with atopic predisposition. At 18 months of age positive Phadiatop was found in 16.1% (5/31) of the BCG group and in 18.5% (5/27) of the placebo group (10). The cut-off level of the positive Phadiatop and the names of the allergens were not provided and cannot be directly compared to Phadiatop Infant®.

Most other studies on the relationship between BCG and atopy have been observational: A study from West Africa of 271 BCG-vaccinated and 53 not-BCG-vaccinated children found BCG associated with less skin prick test positivity against three inhalant allergens (OR 0.19 (0.06 to 0.59)) (6). A cross-sectional study from Greenland found equal risk of sensitization against eight inhalant allergens in BCG-vaccinated and not-BCG-vaccinated children of 8 to 16 years (OR 1.03 (0.72 to 1.48)) (12). In contrast with our study none of these two observational studies included food allergens and their participants were older than ours.

A systematic review found no protective effect of BCG neither on specific IgE (OR 1.31 [1.07-1.60]), nor on skin prick testing (OR 0.87 [0.67-1.13]) (9). It might be a coincidence that OR for skin prick testing was lower than OR for specific IgE; otherwise it could be speculated that BCG has no effect on the risk of sensitization, but lowers the risk of developing skin reactivity to allergens, as has also been seen for parasite infestation (24). In our study we did not perform skin prick testing.

Our results are in line with other studies from high-income countries, finding no protective effect of BCG against sensitization. However, it should be noted that due to the lower than anticipated sensitization rate, our power to detect any effect was limited.

Conclusion

In this RCT from a high-income country, neonatal BCG had no significant effect on the low risk of developing atopic sensitization or suspected food allergy in the first 13 months of life.

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Authors' contributions:

The Danish Calmette Study was planned by LGS, PA, CB, PK and DLJ, with local contribution at one of the three trial sites from AWO. LMT, GTP, TNN, NMB and JK participated in the overall randomization and data collection. LMT and PK led the blood sampling at site A, and TNN and NMB at site B. HFK provided scientific guidance on food allergy and sensitization. AKGJ guided the statistical analyses. This article was drafted by LMT, with valuable input from the other authors. All authors critically reviewed and approved the final version of the manuscript.

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Figure 1:

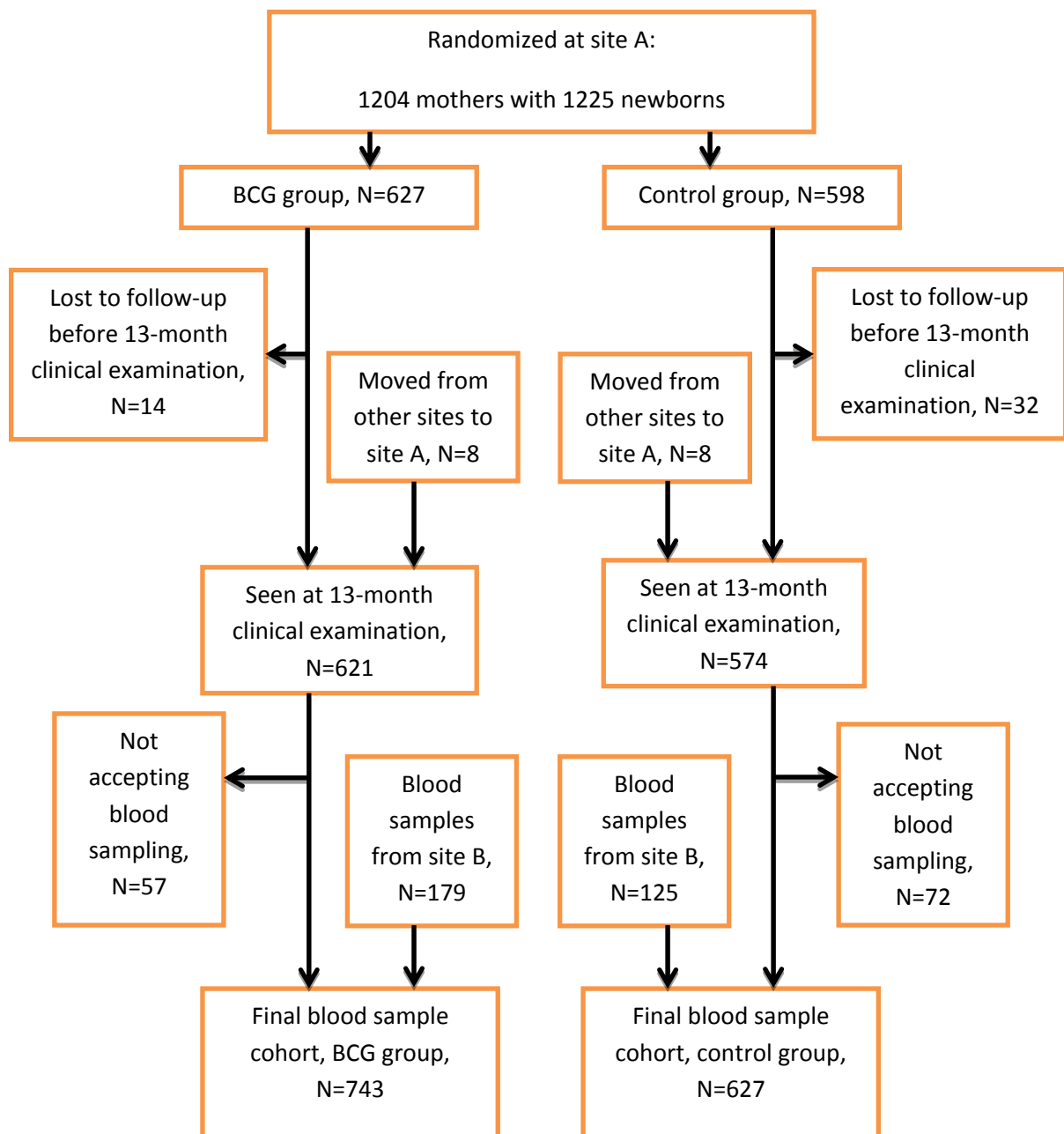


Figure 1: Flowchart of the sensitization cohort.

Table I: Distribution of baseline characteristics and possible confounders in the “sensitization blood sample cohort” of the Danish Calmette Study; N=1370 children

	BCG-group, N = 743	Control-group, N = 627
Male sex	384 (51.7%)	336 (53.6%)
Prematurity (GA<37 weeks)	28 (3.8%)	14 (2.2%)
Caesarean section	163 (21.9%)	113 (18.0%)
Antibiotics during delivery	108 (14.5%)	88 (14.0%)
Twins	22 (3.0%)	14 (2.2%)
Birth weight in grams (median; 10 and 90% percentiles)	3560 (2900-4166)	3550 (2904-4200)
Child <1 day of age at randomization	418 (56.3%)	361 (57.6%)
Maternal age in years at birth (median; 10 and 90% percentiles)	31 (26-38)	31 (25-37)
At least one parent of ethnicity other than Danish	77 (10.4%) [2]	69 (11.1%) [3]
Maternal education	[1]	[1]
No higher education	218 (29.4%)	202 (32.3%)
Short/medium higher education	370 (49.9%)	324 (51.8%)
Long higher education	154 (20.8%)	100 (16.0%)
Parents living together	710 (95.7%) [1]	597 (95.2%)
Mother BCG vaccinated	106 (14.5%)	69 (11.1%)
At least one older sibling	378 (50.9%)	307 (49.0%)
Atopic disposition:		
Maternal atopic disease	320 (43.1%) [1]	262 (41.9%) [1]
Paternal atopic disease	238 (32.7%) [16]	230 (37.7%) [17]
Parental atopic disease	458 (62.3%) [8]	401 (64.8%) [8]
Siblings with atopic disease	127 (33.6%)	96 (31.4%)
Smoking during pregnancy		
Maternal	75 (10.1%)	67 (10.7%)
Paternal	129 (17.7%)*	143 (23.0%)*
Any smoking since birth of the child	177 (23.9%) [3]	170 (27.3%) [5]
Fully breastfed at three months of age	433 (58.4%) [1]	344 (55.0%) [1]
Partly breastfed at thirteen months of age	90 (12.1%)	74 (11.8%)
Use of hydrolyzed infant formulas	34 (4.6%)	41 (6.5%)
Age in months at first introduction to food (other than milk); median (10-90% percentiles)	4.5 (4.0-6.0)	4.0 (4.0-6.0)
Fur animals in the household	340 (45.8%)	268 (42.7%)

[]: missing values; GA: gestational age; BCG: Bacillus Calmette-Guérin; *: Chi2 p<0.05

Table II: Suspected food allergy at 13 months of age, in relation to neonatal BCG-vaccination and potential effect modifiers.

	BCG group No. with suspected food allergy / total no. (%)	Control group No. with suspected food allergy / total no. (%)	Risk Ratio [95% CI] for BCG effect on risk of suspected food allergy	Test of no inter-action
Suspected food allergy	117/2098 (5.6%)	126/2061 (6.1%)	0.91 [0.71-1.16]	
Suspected food allergy in relation to potential effect modifiers:				
Gestational age (GA) at birth				
Premature (GA 32+0 – 36+6); N=135	5/68 (7.4%)	4/67 (6.0%)	1.23 [0.35-4.39]	0.64
Mature (GA at least 37+0); N=4024	112/2030 (5.5%)	122/1994 (6.1%)	0.90 [0.70-1.16]	
Sex				
Boys; N=2194	54/1093 (4.9%)	68/1101 (6.2%)	0.80 [0.57-1.13]	0.30
Girls; N=1965	63/1005 (6.3%)	58/960 (6.0%)	1.04 [0.73-1.47]	
Atopic predisposition^a (missing: 83)				
With atopic predisposition; N=2610	82/1333 (6.2%)	86/1287 (6.7%)	0.87 [0.56-1.40]	0.89
Without atopic predisposition; N=1466	33/726 (4.5%)	38/740 (5.1%)	0.92 [0.69-1.23]	
Maternal BCG-status (missing: 51)				
Mother BCG-vaccinated; N=722	24/366 (6.6%)	17/356 (4.8%)	1.38 [0.75-2.52]	0.15
Mother not BCG-vaccinated; N=3386	92/1710 (5.4%)	106/1676 (6.3%)	0.85 [0.65-1.12]	

Ethnicity (missing: 25)				
Non-Danish ethnicity; N=823	15/370 (4.1%)	36/453 (7.9%)	0.51 [0.28-0.92]	0.03
Danish ethnicity; N=3311	100/1716 (5.8%)	89/1595 (5.6%)	1.04 [0.79-1.38]	
Siblings (missing: 2)				
At least one older sibling; N=1711	53/888 (6.0%)	52/823 (6.3%)	0.94 [0.65-1.37]	0.80
No older siblings; N=2446	64/1210 (5.3%)	74/1236 (6.0%)	0.88 [0.64-1.22]	
Pets at home				
Yes; N=1220	35/636 (5.5%)	44/584 (7.5%)	0.73 [0.47-1.12]	0.22
No; N=2939	82/1462 (5.6%)	82/1477 (5.6%)	1.01 [0.75-1.36]	
Smoking status by 13 months of age (missing: 36)				
Ever smoked since birth of child; N=1151	25/557 (4.5%)	35/594 (5.9%)	0.76 [0.46-1.26]	0.43
Never smoked since birth of child; N=2972	91/1523 (6.0%)	90/1449 (6.2%)	0.96 [0.72-1.28]	
Breast-feeding (missing: 7)				
Not fully breastfed until 3 months; N=1799	46/891 (5.2%)	65/908 (7.2%)	0.72 [0.50-1.04]	0.09
Fully breastfed until 3 months of age; N=2353	71/1204 (5.9%)	61/1149 (5.3%)	1.11 [0.80-1.55]	
Started child day-care before 13 months' follow-up (missing: 1)				
Yes; N=3576	101/1820 (5.5%)	108/1756 (6.2%)	0.90 [0.69-1.17]	0.84
No; N=582	16/278 (5.8%)	18/304 (5.9%)	0.97 [0.51-1.87]	

Log binomial regression analysis of the 4159 children in the food allergy cohort who answered all food allergy questions.

BCG: Bacillus Calmette-Guérin; CI: confidence intervals; GA: gestational age

a: Atopic predisposition: if at least one first degree relative (biological parent or full sibling) currently had, or had had, one or more of the following atopic diseases, diagnosed by a medical doctor: food allergy, atopic dermatitis, hay fever, or asthma.

Table III: Sensitization measured in blood samples at 13 months of age, in relation to neonatal BCG-vaccination and potential effect modifiers.

	BCG group No. with sensitization / total no. (%)	Control group No. with sensitization / total no. (%)	Risk Ratio [95% CI] for BCG effect on sensitization	Test of no inter-action
Sensitization	55/743 (7.4%)	50/627 (8.0%)	0.94 [0.65-1.36]	
Sensitization in relation to potential effect modifiers:				
Gestational age (GA) at birth				
Premature (GA 32+0 – 36+6); N=42	0/28	1/14 (7.1%)	-	-
Mature (GA at least 37+0); N=1328	55/715 (7.7%)	49/613 (8.0%)	0.96 [0.66-1.39]	
Sex				
Boys; N=720	32/384 (8.3%)	33/336 (9.8%)	0.85 [0.54-1.36]	0.49
Girls; N=650	23/359 (6.4%)	17/291 (5.8%)	1.12 [0.61-2.05]	
Atopic predisposition^a (missing: 18)				
With atopic predisposition; N=909	38/490 (7.8%)	36/419 (8.6%)	0.91 [0.59-1.41]	0.92
Without atopic predisposition; N=443	16/243 (6.6%)	14/200 (7.0%)	0.95 [0.48-1.91]	
Maternal BCG-status				

(missing: 14)				
Mother BCG-vaccinated; N=175	11/106 (10.4%)	7/69 (10.1%)	1.07 [0.44-2.64]	0.74
Mother not BCG-vaccinated; N=1181	44/627 (7.0%)	43/554 (7.8%)	0.91 [0.61-1.36]	
Ethnicity (missing: 5)				
Non-Danish ethnicity; N=146	8/77 (10.4%)	7/69 (10.1%)	1.02 [0.39-2.67]	0.82
Danish ethnicity; N=1219	46/664 (6.9%)	43/555 (7.7%)	0.91 [0.61-1.35]	
Siblings				
At least one older sibling; N=685	26/378 (6.9%)	26/307 (8.5%)	0.84 [0.50-1.41]	0.54
No older siblings; N=685	29/365 (7.9%)	24/320 (7.5%)	1.05 [0.63-1.77]	
Pets at home				
Yes; N=608	21/340 (6.2%)	21/268 (7.8%)	0.80 [0.45-1.44]	0.49
No; N=762	34/403 (8.4%)	29/359 (8.1%)	1.05 [0.65-1.69]	
Smoking status by 13 months of age (missing: 8)				
Ever smoked since birth of child; N=347	15/177 (8.5%)	14/170 (8.2%)	1.03 [0.51-2.07]	0.76
Never smoked since birth of child; N=1015	40/563 (7.1%)	36/452 (8.0%)	0.91 [0.59-1.40]	
Breast-feeding (missing: 2)				
Not fully breastfed until 3 months; N=591	26/309 (8.4%)	18/282 (6.4%)	1.34 [0.74-2.37]	0.12
Fully breastfed until 3 months of age; N=777	29/433 (6.7%)	32/344 (9.3%)	0.73 [0.45-1.19]	
Started child day-care before 13 months' follow-up				
Yes; N=1255	52/684 (7.6%)	44/571 (7.7%)	1.00 [0.68-1.47]	0.29
No; N=115	3/59 (5.1%)	6/56 (10.7%)	0.47 [0.12-1.80]	

Log binomial regression analysis of the 1370 children in the sensitization cohort.

Sensitization defined as Phadiatop infant ≥ 0.35 kU/l

BCG: Bacillus Calmette-Guérin; CI: confidence intervals; GA: gestational age

a: Atopic predisposition: if at least one first degree relative (biological parent or full sibling) currently had, or had had, one or more of the following atopic diseases, diagnosed by a medical doctor: food allergy, atopic dermatitis, hay fever, or asthma.

Table IV: *Post-hoc* analysis of the correlation between allergic sensitization against food items^a and suspected food allergy, as well as the correlation with atopic predisposition and atopic dermatitis.

	+ allergic food sensitization^a
All children	109/1370 (8.0%)
No suspicion of food allergy	94/1255 (7.5%)
Food allergy suspected by parents and/or the doctor	14/98 (14.3%)
Food allergy diagnosed by the doctor	4/7 (57.1%)
Children with atopic predisposition	73/909 (8.0%)
Children with atopic dermatitis	38/273 (13.9%)

a: Specific IgE ≥ 0.35 for at least one of the food items (milk, egg, peanut or hazelnut), measured in the 1370 blood samples taken at 13 months of age.

Supplementary Table I: The effect of neonatal BCG vaccination on the risk of suspected food allergy.

	Food allergy suspected by parents		Food allergy known by parents		Food allergy suspected by a doctor		Food allergy diagnosed by a doctor	
	BCG group	Control group	BCG group	Control group	BCG group	Control group	BCG group	Control group
Reported food allergy	89/2098 (4.2%) [11]	97/2060 (4.7%) [19]	28/2098 (1.3%) [11]	27/2060 (1.3%) [19]	16/2109 (0.8%)	19/2079 (0.9%)	15/2109 (0.7%)	10/2079 (0.5%)
Risk ratio for food allergy [95% CI]	RR 0.90 [0.68-1.19]		RR 1.02 [0.60-1.72]		RR 0.83 [0.43-1.61]		RR 1.48 [0.67-3.29]	
Risk ratio for food allergy [95% CI]	RR 0.93 [0.73-1.18] (BCG: 117/2098 = 5.6% vs. control: 124/2060 = 6.0%)				RR 1.05 [0.64-1.74] (BCG: 31/2109 = 1.5% vs. control: 29/2079 = 1.4%)			
Risk ratio for any food allergy [95% CI]	RR 0.91 [0.71-1.16] (BCG: 117/2089 = 5.6% vs. control: 126/2061 = 6.1%)							
Suspected allergy against#:								
Milk	36 (40.5%)	42 (43.3%)	10 (35.7%)	11 (40.7%)	8 (50.0%)	13 (68.4%)	7 (46.7%)	7 (70.0%)
Egg	5 (5.6%)	7 (7.2%)	7 (25.0%)	5 (18.5%)	3 (18.8%)	2 (10.5%)	5 (33.3%)	3 (30.0%)
Fish	2 (2.3%)	1 (1.0%)	1 (3.6%)	1 (3.7%)	2 (12.5%)	0	0	0
Peanut	1 (1.1%)	2 (2.1%)	3 (10.7%)	3 (11.1%)	1 (6.3%)	0	2 (13.3%)	3 (30.0%)
Other foods*	50 (56.2%)	47 (48.5%)	11 (39.3%)	12 (44.4%)	5 (31.3%)	6 (31.6%)	2 (13.3%)	2 (20.0%)

#Answers in the telephone interview at 13 months of age to the question: “Which foods is your child (suspected to be) allergic against?”

BCG: Bacillus Calmette-Guérin; CI: confidence intervals; RR: risk ratios (for children in the BCG group compared with children in the control group)

[] : missing answers. *: examples of “other foods”: gluten, citrus fruits, and nuts.

Each child can be allergic against more than one of the listed foods. The percentages listed for the different foods are in percent of the children with parent-reported suspected food allergy, according to four different definitions.