

MR. NILS SKAJAA (Orcid ID : 0000-0001-8351-7133)

DR. LISBETH M THØSTESSEN (Orcid ID : 0000-0003-3231-1260)

Article type : Letter to the Editor

Type of manuscript: Letter to the Editor

Manuscript ID: ALL-2019-00297

Manuscript title: Cesarean delivery and risk of atopic dermatitis

Short title: Cesarean delivery and atopic dermatitis

Word count: 1000

Letter Summary

Atopic dermatitis is a common and disabling inflammatory skin disease. Cesarean delivery may impact gut colonization, immune system maturation, and ultimately the risk of developing atopic dermatitis. In a study nested within The Danish Calmette Study, a randomized clinical multicenter study, we examined the risk of atopic dermatitis at 3 and 13 months of age, comparing cesarean delivered newborns with those vaginally born. Adjusting for maternal age, gestational age, birth season, number of siblings, randomization group, and atopic predisposition, the adjusted risk ratios showed that cesarean delivery was not associated with an increased risk of atopic dermatitis at 3 months of age (adjusted risk ratio: 1.09 [95% CI: 0.84–1.41]) or at 13 months of age (adjusted risk ratio: 1.05 [95% CI: 0.90–1.23]).

To the Editor,

Atopic dermatitis is a common and disabling inflammatory skin disease.¹ Compared with those born vaginally, cesarean delivered children acquire an altered gut microflora owing to delayed gut colonization.² The diverge bacteria colonization may disrupt the Th1/Th2 lymphocyte balance and

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14093](#)

This article is protected by copyright. All rights reserved

delay adequate immune system development. Children born by elective cesarean delivery lack the stress response that vaginal delivery induces, which may affect hypothalamic-pituitary-adrenal axis activation, ultimately delaying immune system maturation. As the role of the gut microbiota in the development of atopic dermatitis seems plausible,³ cesarean delivery may impact the risk of atopic diseases.⁴

Thus, we examined if cesarean delivery increases the risk of atopic dermatitis compared with vaginal delivery. The present study was nested within The Danish Calmette Study, a randomized clinical multicenter trial.⁵ A total of 4,262 newborns received bacillus Calmette-Guérin (BCG) or no BCG within 7 days of birth and were followed to 13 months of age.

Through structured telephone interviews conducted before randomization by trained study staff, we obtained information on baseline characteristics and covariates. Data on delivery method was obtained during randomization. We considered vaginal and vaginal assisted delivery as vaginal delivery. The outcome was clinically diagnosed atopic dermatitis, *i.e.* confirmed by a medical doctor or during pre-specified clinical examinations at 3 and 13 months after birth.

We calculated cumulative risks, unadjusted (uRRs), and adjusted risk ratios (aRRs) of atopic dermatitis at 3 and 13 months of age comparing cesarean with vaginal delivery using Poisson regression with robust variance. In adjusted analyses, we adjusted for maternal age, gestational age, randomization group, hospital site, and atopic predisposition (*i.e.* having a biological parents or full sibling with a current or previous diagnosis of atopic dermatitis, food allergy, hay fever, or asthma).

Results were stratified by randomization group, sex, hospital site, atopic predisposition, and use of antibiotics during labor. In two additional analyses, we compared the risk of atopic dermatitis between elective and emergency cesarean delivery, and between elective cesarean delivery and any other delivery. These analyses were done on a subset of our analytic population, for which more detailed information were available. We stratified these analyses by hospital site and use of antibiotics during labor.

STATA 15.0 (StataCorp, College Station, Texas, USA) was used for all analyses. 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).

Of the 4,262 children (from 4,184 mothers) included in The Danish Calmette Study, we restricted the analyses to the 3,577 (84%) children with complete information on outcome and covariates. Of these children, 719 (20%) were born by cesarean delivery and 2,858 (80%) by vaginal delivery (227 [8%] instrumentally assisted). Atopic predisposition was slightly more prevalent in the cesarean delivery cohort than in the vaginal delivery cohort (72% vs. 67%, $p=0.02$) (Table 1).

The cumulative risk of atopic dermatitis at 3 months of age was 9.2% for both the cesarean delivery and the vaginal delivery cohorts (uRR: 0.99 [95% CI: 0.77–1.29]). At 13 months of age, the cumulative risks were 22.0% and 21.0% for the cesarean delivery cohort and vaginal delivery cohort (uRR: 1.05 [0.90–1.23]). After covariate adjustment, cesarean delivery was not associated with atopic dermatitis at 3 months of age (aRR: 1.09 [95% CI: 0.84–1.41]) nor at 13 months of age (aRR: 1.05 [95% CI: 0.90–1.23]) (Table 2, Table S1–2).

None of the potential effect modifiers substantially modified the effect of cesarean delivery on the risk of dermatitis (Table 2). The risk of atopic dermatitis was similar between and elective and emergency cesarean delivery; compared with any other delivery types, elective cesarean delivery was associated with a slight increase in risk (Table S3–4).

Our findings agree largely with those from previous studies^{6,7} including a meta-analysis of six studies, which estimated an odds ratio of 1.03 (95% CI: 0.98–1.09).⁶

BCG vaccination may protect against atopic dermatitis in atopic predisposed children;⁸ however, we found no meaningful risk differences in randomization groups. Despite being a strong risk factor for atopic dermatitis, atopic predisposition did not modify our results. Prophylactic administration of antibiotics during labor is more common during a cesarean delivery than during a vaginal delivery (28% vs. 13% in our cohort); conversely, early breastfeeding may be less common for cesarean delivered newborns.⁹ Both factors may impact microflora colonization in the newborn.⁴ As we attempted to assess the total effect of cesarean delivery on the risk of atopic dermatitis, we did not adjust for any of these potential mediators. In stratified analyses, the effect of cesarean section was not modified by use of antibiotics. While an emergency cesarean section may allow for maternal microflora exposure, an elective procedure typically does not. In the additional analyses comprising

88% of the children born by cesarean delivery, the risk of atopic dermatitis tended to be slightly increased for elective cesarean delivery compared with any other delivery type.

Our study has limitations. First, atopic dermatitis is a challenging diagnosis, particularly in infants. We strengthened the validity of the diagnosis by including only clinically diagnosed cases. The prevalence of atopic dermatitis was high in our cohort (21%), likely due to the high prevalence of atopic predisposition (68%). Noteworthy, the effect of cesarean delivery did not differ substantially between children with or without atopic predisposition, suggesting that this did not influence the overall conclusions. Second, socioeconomic status may alter risk of atopic dermatitis, but we were unable to sufficiently control for this. However, the organization of the Danish health care system with unfettered access to care across all socioeconomic gradients and ethnic groups reduced the likelihood of confounding by socioeconomic status.

In conclusion, in this study nested within a randomized controlled trial, we found that cesarean delivery, compared with vaginal delivery, did not increase the risk of developing atopic dermatitis in infancy. Based on the available evidence, cesarean delivery, particularly emergency procedures, may not be a strong risk factor for the development of atopic dermatitis.

REFERENCES

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016; **387**(10023): 1109-22.
2. Stokholm J, Thorsen J, Chawes BL, et al. Cesarean section changes neonatal gut colonization. *J Allergy Clin Immunol* 2016; **138**(3): 881-9 e2.
3. Petersen EBM, Skov L, Thyssen JP, Jensen P. Role of the Gut Microbiota in Atopic Dermatitis: A Systematic Review. *Acta Derm Venereol* 2018.
4. Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. *Am J Obstet Gynecol* 2013; **208**(4): 249-54.
5. Thostesen LM, Nissen TN, Kjaergaard J, et al. Bacillus Calmette-Guerin immunisation at birth and morbidity among Danish children: A prospective, randomised, clinical trial. *Contemp Clin Trials* 2015; **42**: 213-8.
6. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2008; **38**(4): 634-42.
7. Gerlich J, Benecke N, Peters-Weist AS, et al. Pregnancy and perinatal conditions and atopic disease prevalence in childhood and adulthood. *Allergy* 2018; **73**(5): 1064-74.
8. Steenhuis TJ, van Aalderen WM, Bloksma N, et al. Bacille-Calmette-Guerin vaccination and the development of allergic disease in children: a randomized, prospective, single-blind study. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2008; **38**(1): 79-85.
9. Prior E, Santhakumaran S, Gale C, Philipps LH, Modi N, Hyde MJ. Breastfeeding after cesarean delivery: a systematic review and meta-analysis of world literature. *Am J Clin Nutr* 2012; **95**(5): 1113-35.

Authors: Nils Skajaa, MSc^a; Thomas Nørrelykke Nissen, MD, PhD^b; Nina Marie Birk, MD, PhD^b; Dorthe Lisbeth Jeppesen, MD, PhD^b; Lisbeth Marianne Thøstesen, MD, PhD^{c,d}; Christine Stabell Benn, MD, PhD, DMSc^{a,e}

Affiliation:

^aResearch Center for Vitamines and Vaccines, Bandim Health Project, Statens Serum Institute, Denmark

^bDepartment of Pediatrics, Copenhagen University Hospital, Hvidovre, Denmark

^cDepartment of Pediatrics, Kolding Hospital, Denmark

^dDepartment of Pediatrics, Herning Hospital, Denmark

^eOPEN, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

Corresponding author: Nils Skajaa, Research Center for Vitamines and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institute, Artillerivej 5, 2300 Copenhagen S, Denmark
Denmark; Phone: +45 6170 3970; Email: nilsskajaa@clin.au.dk

Author contributions: C.S.B conceived the study idea and designed the study. N.S. directed and conducted the analyses. All authors participated in the discussion and interpretation of the results. N.S. reviewed the literature, organized the writing, and wrote initial drafts. All authors critically revised the manuscript for intellectual content and improved the final version. C.S.B. is the guarantor.

Conflict of interest: The authors report no relation that could be construed as a conflict of interest.

Sources of Funding: The Calmette Study was conducted with funding from The Danish National Research Foundation (DNRF108).

Table 1. Characteristics of children born by cesarean delivery and vaginal delivery.

	Cesarean delivery	Vaginal delivery	Mann-Whitney or joint chi-square test, <i>p</i> -value
	N=719	N=2,858	
Median (25 th –75 th percentiles) maternal age, years	33 (30–36)	32 (29–35)	<0.001
Median (25 th –75 th percentiles) gestational age, days	274 (268–285)	282 (276–288)	<0.001
Siblings			
0	399 (55%)	1,641 (57%)	0.11
1	230 (32%)	946 (33%)	
2	81 (11%)	240 (8%)	
3+	9 (1%)	31 (1%)	
Randomization group			
BCG	371 (52%)	1,469 (51%)	0.92
No BCG	348 (48%)	1,389 (49%)	
Atopic predisposition			
Yes	517 (72)	1,923 (67)	0.02
No	202 (28)	935 (33)	
Sex			
Boys	397 (55%)	1,499 (52%)	0.18
Girls	322 (45%)	1,359 (48%)	
Hospital			
Hvidovre Hospital	259 (36%)	877 (33%)	0.008
Kolding Hospital	222 (31%)	879 (31%)	
Rigshospitalet	238 (33%)	1,102 (39%)	
Antibiotics during			

labor				
Yes	200 (28%)	368 (13%)		<0.001
No	519 (72%)	2,490 (87%)		

Abbreviations: BCG, bacillus Calmette-Guérin.

Table 2. Risk of atopic dermatitis at 3 and 13 months, comparing cesarean delivery with vaginal delivery, and stratified by sex, hospital, atopic predisposition, randomization group, and use of antibiotics during labor.

		Events/At risk (%)		Risk ratio(95% CI)		Test for interaction, <i>p</i> -value
		Cesarean delivery	Vaginal delivery	Unadjusted	Adjusted*	
Main analysis						
3 months		66/719 (9.2)	264/2,858 (9.2)	0.99 (0.77–1.29)	1.09 (0.84–1.40)	-
13 months		158/719 (22.0)	596/2,858 (20.9)	1.05 (0.90–1.23)	1.05 (0.90–1.23)	-
Subgroup analyses						
3 months	BCG	30/371 (8.1)	133/1,469 (9.1)	0.89 (0.61–1.31)	0.98 (0.67–1.43)	0.45
	No BCG	36/348 (10.3)	131/1,389 (9.4)	1.10 (0.77–1.56)	1.19 (0.84–1.69)	
13 months	BCG	77/371 (20.8)	288/1,469 (19.6)	1.06 (0.85–1.32)	1.05 (0.83–1.33)	0.98
	No BCG	81/348 (23.3)	308/1,389 (22.2)	1.05 (0.85–1.30)	1.05 (0.85–1.30)	
3 months	Boys	46/397 (11.6)	160/1,499 (10.7)	1.09 (0.80–1.48)	1.15 (0.85–1.57)	0.40
	Girls	20/322 (6.2)	104/1,359	0.81 (0.51–	0.91 (0.57–	

13 months	Boys	100/397	(7.7)	1.29)	1.45)	0.48
		(25.2)	341/1,499	1.11 (0.91–1.34)	1.09 (0.90–1.33)	
	Girls	58/322 (18.0)	255/1,359	0.96 (0.74–1.24)	0.97 (0.75–1.26)	
3 months	Hvidovre Hospital	30/259 (11.6)	107/877	0.95 (0.65–1.39)	0.98 (0.67–1.43)	0.89
	Kolding Hospital	18/222 (8.1)	73/879 (8.3)	0.98 (0.60–1.60)	1.12 (0.68–1.84)	
	Rigshospitalet	18/238 (7.6)	84/1,102	0.99 (0.61–1.62)	1.11 (0.68–1.81)	
			(7.6)			
13 months	Hvidovre Hospital	64/259 (24.7)	209/877	1.04 (0.81–1.32)	1.03 (0.81–1.32)	0.34
	Kolding Hospital	30/222 (13.5)	139/879	0.85 (0.59–1.23)	0.88 (0.61–1.26)	
	Rigshospitalet	64/238 (26.9)	248/1,102	1.19 (0.94–1.51)	1.20 (0.94–1.53)	
			(22.5)			
3 months	Atopic predisposition	56/517 (10.8)	216/1,923	0.96 (0.73–1.27)	1.09 (0.83–1.44)	0.95
	No atopic predisposition	10/202 (5.0)	48/935 (5.1)	0.96 (0.50–1.87)	1.07 (0.55–2.07)	
13 months	Atopic predisposition	124/517	463/1,923	1.00 (0.84–1.18)	1.01 (0.85–1.21)	0.36
	No atopic predisposition	34/202 (16.8)	133/935	1.18 (0.84–1.67)	1.21 (0.86–1.71)	
3 months	Antibiotics	20/200 (10.0)	22/368 (6.0)	1.67 (0.94–2.99)	1.73 (0.97–3.05)	0.10
	No antibiotics	46/519 (8.9)	242/2,490	0.91 (0.68–1.23)	1.00 (0.74–1.35)	

13 months	Antibiotics	49/200 (24.5)	75/368 (20.4)	1.20 (0.88–1.65)	1.20 (0.88–1.65)	0.33
	No antibiotics	109/519 (21.0)	521/2,490 (20.9)	1.00 (0.84–1.21)	1.00 (0.83–1.21)	

Abbreviations: BCG, bacillus Calmette-Guérin. *Adjusted for maternal age, gestational age, number of siblings, randomization group, and atopic predisposition.

Online Supplementary

METHODS

Setting

This study built on data from The Danish Calmette Study, which is described in detail elsewhere.¹ In short, The Danish Calmette Study was a randomized clinical multicenter trial conducted between 2012 and 2015 in three hospitals in Denmark. Within 7 days of birth, 4262 newborns were allocated 1:1 to bacillus Calmette-Guérin (BCG) vaccination (Statens Serum Institute strain 1331) or no intervention. Exclusion criteria were gestational age <32 weeks, birth weight <1000 g, known immunodeficiency, or no Danish-speaking parent. Randomization was stratified by maturity (gestational age ≥ 37 weeks vs. gestational age <37 weeks). Siblings were randomized together as one randomization unit. Informed consent was obtained before randomization.

Data collection

Before randomization, data on baseline characteristics and covariables was obtained through structured telephone interviews. Data on delivery method (cesarean section, vaginal, and vaginal assisted delivery) was obtained during randomization. Follow-up consisted of structured telephone interviews and subsequent clinical examinations at 3 and 13 months of age. Pertinent to this study, in structured telephone interviews, parents reported if their child had had atopic dermatitis since birth (3-month interview) or since the last interview (13-month interview). If confirmatory, parents reported on the duration, location of eczema, sleep disturbances, use of topical steroids, and if the diagnosis had been confirmed by a medical doctor. In the subsequent

clinical examinations, the Scoring Atopic Dermatitis (SCORAD)² form was used to assess cases with atopic dermatitis.

All structured interviews and clinical examinations were performed by specially trained study staff.

Exposure and outcome assessment

In the present study, we considered vaginal and vaginal assisted delivery as belonging to the same delivery method. Due to a high prevalence of parent-reported atopic dermatitis, we considered as outcome only clinically diagnosed atopic dermatitis (that is, atopic dermatitis confirmed by a medical doctor or during the clinical examinations).³

Statistical analysis

We tabulated the distribution of the baseline characteristics among children delivered by cesarean delivery and vaginal delivery. We reported absolute cumulative risks of atopic dermatitis at 3 and 13 months of age. Using Poisson regression with robust variance, we calculated unadjusted (uRRs) and adjusted risk ratios (aRRs) of atopic dermatitis at 3 and 13 months of age comparing cesarean and vaginal delivery.⁴ In adjusted analyses, we controlled for maternal age (continuous), gestational age (continuous), number of siblings (0, 1, 2, 3+), randomization group (BCG, no BCG), and atopic predisposition (yes/no). We defined atopic predisposition as having a biological parents or full sibling with a current or previous diagnosis of atopic dermatitis, food allergy, hay fever, or asthma, confirmed by a doctor.³ We reported estimates with associated 95% confidence intervals (CIs).

Additional analyses

We stratified the results by randomization group, sex, hospital (Kolding Hospital, Hvidovre Hospital, and Rigshospitalet), atopic predisposition, and use of antibiotics during labor.

In two additional analyses, we compared the risk of atopic dermatitis between elective and emergency cesarean delivery, and between elective Cesarean delivery and any other delivery. These analyses were done on a subset of our analytic population, for which more detailed information were available. We stratified these analyses by hospital site and use of antibiotics during labor.

Table S1. Risk of atopic dermatitis at 3 and 13 months, comparing cesarean delivery with vaginal delivery. Atopic dermatitis diagnosed by general practitioner at 3 and 13 months of age.

	Events/At risk (%)		Risk ratio (95% CI)	
	Cesarean delivery	Vaginal delivery	Unadjusted	Adjusted*
3 months	12/719 (1.7)	31/2,858 (1.1)	1.54 (0.79–2.98)	1.60 (0.84–3.05)
13 months	89/719 (12.4)	339/2,858 (11.9)	1.04 (0.84–1.30)	1.06 (0.85–1.33)

*Adjusted for maternal age, gestational age, number of siblings, randomization group, and atopic predisposition.

Table S2. Risk of atopic dermatitis at 3 and 13 months, comparing cesarean delivery with vaginal delivery. Atopic dermatitis diagnosed during the trial's pre-specified clinical examinations at 3 and 13 months of age.

	Events/At risk (%)		Risk ratio (95% CI)	
	Cesarean delivery	Vaginal delivery	Unadjusted	Adjusted*
3 months	63/719 (8.8)	251/2,858 (8.8)	1.00 (0.76–1.30)	1.09 (0.83–1.41)
13 months	119/719 (16.6)	419/2,858 (14.7)	1.13 (0.94–1.36)	1.10 (0.91–1.32)

*Adjusted for maternal age, gestational age, number of siblings, randomization group, and atopic predisposition.

Table S3. Risk of atopic dermatitis at 3 and 13 months, comparing elective with emergency cesarean delivery, and stratified by hospital site and use of antibiotics during labor.

		Events/At Risk (%)		Risk ratio (95% CI)		Test for interaction, <i>p</i> -value
		Elective cesarean delivery	Emergency cesarean delivery	Unadjusted	Adjusted*	
Main analyses						
3 months		28/280 (10.0)	34/364 (9.3)	1.07 (0.66–1.71)	1.25 (0.72–2.18)	-
13 months		69/280 (24.6)	79/364 (21.7)	1.13 (0.85–1.50)	1.10 (0.80–1.51)	-
Subgroup analyses						
3 months	Hvidovre Hospital	13/111 (11.7)	17/146 (11.6)	1.00 (0.51–1.98)	1.40 (0.73–2.69)	0.45
	Kolding Hospital	7/60 (11.6)	7/81 (8.6)	1.35 (0.50–3.64)	1.66 (0.73–3.80)	
	Rigshospitalet	8/109 (7.3)	10/137 (7.3)	1.01 (0.41–2.46)	0.93 (0.42–2.07)	
13 months	Hvidovre Hospital	26/111 (23.4)	38/146 (26.0)	0.90 (0.58–1.39)	1.00 (0.66–1.51)	0.10
	Kolding Hospital	10/60 (16.7)	9/81 (11.1)	1.50 (0.65–3.46)	0.72 (0.39–1.33)	
	Rigshospitalet	33/109 (30.3)	32/137 (23.4)	1.30 (0.85–1.97)	1.38 (0.95–1.99)	
3 months	Antibiotics	4/62 (6.5)	14/126 (11.1)	0.58 (0.20–1.69)	0.68 (0.22–2.02)	0.19
	No antibiotics	24/218 (11.0)	20/238 (8.4)	1.31 (0.75–2.30)	1.51 (0.80–2.86)	
13 months	Antibiotics	18/62 (29.0)	27/126 (21.4)	1.35 (0.81–2.26)	1.13 (0.77–2.22)	0.45
	No antibiotics	51/218 (23.4)	52/238 (21.8)	1.07 (0.76–1.50)	1.03 (0.71–1.49)	

*Adjusted for maternal age, gestational age, number of siblings, randomization group, and atopic predisposition.

Table S4. Risk of atopic dermatitis at 3 and 13 months, comparing elective with any other delivery type, and stratified by hospital site and use of antibiotics during labor.

		Events/At Risk (%)		Risk ratio (95% CI)		Test for interaction, <i>p</i> -value
		Elective cesarean delivery	Any other delivery type	Unadjusted	Adjusted*	
Main analyses						
3 months		28/280 (10.0)	298/3,211 (9.3)	1.09 (0.76–1.57)	1.36 (0.92–2.01)	
13 months		69/280 (24.6)	673/3,211 (21.0)	1.17 (0.95–1.46)	1.23 (0.98–1.55)	
Subgroup analyses						
3 months	Hvidovre Hospital	13/111 (11.7)	124/1,023 (12.1)	0.97 (0.56–1.65)	1.49 (0.87–2.53)	0.82
	Kolding Hospital	7/60 (11.6)	80/960 (8.3)	1.40 (0.68–2.90)	1.41 (0.69–2.87)	
	Rigshospitalet	8/109 (7.3)	94/1,228 (7.7)	0.96 (0.48–1.92)	1.14 (0.57–2.28)	
13 months	Hvidovre Hospital	26/111 (23.4)	247/1,023 (24.1)	0.97 (0.68–1.38)	1.15 (0.81–1.63)	0.09
	Kolding Hospital	10/60 (16.7)	148/960 (15.4)	1.08 (0.60–1.94)	0.81 (0.46–1.44)	
	Rigshospitalet	33/109 (30.3)	278/1,228 (22.6)	1.34 (0.99–1.81)	1.57 (1.15–2.14)	
3 months	Antibiotics	4/62 (6.5)	36/493 (7.3)	0.88 (0.33–2.40)	1.11 (0.41–3.03)	0.67
	No antibiotics	24/218 (11.0)	262/2718 (9.6)	1.14 (0.77–1.69)	1.40 (0.92–2.12)	
13 months	Antibiotics	18/62 (29.0)	101/493 (20.5)	1.42 (0.93–2.17)	1.53 (1.00–2.35)	0.26
	No antibiotics	51/218 (23.4)	572/2,718 (21.0)	1.11 (0.86–1.43)	1.15 (0.89–1.50)	

*Adjusted for maternal age, gestational age, number of siblings, randomization group, and atopic predisposition.

References

1. Thostesen LM, Nissen TN, Kjaergaard J, et al. Bacillus Calmette-Guerin immunisation at birth and morbidity among Danish children: A prospective, randomised, clinical trial. *Contemp Clin Trials* 2015; **42**: 213-8.
2. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol* 2007; **157**(4): 645-8.
3. Thostesen LM, Kjaergaard J, Pihl GT, et al. Neonatal BCG vaccination and atopic dermatitis before 13 months of age: A randomized clinical trial. *Allergy* 2018; **73**(2): 498-504.
4. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol* 2003; **3**: 21.