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Neonatal BCG-vaccination and atopic dermatitis before 13 months of age. A randomised clinical trial

Short title: BCG and atopic dermatitis

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Abstract

Studies have suggested that Bacillus Calmette-Guérin (BCG) vaccination may reduce the risk of allergic diseases, including atopic dermatitis.

The Danish Calmette Study was conducted 2012-2015. Within 7 days of birth new-borns were randomised 1:1 to BCG or no BCG. Exclusion criteria were gestational age <32 weeks, birth weight <1000 g, known immunodeficiency or no Danish-speaking parent. Data were collected through telephone interviews and clinical examinations until 13 months.

Clinical atopic dermatitis was diagnosed in 466/2,052 (22.7%) children in the BCG group and 495/1,952 (25.4%) children in the control group (RR=0.90 (95% confidence intervals 0.80 to 1.00)). The effect of neonatal BCG vaccination differed significantly between children with atopic predisposition (RR 0.84 (0.74 to 0.95)) and children without atopic predisposition (RR 1.09 (0.88 to 1.37)) (test of no interaction, p=0.04).

Among children with atopic predisposition, the number-needed-to-treat with BCG to prevent one case of atopic dermatitis was 21 (12 to 76).

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Key words

Atopic dermatitis; Bacillus Calmette-Guérin (BCG); heterologous immunity; infants; randomised controlled trial

Abbreviations:

AD: atopic dermatitis

BCG: Bacillus Calmette-Guérin

CI: confidence interval

NNT: number needed to treat

objSCORAD: objective Scoring Atopic Dermatitis values

RCT: randomised clinical trial

RR: relative risk

SCORAD: Scoring Atopic Dermatitis

Introduction

Atopic dermatitis (AD) is frequent in childhood (1). The tuberculosis vaccine Bacillus Calmette-Guérin (BCG) (2) might have a protective effect against atopy (3, 4). A Dutch randomised clinical trial (RCT) from 2008 among infants of atopic parents found BCG associated with less use of medication for eczema (5).

The Danish Calmette Study aimed to study non-specific effects of neonatal BCG vaccination in a high-income country, with hospital admissions as primary outcome (6). The aim of the present study was to assess the effect of neonatal BCG on the cumulative incidence of AD up to 13 months of age.

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Methods

The Danish Calmette Study was an RCT conducted from 2012-2015 at three Danish hospitals (6). Exclusion criteria were gestational age <32 week, birth weight <1000 g, known immunodeficiency, or no Danish-speaking parent. Within 7 days of birth, neonates were allocated 1:1 to BCG vaccination (SSI strain 1331) or no intervention. Before randomisation, a structured telephone interview collected data on background characteristics. Follow-up consisted of telephone interviews and clinical examinations at age 3 and 13 months.

Outcome assessment

Parents were asked if their child had had AD, duration and localization of the eczema, sleep disturbances due to itching, use of topical steroids, and whether the diagnosis had been confirmed by a doctor. The clinical examinations were conducted by doctors or trained health staff. The severity of AD was graded using SCORAD (7).

The Statistical Analysis Plan intended to include all cases of parent-suspected or clinically diagnosed AD as the main outcome, and to use clinically diagnosed AD as a more specific secondary outcome. However, given the high prevalence using the broad definition, *post hoc* we emphasised the more specific "clinically diagnosed AD". Thus, the main outcome of the present study was cumulated incidence of AD at 13 months of age, diagnosed by a doctor, or by our study staff. (The AD-outcomes are further explained in Supplementary Material).

Blinding

Parents were instructed not to reveal the child's BCG-vaccination status, and to cover the vaccination site with a plaster prior to the clinical examinations, irrespective of the child's randomisation group.

Definition of atopic predisposition

A biological parent or full sibling currently or previously having a doctor-diagnosed atopic disease (food allergy, AD, hay fever, or asthma).

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Statistical analyses

Analyses were intention-to-treat (ITT). AD frequencies in the two randomisation groups were compared using log binomial regression, providing Risk Ratios (RR) with 95% confidence intervals (CI). This statistical model assumes full follow-up, so the main analyses were based on children participating in the final clinical examination.

Subgroup analyses

As randomisation was stratified for maturity (≥37 weeks of gestation versus <37 weeks) all results were presented by maturity. Since previous studies of non-specific effects have emphasised children with atopic predisposition (5), and shown differential effects by sex (8, 9) and by maternal immunity (10), we pre-specified analyses of the main outcome stratified by these subgroups, as well as by factors previously associated with development of atopic diseases (Table 2).

STATA 14.1 (StataCorp, College Station, Texas, USA) was used for the analyses.

Sample size

The Danish Calmette Study was specifically powered to detect an effect of BCG on AD (6). Assuming 5% developed AD, we needed to include 4,230 infants (2,115 in each randomisation group) to detect 40% protection against AD.

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). The study was registered at www.ClinicalTrials.gov (NCT01694108), and supervised by the Good Clinical Practice Units and a Data Safety and Monitoring Board. All parents gave verbal and written consent.

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Results

From October 2012 to November 2013, 16,521 pregnant women were identified at the three recruitment sites, and 4,184 women and 4,262 new-born infants were enrolled (6). Atopic predisposition was reported for 63% of the families (2,639/4,184). Of the 2,133 infants (from 2,089 families) randomised to neonatal BCG, 2,118 new-born infants were BCG vaccinated according to the protocol. The control group consisted of 2,129 new-born infants (from 2,095 families). The flowchart of the Danish Calmette Study is published elsewhere (11).

Of the 4,262 included children, 4,004 (93.9 %) completed the clinical examination at age 13 months. Fewer children were lost to follow-up in the BCG group (n = 77; completion rate 96.4%) compared to the control group (n = 181; completion rate 91.5%) (p(Chi2)<0.001). Among the children lost to follow-up there were no differences in background characteristics between the two randomisation groups. In both groups, the median age at the last clinical examination was 393 days (10-90% percentiles: 378-406 days).

Main outcome

At age 13 months, the cumulative incidence of "clinically diagnosed AD" was 22.7% (466/2,052) in the BCG group and 25.4% (495/1,952) in the control group (RR = 0.90 (95% CI: 0.80 to 1.00)) (Table 1). Using the broader pre-specified definition of AD (including also parent-suspected AD), 26.2% of the BCG group and 28.1% of the control group had AD (RR=0.93 (0.84 to 1.03)) (Supplementary Table 1).

A beneficial effect of BCG was observed only in data from clinical examinations and not in telephone interviews (Table 1). BCG did not decrease the risk of more severe manifestations of AD (Table 1). No effect of BCG was found at age 3 months; 8.6% (176/2,050) had AD in the BCG group and 9.4% (184/1,966) in the control group (RR = 0.92 (0.75 to 1.12)).

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At age 3 months, median objSCORAD was 14.2 [4-68] in the BCG group and 12.5 [4-54] in the control group (p(Kruskal-Wallis) 0.80). At age 13 months the numbers were 14.8 [4-59] and 15.2 [0-67], respectively (p=0.30).

Subgroup analyses

The effect of BCG-vaccination on AD differed for children with and without atopic predisposition (test of no interaction, p=0.04) (Table 2). For children with atopic predisposition the RR was 0.84 (0.74-0.95). Hence, the number needed to treat (NNT) with BCG to prevent one case of AD among children with atopic predisposition was 21 (95% CI: 12 to 76). Except from atopic predisposition, we found no significant effect modification by the pre-specified potential effect modifiers (Table 2).

Discussion

Among children with atopic predisposition neonatal BCG reduced the cumulative incidence of AD by 16% (5-26%), corresponding to a NNT of 21.

Strengths and limitations

This is the largest RCT assessing the effect of BCG on AD. With 94% of enrolled children seen at the clinical examination at age 13 months, we had high follow-up rates. We used the internationally accepted SCORAD form in the clinical evaluation. Study staff was blinded with respect to the allocation status of the children.

Of the 16,521 invited women 25.3% (4184) participated; families with atopic predisposition and mothers with longer educations were overrepresented. However, these families were randomised equally to BCG and to the control group.

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Parents were not blinded, and one could fear that this could have led to differential reporting of AD in favour of BCG. This did not seem to be the case, as we found no effect of BCG on parent-reported AD.

It is a cause for concern that the effect of BCG seemed to differ by mode of assessment, but based on subsequent contacts with parents, we learned that some children with parent-reported AD later turned out to have e.g. a fungal skin infection instead. The original AD definition from the Statistical Analysis Plan thus included other skin symptoms than just AD.

The shift of primary outcome is a limitation, and it is the main reason for the cautiousness in the conclusions.

The main outcome “cumulative incidence of AD” was diagnosed either by the family's general practitioner, another doctor, or the study staff. There might be differences in their expertise in terms of diagnosing AD. The trial design had two scheduled clinical examinations, and study staff seldom saw the children when the AD was most pronounced. Without the inclusion of AD diagnoses from other doctors we would have underestimated the true number of children with AD.

Comparison with other studies

In our trial, 63% of the participants had atopic predisposition and more than 20% fulfilled our definition of AD at age 13 months. In a Danish study of AD in 1998-1999 (12) 53% had atopic predisposition and the cumulative 1-year prevalence of visible AD was 12% (12). In a recently published Danish study the cumulative incidence of AD at 18 months was 15% (13).

The incidence of AD and potential BCG-associated protection against AD in children with atopic predisposition found in our trial is in accordance with the results from a small Dutch RCT, which in 1999-2002 enrolled 121 children with atopic predisposition and randomised them to BCG or no BCG at age 6 weeks (5). At age 18 months, 52% (60/115) of the children had parent-suspected AD and 26% (30/114) had clinically diagnosed AD. The Dutch trial reported a significant protective effect of BCG on use of eczema medication at 18 months (5), which we could not confirm. Other studies on

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the relationship between BCG and AD have been observational, some showing a protective association (14, 15) and some no association (4, 16).

The low RRs among the 3% premature and the 17% with maternal BCG vaccination (Table 2) might reflect coincidences; or it might indicate a trend towards a differential effect of BCG, as reported in a recent immunological study (17). Due to low power in some strata our trial can neither confirm nor contradict a differential effect of BCG in these subgroups.

In the Danish Calmette Study no overall effect of neonatal BCG was found on all cause hospitalisation (11), recurrent wheeze (18), or sensitisation/suspected food allergy (19).

Implications

The incidence of AD is increasing (1) and BCG has been among the proposed preventive measures (3, 4), but based on the present study we would not recommend BCG vaccination for all Danish neonates. BCG vaccination at birth might be associated with less AD among children with atopic predisposition. If this finding is confirmed in other studies, BCG might give partial protection against AD in predisposed children. However, it should be kept in mind that BCG can cause side effects like suppurating lymphadenitis (20).

Conclusion

In this large RCT from a high-income country, neonatal BCG did not prevent the development of AD in all children, but modestly reduced the cumulative incidence of AD among infants with atopic predisposition. The NNT among atopic predisposed children to prevent one case of AD in first year of life with neonatal BCG vaccination was 21.

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Author contributions:

The Danish Calmette Study was designed by PA, LGS, CB, PEK and DLJ, with local contribution to practical issues at one trial site by AWO. LMT, GTP, JK, NMB and TNN participated in the data collection, supervised by PEK, LGS and DLJ. AKGJ supervised the statistical analyses. LMT drafted the manuscript with valuable inputs from the other authors. All authors read and approved the final version of the manuscript.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration:

LMT affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Data sharing: A check of the validity of the data and analyses for this study can be arranged with the corresponding author. Request for access to a data copy should be directed to the Trial Steering Committee.

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Table 1: Clinically diagnosed atopic dermatitis (AD) in first year of life and different measures of severity of AD, in relation to neonatal BCG-vaccination.

	BCG group **No. with AD / total no. (%)**	**Control group** **No. with AD / total no. (%)**	**Risk Ratio [95% CI] for BCG effect on AD**
Primary outcome: Intention-to-treat analysis: Clinically diagnosed AD	466/2052 (22.7%)	495/1952 (25.4%)	0.90 [0.80-1.00]
Different measures of severity of AD:			
At 3 months of age[c]:	**176 AD-cases among 2050 children (8.6%)**	**184 AD-cases among 1966 children (9.4%)**	
Telephone interview:			
Parent-suspected AD	77 (3.8%)	83 (4.2%)	0.89 [0.66-1.20]
Doctor-diagnosed AD*	22 (1.1%)	20 (1.0%)	1.06 [0.58-1.93]
Atopic dermatitis lasting >1 month	8 (0.4%)	7 (0.4%)	1.09 [0.40-3.01]
Use of topical steroid	16 (0.8%)	14 (0.7%)	1.10 [0.54-2.24]
Sleep disturbances (always or often) because of pruritus	3 (0.1%)	3 (0.2%)	0.96 [0.19-4.75]
Current use of tacrolimus or pimecrolimus	1 (0.05%)	0	-
Generalized eczema (tel. int.)	2 (0.1%)	7 (0.4%)	0.27 [0.06-1.31]
Clinical examination:			
AD at the clinical examination*	168 (8.2%)	177 (9.0%)	0.91 [0.75-1.12]
Generalized eczema (clin. ex.)	37 (1.8%)	31 (1.6%)	1.14 [0.71-1.84]
Mild AD (objSCORAD<15)	91 (4.4%)	91 (4.6%)	0.92 [0.69-1.22]
Moderate or severe AD *Moderate AD (objSCORAD 15-40)*	76 (3.7%) *70 (3.4%)*	82 (4.2%) *73 (3.7%)*	0.89 [0.66-1.21] *0.92 [0.67-1.27]*

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Severe AD (objSCORAD>40)	*6 (0.3%)*	*9 (0.5%)*	*0.64 [0.23-1.79]*
At 13 months of age[d]:	**400 AD-cases among 2052 children (19.5%)**	**427 AD-cases among 1952 children (21.9%)**	
Telephone interview:			
Parent-suspected AD	347 (16.9%)	308 (15.8%)	1.06 [0.93-1.22]
Doctor-diagnosed AD*	241 (11.7%)	211 (10.8%)	1.09 [0.91-1.29]
Atopic dermatitis lasting >1 month	200 (9.7%)	177 (9.1%)	1.07 [0.89-1.30]
Use of topical steroid	162 (7.9%)	150 (7.7%)	1.03 [0.83-1.27]
Sleep disturbances (always or often) because of pruritus	26 (1.3%)	20 (1.0%)	1.24 [0.69-2.21]
Current use of tacrolimus or pimecrolimus	5 (0.2%)	6 (0.3%)	0.79 [0.24-2.60]
Generalized eczema (tel. int.)	49 (2.4%)	38 (1.9%)	1.23 [0.81-1.86]
Clinical examination:			
AD at the clinical examination*	285 (13.9%)	321 (16.4%)	0.84 [0.73-0.98]
Generalized eczema (clin. ex.)	51 (2.5%)	51 (2.6%)	0.95 [0.65-1.40]
Mild AD (objSCORAD<15)	142 (6.9%)	144 (7.4%)	0.93 [0.75-1.17]
Moderate or severe AD	137 (6.7%)	172 (8.8%)	0.76 [0.61-0.94]
Moderate AD (objSCORAD 15-40)	*120 (5.8%)*	*149 (7.6%)*	*0.77 [0.61-0.97]*
Severe AD (objSCORAD>40)	*17 (0.8%)*	*23 (1.2%)*	*0.70 [0.38-1.31]*

a: Percentages and Risk Ratio based on total number of children in the two randomisation groups with full follow-up at 3 and 13 months of age, respectively.

b: Log binomial regression analysis of the 4004 children who participated in the clinical examination at 13 months of age (93.9% of the randomised children).

c: 4,016 children participated in both the telephone interview and the clinical examination at 3 months of age; of these 360 had been clinically diagnosed with atopic dermatitis at some point before or at 3 months of age.

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d: 4,004 children participated in both the telephone interview and the clinical examination at 13 months of age; of these 827 had been clinically diagnosed with atopic dermatitis at some point between 3 and 13 months, or at 13 months of age.

objSCORAD: objective SCORAD (Scoring Atopic Dermatitis) values, based on extent and intensity of the atopic dermatitis lesions.

AD: atopic dermatitis; CI: confidence intervals

*: variables defining the composite outcome "clinically diagnosed AD".

Table 2: Clinically diagnosed atopic dermatitis (AD) in first year of life, in relation to neonatal BCG-vaccination and potential effect modifiers[a].

	BCG group **No. with AD / total no. (%)**	**Control group** **No. with AD / total no. (%)**	**Risk Ratio [95% CI] for BCG effect on AD**	**Test of no inter-action**
Primary outcome: Clinically diagnosed AD	466/2052 (22.7%)	495/1952 (25.4%)	0.90 [0.80-1.00]	
Gestational age (GA) at birth				
Premature (GA 32+0 to 36+6); N=124	13/63 (20.6%)	18/61 (29.5%)	0.70 [0.38-1.30]	.43
Mature (GA at least 37+0); N=3880	453/1989 (22.8%)	477/1891 (25.2%)	0.90 [0.81-1.01]	
Sex				
Boys; N=2109	259/1069 (24.2%)	298/1040 (28.7%)	0.85 [0.73-0.98]	.22
Girls; N=1895	207/983 (21.1%)	197/912 (21.6%)	0.97 [0.82-1.16]	
Atopic predisposition (missing: 69)				
With atopic predisposition; N=2528	329/1305 (25.2%)	367/1223 (30.0%)	0.84 [0.74-0.95]	.04
Without atopic predisposition; N=1407	133/708 (18.8%)	120/699 (17.2%)	1.09 [0.88-1.37]	

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Maternal BCG-status (missing: 49)				
Mother BCG-vaccinated; N=694	72/358 (20.1%)	88/336 (26.2%)	0.77 [0.58-1.01]	.43
Mother not BCG-vaccinated; N=3261	390/1672 (23.3%)	401/1589 (25.2%)	0.92 [0.82-1.04]	
Ethnicity (missing: 22)				
Danish ethnicity; N=3204	379/1681 (22.5%)	377/1523 (24.8%)	0.91 [0.80-1.03]	.74
Non-Danish ethnicity; N=778	86/360 (23.9%)	115/418 (27.5%)	0.87 [0.68-1.11]	
Siblings (missing: 2)				
No older siblings; N=2359	279/1187 (23.5%)	309/1172 (26.4%)	0.89 [0.77-1.03]	.91
At least one older sibling; N=1643	187/865 (21.6%)	186/778 (23.9%)	0.90 [0.76-1.08]	
Pets at home				
Yes; N=1180	119/628 (18.9%)	116/552 (21.0%)	0.90 [0.72-1.13]	.996
No; N=2824	347/1424 (24.4%)	379/1400 (27.1%)	0.90 [0.79-1.02]	
Age in days at randomisation				
0-1; N=3048	343/1542 (22.2%)	369/1506 (24.5%)	0.91 [0.80-1.03]	.65
2-7; N=956	123/510 (24.1%)	126/446 (28.3%)	0.85 [0.69-1.06]	
Had received first pentavalent vaccination before 3-month-follow-up (missing: 2)				
Yes; N=692	78/354 (22.0%)	92/338 (27.2%)	0.81 [0.62-1.05]	.41
No; N=3310	388/1697 (22.9%)	403/1613 (25.0%)	0.91 [0.62-1.05]	

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Breast-feeding (missing: 4)				
Fully breastfed until 3 months of age; N=2274	264/1178 (22.4%)	282/1096 (25.7%)	0.87 [0.75-1.01]	.60
Not fully breastfed until 3 months; N=1726	201/872 (23.1%)	213/854 (24.9%)	0.92 [0.78-1.09]	
Use of hydrolysed infant formulas at 3 months				
Yes; N= 274	37/138 (26.8%)	43/136 (31.6%)	0.85 [0.58-1.23]	.76
No; N= 3719	427/1909 (22.4%)	450/1810 (24.9%)	0.90 [0.80-1.01]	
Smoking status by 13 months of age (missing: 31)				
Ever smoked since birth of child; N=1102	121/547 (22.1%)	116/555 (20.9%)	1.06 [0.85-1.33]	.09
Never smoked since birth of child; N=2871	342/1488 (23.0%)	375/1383 (27.1%)	0.85 [0.75-0.96]	
Started institutional child care before 13-month-follow-up (missing: 1)				
Yes; N=3441	405/1781 (22.7%)	416/1660 (25.1%)	0.91 [0.81-1.02]	.63
No; N=562	61/271 (22.5%)	78/291 (26.8%)	0.84 [0.63-1.12]	

a: Log binomial regression analysis of the 4004 children who participated in the clinical examination at 13 months of age (93.9% of the randomised children).

b: Based on information from the telephone interview at 13 months of age, in which 2100 children from the BCG group and 2071 children from the control group participated.

c: Based on information from the clinical examination at 13 months of age, in which 2044 children from the BCG group and 1946 children from the control group participated.

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

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Supplementary Table 1: Sensitivity analyses. Different definitions of atopic dermatitis (AD) in first year of life, in relation to neonatal BCG-vaccination and potential effect modifiers.

	Including parent-suspected AD (pre-specified main outcome)[a]	**Per Protocol[b]**	**Complete cases[c]**	**More specific AD definition[d]**	**Complementary log-log analysis[e]**
Number of children in the analysis	4004	3966	3880	4004	4228
RR [95% CI] of AD	0.93 [0.84-1.03]	0.90 [0.81-1.01]	0.91 [0.81-1.01]	0.87 [0.77-0.98]	0.89 [0.78-1.00]
AD in BCG group; N (%)	538/2052 (26.2%)	466/2046 (22.8%)	459/2003 (22.9%)	384/2052 (18.7%)	473/2118 (22.3%)
AD in control group; N (%)	548/1952 (28.1%)	484/1920 (25.2%)	475/1877 (25.3%)	420/1952 (21.5%)	517/2110 (24.5%)
AD in relation to potential effect modifiers:					
Gestational age (GA) at birth					
Premature (GA 32+0 to 36+6)	0.81 [0.45-1.45]	0.69 [0.37-1.28]	0.64 [0.34-1.22]	0.77 [0.40-1.52]	0.70 [0.35-1.44]
Mature (GA at least 37+0)	0.93 [0.84-1.03]	0.91 [0.81-1.02]	0.92 [0.82-1.03]	0.87 [0.77-0.99]	0.89 [0.79-1.01]
Sex					
Boys	0.86 [0.76-0.98]	0.85 [0.74-0.98]	0.86 [0.74-0.99]	0.86 [0.73-1.00]	0.83 [0.70-0.98]
Girls	1.03 [0.88-1.21]	0.98 [0.83-1.17]	0.99 [0.83-1.18]	0.89 [0.74-1.09]	0.97 [0.80-1.18]
Atopic predisposition					
With atopic predisposition	0.89 [0.79-0.99]	0.85 [0.75-0.96]*	0.84 [0.74-0.96]*	0.81 [0.70-0.93]*	0.82 [0.70-0.94]*
Without atopic predisposition	1.08 [0.88-1.33]	1.11 [0.89-1.39]*	1.13 [0.90-1.42]*	1.10 [0.86-1.41]*	1.12 [0.88-1.43]*

Maternal BCG-status					
Mother BCG-vaccinated	0.84 [0.65-1.07]	0.77 [0.58-1.01]	0.77 [0.59-1.02]	0.70 [0.52-0.95]	0.74 [0.55-1.00]
Mother not BCG-vaccinated	0.95 [0.85-1.06]	0.93 [0.83-1.05]	0.94 [0.83-1.06]	0.91 [0.79-1.04]	0.92 [0.80-1.06]
Ethnicity					
Danish ethnicity	0.93 [0.83-1.04]	0.92 [0.81-1.04]	0.92 [0.81-1.05]	0.87 [0.76-1.01]	0.91 [0.79-1.04]
Non-Danish ethnicity	0.94 [0.75-1.17]	0.87 [0.68-1.11]	0.88 [0.68-1.12]	0.90 [0.69-1.16]	0.85 [0.65-1.12]
Siblings					
No older siblings	0.91 [0.80-1.04]	0.90 [0.78-1.04]	0.90 [0.78-1.04]	0.85 [0.73-1.00]	0.88 [0.75-1.04]
At least one older sibling	0.95 [0.81-1.12]	0.90 [0.76-1.08]	0.91 [0.76-1.09]	0.90 [0.74-1.09]	0.89 [0.73-1.09]
Pets at home					
Yes	0.96 [0.78-1.19]	0.91 [0.72-1.15]	0.92 [0.73-1.17]	0.88 [0.68-1.14]	0.88 [0.68-1.13]
No	0.92 [0.82-1.04]	0.91 [0.80-1.03]	0.91 [0.80-1.03]	0.87 [0.76-1.00]	0.89 [0.77-1.03]
Age in days at randomisation					
0-1	0.92 [0.82-1.04]	0.92 [0.80-1.04]	0.92 [0.80-1.04]	0.88 [0.77-1.02]	0.90 [0.78-1.04]
2-7	0.85 [0.69-1.06]	0.85 [0.69-1.06]	0.87 [0.70-1.08]	0.82 [0.64-1.04]	0.85 [0.67-1.09]
Had received first pentavalent vaccination before 3-month-follow-up					
Yes	0.95 [0.75-1.19]	0.80 [0.61-1.03]	0.85 [0.65-1.11]	0.77 [0.58-1.04]	0.77 [0.57-1.03]
No	0.92 [0.83-1.03]	0.93 [0.82-1.05]	0.92 [0.81-1.04]	0.89 [0.78-1.02]	0.91 [0.80-1.05]

Breast-feeding					
Fully breastfed until 3 months of age	0.93 [0.81-1.06]	0.88 [0.76-1.02]	0.86 [0.74-1.00]	0.83 [0.71-0.98]	0.86 [0.73-1.02]
Not fully breastfed until 3 months	0.92 [0.79-1.08]	0.93 [0.79-1.11]	0.97 [0.81-1.15]	0.92 [0.76-1.11]	0.91 [0.75-1.10]
Use of hydrolysed infant formulas at 3 months					
Yes	0.89 [0.62-1.26]	0.86 [0.59-1.25]	0.86 [0.59-1.25]	0.85 [0.57-1.26]	0.83 [0.54-1.28]
No	0.93 [0.84-1.03]	0.91 [0.81-1.02]	0.91 [0.81-1.02]	0.88 [0.77-1.00]	0.89 [0.78-1.02]
Smoking status by 13 months of age					
Ever smoked since birth of child	1.12 [0.91-1.37]*	1.07 [0.85-1.34]	1.06 [0.84-1.33]	1.01 [0.79-1.30]	1.02 [0.79-1.30]
Never smoked since birth of child	0.87 [0.77-0.98]*	0.86 [0.75-0.97]	0.86 [0.76-0.98]	0.82 [0.71-0.95]	0.84 [0.73-0.97]
Started institutional child care before 13-month-follow-up					
Yes	0.94 [0.84-1.05]	0.91 [0.81-1.03]	0.92 [0.81-1.03]	0.87 [0.76-1.00]	0.89 [0.78-1.02]
No	0.89 [0.69-1.15]	0.85 [0.63-1.14]	0.86 [0.64-1.15]	0.86 [0.62-1.18]	0.83 [0.60-1.16]

RR: Risk Ratio; CI: Confidence Intervals; *: P-value<.05 in the test of no interaction.

a: Pre-specified main outcome: Any parent-suspected or clinically diagnosed AD in first year of life. Log binomial regression analysis on the 4,004 children (93.9% of randomized children) who participated in the clinical examination at 13 months of age. The study protocol planned to include all cases of parent-suspected or clinically diagnosed AD as the primary outcome, and to use “clinically diagnosed AD” (diagnosed by a physician or verified at the clinical examinations) as a more specific secondary outcome. Given the high prevalence and presumed imprecision of the broad definition, we in the article emphasized the more specific “clinically diagnosed AD”.

b: Clinically diagnosed AD in first year of life, Per Protocol analysis. Log binomial regression analysis on the 3,966 children (93.1% of the randomized children) who participated in the clinical examination at 13 months of age and followed their randomization-group. Of the 4,004 children participating in the clinical examination at 13 months of age 5 children from the BCG group were excluded from this Per Protocol analysis because of declination of the BCG vaccination, and 1 child because it by mistake did not receive a BCG-vaccination. Among the children from the control group 16 had a BCG-vaccination elsewhere and the BCG-vaccination status of 16 children was not confirmed.

c: Clinically diagnosed AD in first year of life. Log binomial regression analysis on the 3,880 children (91.0% of the randomized children) with full follow-up (participated in both telephone interviews and in both clinical examinations).

d: Specific AD-diagnosis: objective SCORAD values at least 8.0; or steroid-treated AD diagnosed at the clinical examination or by a medical doctor. Log binomial regression analysis on the 4,004 children (93.9% of the randomized children) who participated in the clinical examination at 13 months of age.

e: Clinically diagnosed AD in first year of life. Complementary log-log analysis, a discrete time survival analysis, which takes incomplete follow-up time into account. Analyzed on 4,228 children (99.2% of the randomized children), i.e. on all children with any (full or partial) follow-up information, as the families of 34 randomized children withdrew their consent before the first follow-up telephone interview at 3 months of age.