

# Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases

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**Background:** Whether probiotics, which can influence the microbiome, prevent infant eczema or allergic disease remains an open question. Most studies have focused on high-risk infants.

**Objectives:** We sought to assess whether consumption of probiotic milk products protects against atopic eczema, rhinoconjunctivitis, and asthma in early childhood in a large population-based pregnancy cohort (the Norwegian Mother and Child Cohort study).

**Methods:** We examined associations between consumption of probiotic milk products in pregnancy and infancy with questionnaire-reported atopic eczema, rhinoconjunctivitis, and asthma in 40,614 children. Relative risks (RRs) were calculated by using general linear models adjusted for potential confounders.

**Results:** Consumption of probiotic milk in pregnancy was associated with a slightly reduced relative risk (RR) of atopic eczema at 6 months (adjusted RR, 0.94; 95% CI, 0.89-0.99) and of rhinoconjunctivitis between 18 and 36 months (adjusted RR, 0.87; 95% CI, 0.78-0.98) compared with no consumption during pregnancy. Maternal history of allergic disease did not notably influence the associations. When both the mother (during pregnancy) and infant (after 6 months of age) had consumed probiotic milk, the adjusted RR of rhinoconjunctivitis was 0.80 (95% CI, 0.68-0.93) relative to no consumption by either. Probiotic milk consumption was not associated with asthma at 36 months.

**Conclusions:** In this population-based cohort consumption of probiotic milk products was related to a reduced incidence of atopic eczema and rhinoconjunctivitis, but no association was seen for incidence of asthma by 36 months of age. (*J Allergy Clin Immunol* 2013;■■■:■■■-■■■.)

**Key words:** Allergy, asthma, eczema, microbiome, Norwegian Mother and Child Cohort Study, probiotics, rhinoconjunctivitis

The development of allergic diseases in childhood is influenced by factors that stimulate the immune system. Intestinal microbes influence immunologic maturation in infants.<sup>1</sup> The fecal flora has been found to differ between infants who later have allergic diseases and those who do not.<sup>2-4</sup> The composition of the intestinal microbiome is determined by exposure to maternal vaginal inoculum at birth, diet, and other factors.<sup>5,6</sup> Manipulation of the intestinal microbiome in infants might provide an approach to the prevention of allergic diseases.

Probiotics are defined as “live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host.”<sup>7</sup> One meta-analysis of clinical trials concluded that probiotics given as supplements in pregnancy or infancy might reduce the risk of atopic eczema in infants.<sup>8</sup> Most of the trials have been conducted among high-risk infants.<sup>8-10</sup> However, a consensus report and other publications have concluded that a role for probiotics in the prevention of eczema and other allergic diseases is not established and that further data are needed.<sup>11-13</sup> In a large European birth cohort the timing of infantile intestinal colonization was not associated with early childhood atopic eczema or food allergy.<sup>14</sup> Thus even if probiotic supplementation can provide some beneficial effect, the timing of probiotic supplementation and whether continued supplementation in infancy is necessary are still unclear.<sup>9,10</sup> Thus questions remain about efficacy, and there are few data on outcomes other than eczema or on potential differential effects of treatment in pregnancy versus infancy.<sup>12</sup>

Data from clinical trials are the gold standard for establishing causality but also have limitations.<sup>15,16</sup> In the case of probiotic supplementation and infant eczema, the trials have been relatively modest in size (median of 175 [range, 69-925] infants in the 13 studies included in the meta-analysis<sup>8</sup>).<sup>12</sup> Furthermore, they have been conducted in high-risk infants, and thus their generalizability to the population as a whole remains uncertain.

Consumption of probiotic foods and dietary supplements is becoming increasingly common<sup>17,18</sup>; in the United States new formulations of probiotic dietary supplements and foods are introduced almost daily.<sup>19</sup> Thus questions about the generalizability of the trial results are of growing importance.

To address these issues, we examined data from a large, prospective pregnancy cohort, the Norwegian Mother and Child Cohort Study (MoBa), to assess whether maternal intake of lactobacilli-containing yogurt and milk, the only probiotic foods widely available in Norway at the time of the study, protect against eczema, rhinoconjunctivitis, and asthma in early childhood. We also considered the effect of consumption of probiotic milk products by the infant in combination with maternal intake during pregnancy.

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**Abbreviations used**

BMI: Body mass index  
 FFQ: Food frequency questionnaire  
 MJ: Megajoules  
 MoBa: Norwegian Mother and Child Cohort Study  
 RR: Relative risk

**METHODS**

We analyzed data from subjects in MoBa, which was initiated and maintained at the Norwegian Institute of Public Health.<sup>20</sup> Participants were recruited throughout Norway from 1999–2008, and 38.5% of the invited women consented to participate. The cohort now includes 108,000 children from 90,700 mothers. Follow-up is conducted by using questionnaires at regular intervals.<sup>21</sup> The study was approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway. Informed consent was obtained from each MoBa participant on recruitment.

The present study was based on version 6 of the quality-ensured data files released in 2011. The schedule for completion of questionnaires was as follows: baseline at gestational week 18, food frequency questionnaire (FFQ) at gestational week 22, third prenatal questionnaire at gestational week 30, and postnatal questionnaires at 6, 18, and 36 months. We also used information collected by the Medical Birth Registry of Norway. The version of the FFQ that includes questions on probiotic milk and yogurt consumption during pregnancy has been in use from March 1, 2002,<sup>22</sup> and thus we included mothers who enrolled in the study after this date ( $n = 76,218$  eligible, see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Among these 76,218 mothers, there were 74,751 singletons whose mothers responded to both the baseline questionnaire and the FFQ. In total, 40,614 of the eligible mothers completed all the postnatal questionnaires (up to 36 months age), of which 4,325 (10.6%) contributed more than 1 pregnancy.

**Outcomes**

Eczema was classified based on mothers' responses to a question about "atopic eczema (childhood eczema)" asked on both the 6- and 18-month questionnaires. A child was classified as having rhinoconjunctivitis based on a mother's "yes" response to a question about "allergy affecting eyes or nose, eg, hay fever" on the 36-month questionnaire. "Current asthma with asthma medication 36 months" was defined by current asthma and reported use of an inhaled asthma medication in the past 12 months on the 36-month questionnaire. Inhaled asthma medications included inhaled glucocorticoids,  $\beta_2$ -agonists, or both (see Table E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). These are the main medications dispensed for asthma at this age in Norway.

**Dietary information**

Intake of milk-based probiotic products during pregnancy was recorded in the FFQ. The women were asked how often they consumed milk and yogurt, clearly distinguishing probiotic milk and yogurt from other milk items (see page 5 of the FFQ, which is available at <http://www.fhi.no/dokumenter/011fbd699d.pdf>). The probiotic items queried were Biola milk (Tine SA, Oslo, Norway), Biola yogurt (Tine SA), and Cultura milk (Tine SA). These were the only probiotic foods widely available in Norway at the time of the study. Biola milk and yogurt contained *Lactobacillus acidophilus* LA-5, *Bifidobacterium lactis* Bb12, and *Lactobacillus rhamnosus*, and Cultura milk contained *L acidophilus* LA-5 and *B lactis* Bb12. These probiotic species are commonly used in clinical trials assessing prevention of atopic eczema because early colonization of lactobacilli is believed to protect against atopic diseases,<sup>23,24</sup> and higher bifidobacteria colonization has been reported among nonatopic compared with atopic children.<sup>25</sup> Reported pregnancy consumption across all probiotic milk products was categorized into one dichotomous variable for any intake versus no intake and one 3-level variable based on intake in milliliters per day categorized as "none," "13.0–28.3 mL/d," and "≥28.4 mL/d" (see the Methods section in this article's

Online Repository at [www.jacionline.org](http://www.jacionline.org)). The child's consumption of Biola milk between the ages of 6 and 18 months was reported in the 18-month questionnaire. We constructed a variable with 4 groups of probiotic milk consumption: no intake and intake reported for the child only, for the mother only, and for both the mother and child.

**Maternal, pregnancy, and child characteristics**

The following variables were retrieved from the MoBa questionnaires: maternal body mass index (BMI) before pregnancy (based on self-reported weight and height), maternal education, smoking status in pregnancy, maternal history of allergic disease (asthma, rhinoconjunctivitis, or both), probiotic-containing supplements, and breast-feeding (full or partial) for at least 6 months. The data retrieved from the Medical Birth Registry of Norway were marital status, parity, maternal age at delivery, delivery by cesarean section or vaginally, infant's sex, and birth weight in grams.

**Statistical analyses**

We used generalized linear models with a log-link for binary data, which produces relative risks (RR) as association measures. Robust variance estimations with cluster adjustments were used to account for siblings. In the multivariate analyses 94% to 95% of the observations were available in the analyses of atopic eczema, rhinoconjunctivitis, and asthma. Covariates were selected based on a directed acyclic graph.<sup>26</sup> The minimal sufficient adjustment set for estimating the total effect of maternal consumption of probiotic milk for allergic disease in the child was as follows: prepregnancy BMI, maternal education, smoking in pregnancy, maternal age at delivery, and dietary fiber intake. We also fitted models that took into account additional covariates: maternal history of allergic disease, total energy intake (megajoules [MJ] per day), mode of delivery (cesarean section vs vaginal), breast-feeding, parity, and infant's sex. Maternal age, dietary fiber intake, and total energy intake are reported in categories in Table I but were used as continuous variables in the statistical models. We examined the association between the child's consumption of probiotic milk products (after 6 months of age) and current atopic eczema at 18 months, rhinoconjunctivitis at 18 to 36 months, and current asthma with asthma medication at 36 months. We also performed stratified analyses by maternal history of allergic disease, mode of delivery, and sex.

*P* values of .05 or less (2-sided) were considered statistically significant. Data were analyzed with Stata 12.1 software (StataCorp, College Station, Tex).

**RESULTS**

The 40,614 children in this study were born from 2003 to 2009. In the FFQ 37% of the women reported consumption of at least 1 of the probiotic milk or yogurt products (Table I), and approximately 50% of these women also gave their child Biola milk after 6 months of age. Only 0.4% of the mothers reported taking probiotic-containing supplements (eg, in capsule form) in pregnancy. Maternal consumption of probiotic milk and yogurt in pregnancy were more common among the more highly educated women, women who did not smoke in pregnancy, primiparous women, older women, women who breast-fed their infants for at least 6 months, women with normal prepregnancy BMI, and the women with the highest daily fiber intake during pregnancy (Table I). Compared with the underlying MoBa cohort of women who entered the study after February 2002, the study population had a slightly lower proportion of women with less than a high school education, women who smoked during pregnancy, and multiparous women. However, the proportion of mothers who consumed probiotic milk during pregnancy was similar in the underlying MoBa cohort and the study population overall and across virtually all categories of covariates (see Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Among the 40,614 children, 12.2% had symptoms of atopic eczema by 6 months of age, 13.6% had current atopic eczema at 18 months of age,

**TABLE I.** Demographic and perinatal characteristics by maternal probiotic intake of 40,614 children enrolled in MoBa between March 2002 and November 2008 who had completed all questionnaires up to the 36-month questionnaire

	No. with characteristic	Percentage of total (n = 40,614)	Percentage of probiotic consumers by levels of characteristic*
Consumed probiotic milk or yogurt			
No	25,572	63	
Yes	15,042	37	
Marital status			
Married	20,209	50	37
Cohabitated	19,213	47	37
Single	1,082	3	35
Maternal education			
Less than high school	2,229	6	26
High school	11,032	27	29
Up to 4 y of college	17,692	44	38
>4 y of college	9,512	23	46
Prepregnancy BMI (kg/m <sup>2</sup> )			
<18.5	1,130	3	35
18.5-24.9	26,351	66	40
25-29.9	8,699	22	34
≥30	3,544	9	26
Daily smoking at least once during pregnancy			
No	37,091	92	38
Yes	3,155	8	24
Maternal history of asthma/allergy			
No	30,135	74	37
Yes	10,479	26	39
Parity			
Primiparous	19,756	49	40
Multiparous	20,831	51	34
Maternal age at delivery (y)			
<20-24	3,601	9	30
25-29	13,529	33	37
30-34	16,311	40	38
≥35	7,173	18	39
Probiotic milk and yogurt in pregnancy			
None	25,572	63	NA
13-28.3 mL/d	6,644	16	NA
≥28.4 mL/d	8,398	21	NA
Total energy intake (MJ/d)			
Quartile 1 (4.5-7.8)	10,033	25	32
Quartile 2 (7.9-9.2)	10,032	25	37
Quartile 3 (9.3-10.9)	10,033	25	40
Quartile 4 (≥11.0)	10,032	25	40
Dietary fiber intake (g/10 MJ)			
Quartile 1 (13-27)	10,033	25	31
Quartile 2 (>27-31)	10,032	25	37
Quartile 3 (>31-36)	10,033	25	40
Quartile 4 (>36)	10,032	25	41
Cesarean section			
No	35,057	86	37
Yes	5,557	14	36
Birth weight (g)			
<2,500	1,094	3	35
2,500-2,999	3,455	9	37
3,000-3,499	11,831	29	38
3,500-4,000	15,490	38	37
>4,000	8,744	21	36
Breast-feeding for at least 6 mo			
No	8,601	21	31
Yes	32,013	79	39

(Continued)

**TABLE I. (Continued)**

	No. with characteristic	Percentage of total (n = 40,614)	Percentage of probiotic consumers by levels of characteristic*
Sex			
Boys	20,725	51	37
Girls	19,899	49	37

NA, Not applicable.

\*All *P* values from  $\chi^2$  tests for differences in characteristics between nonconsumers and consumers were less than .05, except for marital status, sex, and birth weight. Information is missing for marital status (n = 110), smoking (n = 368), parity (n = 27), prepregnancy BMI (n = 890), and maternal education (n = 149). Prenatal questionnaire 1 is available at <http://www.fhi.no/dokumenter/1f32a49514.pdf>, and prenatal questionnaire 3 is available at <http://www.fhi.no/dokumenter/7b6b32b0cd.pdf>.

3.6% had experienced rhinoconjunctivitis symptoms between 18 and 36 months age, and 5.7% had current asthma with asthma medication at 36 months of age.

### Probiotic milk consumption and allergic disease

Probiotic milk and yogurt consumption during pregnancy compared with no consumption during pregnancy was associated with a small reduction in the adjusted RR of atopic eczema by 6 months of age (0.94; 95% CI, 0.89-0.99), but this association was no longer seen for current eczema at 18 months of age (1.00; 95% CI, 0.95-1.05; [Table II](#)). However, in an analysis considering both intake during pregnancy and childhood intake, consumption by both the mother during pregnancy and the child after 6 months of age compared with no intake by either the mother or child was associated with a slightly reduced risk of current eczema at 18 months of age (adjusted RR, 0.93; 95% CI, 0.86-1.00; [Table III](#)). For rhinoconjunctivitis between 18 and 36 months of age, the adjusted RR for probiotic intake during pregnancy compared with no intake during pregnancy was 0.87 (95% CI, 0.78-0.98; [Table II](#)), and the adjusted RR was 0.80 (0.95% CI, 0.68-0.93) in analyses incorporating pregnancy and childhood intake compared with no intake during either period ([Table III](#)). The results from the models with the directed acyclic graph-selected covariates and the additionally adjusted models were essentially the same ([Table II](#)).

No association was seen for consumption of probiotic milk products in pregnancy and asthma with asthma medication at 36 months ([Table II](#)). When we used a less stringent definition of current asthma at age 36 months that is not restricted to those using medication in the past 12 months, we had 2,556 cases compared with 2,260 with medication use. Results were similar for either outcome. For example, the adjusted RR for asthma without the medication restriction for maternal probiotic milk and yogurt consumption in pregnancy is 0.98 (95% CI, 0.90-1.06) compared with the RR for current asthma with medication use (0.99; 95% CI, 0.91-1.08; [Table II](#)). We found no evidence of a monotonic relation across the 3 categories of consumption of probiotic milk and yogurt (none, 13.0-28.3 mL/d, and ≥28.4 mL/d) for any of the outcomes (see [Table E3](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Sensitivity analyses

The estimates for atopic eczema and rhinoconjunctivitis were similar to our main results reported in [Tables II and III](#) after

**TABLE II.** Association between maternal probiotic milk and yogurt consumption in patients with pregnancy and atopic eczema, rhinoconjunctivitis, and asthma among 40,614 children in MoBa whose mothers had completed the 6-, 18-, and 36-month postnatal questionnaires

	Cases (no.)	Cases (%) <sup>*</sup>	Unadjusted RR (95% CI)	Adjusted <sup>†</sup> RR (95% CI)	Adjusted <sup>‡</sup> RR (95% CI)
Atopic eczema at 6 mo	4,849	12.2	0.94 (0.89-1.00)	0.93 (0.88-0.99)	0.94 (0.89-0.99)
Current atopic eczema at 18 mo	5,440	13.6	0.99 (0.94-1.04)	1.00 (0.94-1.05)	1.00 (0.95-1.05)
Rhinoconjunctivitis at 18-36 mo	1,425	3.6	0.85 (0.76-0.95)	0.90 (0.81-1.00)	0.87 (0.78-0.98)
Current asthma at 36 mo with asthma medication	2,260	5.7	0.97 (0.90-1.05)	0.99 (0.91-1.08)	0.99 (0.91-1.08)

<sup>\*</sup>There were missing outcome data for the following: atopic eczema at 6 months (2.1%), current atopic eczema at 18 months (1.3%), rhinoconjunctivitis at 18 to 36 months (2.9%), and current asthma at 36 months with asthma medication (2.6%). The case percentage is calculated with the total N in the denominator with no missing information.

<sup>†</sup>Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, and dietary fiber intake (in grams per 10 MJ).

<sup>‡</sup>Additional adjustment for total energy intake (in MJ per day), breast-feeding, maternal history of allergic disease, parity, infant's sex, and mode of delivery (cesarean section vs vaginal).

**TABLE III.** Association between consumption of probiotic milk products by the child only, mother only (in pregnancy), and both the mother and child and atopic eczema, rhinoconjunctivitis, and asthma among 40,614 children in MoBa who had completed the 6-, 18-, and 36-month postnatal questionnaires

Probiotic milk products	No.	Current atopic eczema at 18 mo		Rhinoconjunctivitis at 18-36 mo		Current asthma with asthma medication at 36 mo	
		Cases (%)	Adjusted <sup>*</sup> RR (95% CI)	Cases (%)	Adjusted <sup>*</sup> RR (95% CI)	Cases (%)	Adjusted <sup>*</sup> RR (95% CI)
No intake (reference)	18,572	13.6	1	3.9	1	5.8	1
Child intake only	7,000	13.6	1.01 (0.94-1.08)	3.7	0.98 (0.85-1.13)	5.9	1.08 (0.96-1.21)
Mother intake only	7,437	14.6	1.08 (1.01-1.15)	3.6	0.94 (0.81-1.08)	5.3	0.96 (0.85-1.08)
Mother and child	7,605	12.5	0.93 (0.86-1.00)	3.0	0.80 (0.68-0.93)	5.8	1.07 (0.95-1.19)

<sup>\*</sup>Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, dietary fiber intake (grams per 10 MJ), total energy intake (MJ per day), breast-feeding, maternal history of allergic disease, parity, infant's sex, and mode of delivery.

controlling for maternal income, gestational age, and day care; variables considered surrogates for antibiotic use in pregnancy (ie, reported use of medication because of upper respiratory tract infections, lower respiratory tract infections, and urinary tract infections); and variables considered surrogates for paracetamol use in pregnancy (ie, reported use of medication for headache/migraine, fever, and the common cold/flu; see Tables E4-E6 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Stratified analyses

In stratified analyses a maternal history of allergic disease did not notably influence our findings. The adjusted RR was less than 1 in both strata for both atopic eczema and rhinoconjunctivitis. Although the RR was slightly lower in the much larger group of children (74%) whose mothers did not have allergic disease (Table IV), the differences by strata were not statistically significant (interaction  $P = .5$  for atopic eczema at 6 months and  $P = .2$  for rhinoconjunctivitis).

On stratification by mode of delivery, maternal probiotic milk consumption was associated with a statistically significant reduced risk of atopic eczema at 6 months and of rhinoconjunctivitis at 18 to 36 months in the larger group (86% of subjects) born by means of vaginal delivery (Table V). There was no statistical evidence for interaction between probiotic consumption and mode of delivery ( $P > .5$  for all outcomes).

Associations were similar in girls and boys (data not shown), and there was no statistically significant interaction between probiotic consumption and child's sex ( $P > .3$  for all outcomes).

### DISCUSSION

Intake of probiotic-containing milk products in pregnancy was associated with a reduced RR of atopic eczema and

rhinoconjunctivitis in children. Although most clinical trials have focused on infants at increased risk for allergies by virtue of family history, we observed this association in a large population-based cohort, which mostly (74%) consisted of children without a maternal history of allergic disease. The association between probiotics and rhinoconjunctivitis appeared to be enhanced if both the mother (during pregnancy) and child (after 6 months of age) had consumed these products compared with no consumption or consumption only by the mother or child. Similar to results reported from randomized controlled trials, probiotics did not reduce the risk of asthma.

The modest reduction in the incidence of atopic eczema with probiotic intake in pregnancy that we observed is in line with the most recent reviews and meta-analysis of randomized controlled trials among high-risk children.<sup>8,9,13</sup> However, a consensus report, a Cochrane review, and others have concluded that there was insufficient evidence to recommend probiotic supplementation to infants in the prevention of allergic disease because of the substantial heterogeneity between the studies and the excess losses in patient follow-up.<sup>11-13</sup>

The preventive effects of probiotics have usually been seen in clinical trials that have used a combination of prenatal and postnatal supplementation,<sup>8,27</sup> and it is hard to draw conclusions regarding the relative importance of intake during the 2 periods.<sup>8</sup> Probiotic intake during pregnancy might modulate the maternal vaginal bacterial inoculum<sup>28</sup> and influence the infants' intestinal colonization during vaginal delivery. However, the evidence that probiotic supplementation in pregnancy improves the balance of the infants' gut flora have been inconclusive.<sup>2,29</sup> Probiotic supplementation is assumed to be of particular importance during the first few months after birth,<sup>2,30</sup> and continuous supplementation has been claimed to be necessary to achieve beneficial effects later in childhood.<sup>9,10</sup> Consistent with this assertion, in our study



**TABLE IV.** Association between maternal intake of probiotic-containing milk and yogurt in pregnancy and atopic eczema, rhinoconjunctivitis, and asthma for children without and with a mother with a history of asthma and allergy

	No maternal history of asthma/allergy (n = 30,135)		Maternal history of asthma/allergy (n = 10,479)	
	Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)
Atopic eczema at 6 mo	11.2	0.92 (0.86-0.99)	14.9	0.98 (0.89-1.08)
Current atopic eczema at 18 mo	12.5	1.00 (0.94-1.07)	16.5	0.99 (0.90-1.09)
Rhinoconjunctivitis at 18-36 mo	2.7	0.80 (0.69-0.94)	6.3	0.96 (0.81-1.12)
Current asthma with asthma medication at 36 mo	4.7	0.95 (0.84-1.06)	8.7	1.06 (0.92-1.21)

\*Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, dietary fiber intake (grams per 10 MJ), total energy intake (MJ per day), breast-feeding, parity, infant's sex, and mode of delivery.

**TABLE V.** Association between maternal intake of probiotic-containing milk and yogurt in pregnancy and atopic eczema, rhinoconjunctivitis, and asthma for children delivered vaginally or by means of cesarean section

	Vaginal delivery (n = 35,057)		Cesarean section (n = 5,557)	
	Cases (%)	Adjusted* aRR (95% CI)	Cases (%)	Adjusted* aRR (95% CI)
Atopic eczema by 6 mo	12.2	0.94 (0.88-1.00)	12.5	0.93 (0.80-1.09)
Current atopic eczema at 18 mo	13.7	1.00 (0.95-1.06)	12.7	0.97 (0.83-1.13)
Rhinoconjunctivitis at 18-36 mo	3.5	0.86 (0.76-0.98)	4.4	0.92 (0.70-1.22)
Current asthma with asthma medication at 36 mo	5.5	0.99 (0.90-1.09)	7.4	1.01 (0.82-1.24)

aRR, Adjusted RR.

\*Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, dietary fiber intake (grams per 10 MJ), total energy intake (MJ per day), breast-feeding, maternal history of allergic disease, parity, and infant's sex.

probiotic milk consumption in pregnancy was associated with reduced risk of atopic eczema by 6 months but not current atopic eczema at 18 months. The lack of a dose-response relationship between the amount of probiotic milk consumed and the outcome might be regarded as an argument against causality. However, the variability in consumption might not have been sufficient to detect a trend. Our highest category starts at only 1 ounce per day. However, when both the mother and child consumed probiotics, the risk of current eczema at 18 months of age was reduced. As further support for the importance of sustained exposure after birth, we found a larger reduced risk of rhinoconjunctivitis at 18 to 36 months when both the mother and child had consumed probiotic milk. We do not have information about maternal probiotic intake after pregnancy. However, a woman who consumed probiotic milk in pregnancy and has probiotic milk in her refrigerator to serve to her child is more likely to consume it herself after delivery than a woman who does not give her child probiotic milk. Most mothers in our sample breast-fed (fully or partially) for at least 6 months, and thus probiotic intake by the mother could exert additional effects on the child during breast-feeding. In mice translocation of bacterial components from the gut to the mammary gland increased during lactation.<sup>31</sup> Human breast milk contains both viable bacteria and a large range of bacterial DNA signatures, some of gut origin.<sup>32,33</sup> Thus manipulation of the maternal gut microbiota by probiotics could influence bacteria and bacterial products found in breast milk. Probiotic supplementation in pregnancy, in particular by the strain *L rhamnosus*, which is contained in the Biola milk consumed by study subjects, has been found to increase IL-10 levels in breast milk.<sup>32,34</sup> IL-10 has anti-inflammatory effects and is involved in pathways of downregulation of IgE synthesis.<sup>35</sup> This mechanism of transmission of bacterial components or cytokines through breast-feeding from mother to infant occurs independently of the mode of delivery. This could explain the minimal difference in associations between probiotic consumption in pregnancy and outcomes

for infants born vaginally versus by means of cesarean section in our study. Of note, in several of the clinical trials, the postnatal probiotic supplementation was given to the lactating mother rather than directly to the infant.

Rather than focusing on high-risk children, as in most of the clinical trials, we were able to examine effects in the whole population. Few randomized controlled trials have examined low-risk children.<sup>36-38</sup> In a trial from Norway, in which women were given the same Biola product examined here, a statistically significant effect on atopic dermatitis was seen only in children without a family history of allergic disease.<sup>36</sup> Another randomized controlled trial reported a reduced incidence of eczema in both high- and low-risk infants after probiotic supplementation in mothers during breast-feeding.<sup>38</sup> Although the differences were not statistically significant, the RRs for atopic eczema and rhinoconjunctivitis were slightly lower in the larger group of children without a family history of allergic disease compared with those seen in children with a family history of allergic disease. It is possible that the dose of probiotic milk products consumed by the mothers in this study is too low to provide a beneficial effect in children who are genetically predisposed to allergic disease. Nevertheless, our results increase the body of evidence on beneficial effects of probiotics on allergic diseases in children without a family history of allergic disease.

When we considered both maternal and childhood consumption of probiotic milk, the children with maternal (pregnancy) consumption appeared to be at slightly increased risk of current atopic eczema at 18 months. We saw no increased risk from maternal consumption during pregnancy when ignoring the child's consumption. Mothers of children with early signs of atopic eczema might have suspected a milk allergy and therefore avoided giving the child probiotic milk. This could produce a higher prevalence of atopic eczema in this group.

There are few data on rhinitis in clinical trials. We found a reduced RR of rhinoconjunctivitis at 18 to 36 months in relation to

probiotic milk consumption. In one randomized controlled trial of 56 high-risk children given probiotic food supplementation, the treatment group had a lower frequency of rhinoconjunctivitis at 42 months of age than the placebo group.<sup>39</sup> However, because most of the trials were designed to assess atopic eczema, the infants were usually only followed up until 1 to 2 years of age and therefore were too young to have rhinoconjunctivitis symptoms or sensitization to inhaled allergens. We assessed rhinoconjunctivitis on the 36-month questionnaire, which is an appropriate time for the earliest onset of symptoms.

Our reliance on questionnaire-based outcomes is a limitation. However, rhinoconjunctivitis is a condition that is mainly based on symptoms rather than on examination and thus might be more accurately captured by questionnaires than other allergic disease outcomes for which objective clinical examinations are preferred. The overall prevalence of rhinoconjunctivitis symptoms among the children at 18 to 36 months was 3.6%, which does not suggest overreporting by the mothers.<sup>40</sup> The prevalence was higher among children of mothers with allergic disease compared with that among children of mothers without allergic disease, which is consistent with expectations.

The use of questionnaires to identify atopic eczema is not ideal. However, in a recent meta-analysis of genome-wide association of atopic dermatitis in population-based studies, which included MoBa, most of the studies of children ascertained this condition only through maternal report on questionnaires. Despite this limitation, replicable novel genetic loci were ascertained.<sup>41</sup> Self-reported atopic eczema might include a substantial amount of nonatopic disease, and more detailed information about the distribution of the rash in, for example, flexures might have provided more specificity. However, in Norway mothers bring children for frequent visits to public health nurses for free during the first 6 months of life. Thus mothers who notice a rash are likely to have shown this to the nurse, who can provide feedback regarding the diagnosis of atopic eczema. In this prospective study the misclassification of the child's skin problems as atopic eczema should be nondifferential according to probiotic intake during pregnancy and thus would generally lead to a bias toward the null rather than explaining an inverse association.

Some cases of reported asthma at 36 months might represent transient wheezing illness that could resolve by school age. In this cohort, however, although early wheezing was commonly reported (41% at 18 months), asthma at age 36 months was not (6.5%). Nonetheless, to address this issue, we used a more stringent definition of current asthma at 36 months, which also required reported use of asthma medication in the last 12 months. Mother-reported use of asthma medication has previously been evaluated for 2,056 children in MoBa and showed high validity when the reported medications were compared with the Norwegian Prescription Database.<sup>42</sup>

MoBa mothers who consumed probiotic milk products in pregnancy differ from the mothers who do not consume these products according to education and health patterns, such as smoking, fiber intake, and BMI. Therefore unmeasured confounding might occur. However, we controlled for factors related to a healthy lifestyle by adjusting for maternal education, prepregnancy BMI, total fiber intake, smoking in pregnancy, and maternal age.

In conclusion, in this large population-based pregnancy cohort study, the mothers were asked specifically about consumption of 2 brands of milk and yogurt that contain probiotic bifidobacteria

and lactobacilli strains, which are suggested to be beneficial in the prevention of allergic disease. These were the only widely available probiotic foods in Norway at the time of the study, and probiotic supplements, such as capsules, were uncommon. Thus we had a unique opportunity to study the association between consumption of probiotic milk products and allergic and respiratory disease in early childhood in a population without selection for increased risk of allergic disease. To the best of our knowledge, this is the first large observational study to assess probiotic intake and allergic disease in childhood. Most randomized controlled trials have mainly focused on children at genetically increased risk. Our findings indicate that probiotic intake might be beneficial for the prevention of atopic eczema and rhinoconjunctivitis in the general population of children who mostly have no genetic predisposition for allergic disease development.

We thank all the participating families in Norway who are taking part in this ongoing cohort study.

**Clinical implications:** These results provide support for the hypothesis that probiotics in pregnancy might help prevent eczema and rhinoconjunctivitis in early childhood for the general population; continued probiotic intake after birth might also contribute.

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## METHODS

### Dietary information and exposure assessment

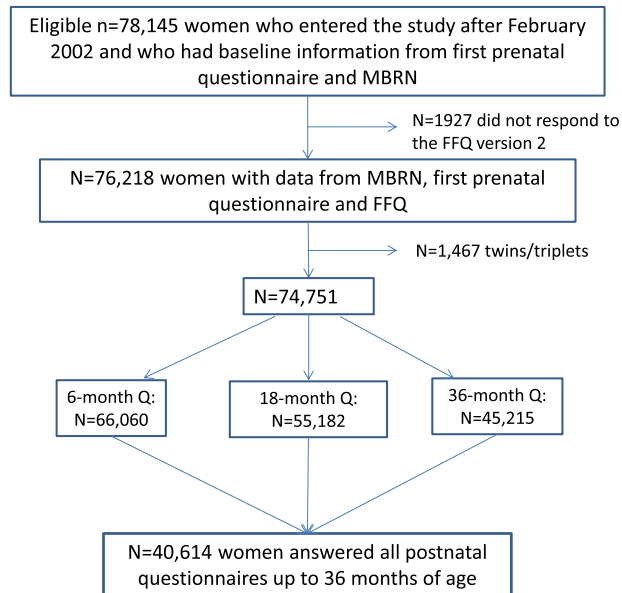
Intake of milk-based probiotic products during pregnancy was recorded in the FFQ. The FFQ is a semiquantitative questionnaire designed to capture dietary habits and intake of dietary supplements during the first 4 to 5 months of pregnancy<sup>E1</sup> and produce realistic estimates of habitual intake.<sup>E2</sup> Intake was reported by marking 1 of 11 intake frequencies ranging from “never” to “8 or more glasses per day” (a glass is defined as 2.0 dL for the probiotic items; see FFQ page 5, which is available at <http://www.fhi.no/dokumenter/011fbd699d.pdf>). Among those using a product, the lowest intake category for each item was 1 glass monthly, which is equivalent to 6.6 mL/d, and the maximum possible intake category was 8 glasses daily (1600 mL/d), as previously described.<sup>E3</sup>

Dietary fiber intake in grams per 10 MJ of total energy intake per day was calculated based on information from the FFQ. Dietary fiber intake is regarded as a proxy for a healthy diet. Foods that are high in fiber are typically whole grains, vegetables, fruits, and legumes.<sup>E4</sup> In MoBa dietary fiber intake reflects intake of fruits, vegetables, and whole grains and is a good reflection of a healthy dietary pattern.<sup>E5,E6</sup>

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**FIG E1.** Flow chart of inclusion of study participants from all eligible participants in MoBa who entered the study after February 2002. Q, Questionnaire.

**TABLE E1.** Questionnaire items related to atopic symptoms and diseases in MoBa

Questionnaire	Questionnaire item	Alternatives	Variable name
6 mo	Does your child have or has he/she had atopic eczema (childhood eczema)?	1) No 2) Yes	Atopic eczema at 6 mo
18 mo	Does your child have or has he/she had atopic eczema (childhood eczema)?	1) No 2) Yes, has now 3) Yes, had previously	Current atopic eczema at 18 mo <i>If "Yes, has now"</i>
36 mo	Has your child had allergy affecting eyes or nose, such as hay fever, since the age of 18 mo?	1) No 2) Yes, has now 3) Yes, had previously	Rhinoconjunctivitis, 18-36 mo <i>If "Yes, has now" and/or "Yes, had previously"</i>
36 mo	Has your child had asthma since the age of 18 mo?	1) No 2) Yes, has now 3) Yes, had previously	Current asthma at 36 mo and asthma medication <i>If "yes, has now" and reported use of inhaled glucocorticoids and/or <math>\beta_2</math>-agonists</i>
	Has your child taken any medication during the last 12 mo?	1) No 2) Yes. If yes, give the name of the medication (free text)	

The 6-month postnatal questionnaire is available at <http://www.fhi.no/dokumenter/9eccalc459.pdf>, the 18-month postnatal questionnaire is available at <http://www.fhi.no/dokumenter/2640dd4bcc.pdf>, and the 36-month postnatal questionnaire is available at <http://www.fhi.no/dokumenter/1927d528c2.pdf>.

**TABLE E2.** Demographic and perinatal characteristics with distribution of probiotic milk consumption in pregnancy for the study population with information from postnatal questionnaires at 6, 18, and 36 months and the total population (including nonresponders to the postnatal questionnaires)

	Percentage with characteristics		Percentage of probiotic consumers by levels of characteristics*	
	Study population (n = 40,614)	Total population (n = 76,226)	Study population (n = 40,614)	Total population (n = 76,226)
Consumed probiotic milk or yogurt				
No	63	64		
Yes	37	36		
Marital status				
Married	50	48	37	37
Cohabitated	47	49	37	36
Single	3	3	35	32
Maternal education				
Less than high school	6	20	26	26
High school	27	12	29	29
Up to 4 y of college	44	43	38	38
>4 y of college	23	25	46	46
Prepregnancy BMI (kg/m <sup>2</sup> )				
<18.5	3	3	35	34
18.5-24.9	66	65	40	39
25-29.9	22	22	34	33
≥30	9	10	26	27
Daily smoking at least once during pregnancy				
No	92	90	38	38
Yes	8	10	24	24
Maternal history of asthma/allergy				
No	74	75	37	36
Yes	26	25	39	38
Parity				
Primiparous	49	46	40	40
Multiparous	51	54	34	33
Maternal age at delivery (y)				
<20-24	9	11	30	30
25-29	33	33	37	36
30-34	40	39	38	37
≥35	18	17	39	38
Cesarean section				
No	86	86	37	36
Yes	14	14	36	35
Birth weight (g)				
<2,500	3	3	35	34
2,500-2,999	9	9	37	36
3,000-3,499	29	28	38	37
3,500-4,000	38	37	37	37
>4,000	21	23	36	35
Sex				
Boys	51	51	37	36
Girls	49	49	37	36

\*Less than 3% missing for probiotic milk consumption in pregnancy, maternal history of asthma/allergy, parity, maternal age at delivery, cesarean section, birth weight, and child's sex. Three percent to 5% are missing for marital status, maternal education, prepregnancy BMI, and daily smoking at least once during pregnancy.

**TABLE E3.** Association between maternal (pregnancy) intake of probiotic milk and yogurt in milliliters per day and atopic eczema, rhinitis, and asthma

Maternal probiotic consumption (mL/d)	No.	Atopic eczema at 6 mo		Current atopic eczema at 18 mo		Rhinoconjunctivitis at 18-36 mo		Current asthma at 36 mo and asthma medication	
		Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)
None (reference)	25,239	12.5	1	13.6	1	3.8	1	5.8	1
13-28.3 mL/d	6,596	11.6	0.93 (0.86-1.00)	13.9	1.03 (0.96-1.10)	3.0	0.81 (0.69-0.94)	5.4	0.97 (0.86-1.09)
≥28.4 mL/d	8,295	11.9	0.95 (0.88-1.02)	13.2	0.97 (0.91-1.04)	3.5	0.93 (0.81-1.07)	5.7	1.02 (0.92-1.14)

\*Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, dietary fiber intake (grams per 10 MJ), total energy intake, breast-feeding, maternal history of allergic disease, parity, and infant's sex.



**TABLE E4.** Demographic and perinatal characteristics by maternal probiotic intake of 40,614 children enrolled in MoBa between March 2002 and November 2008 who had completed all questionnaires up to the 36-month questionnaire

	No. with characteristic	Percentage of total (n = 40,614)	Percentage of probiotic consumers by levels of characteristic*
Maternal income (in 1,000 Norwegian Kroner)			
>200	10,427	26	33
200-400	24,677	63	38
>400	4,326	11	45
Medication use because of URTI in pregnancy†			
No	37,624	93	37
Yes	2,990	7	38
Medication use because of LRTI in pregnancy‡			
No	39,745	98	37
Yes	869	2	39
Medication use because of UTI in pregnancy			
No	37,432	92	37
Yes	3,182	8	37
Medication use because of headache/migraine in pregnancy			
No	31,986	79	37
Yes	8,628	21	37
Medication use because of common cold/flu in pregnancy			
No	38,591	95	37
Yes	2,023	5	39
Medication use because of fever in pregnancy			
No	39,870	98	37
Yes	744	2	43
Gestational age (wk)			
<37	1,900	5	35
37-39	15,561	38	36
40-41	19,741	49	38
>41	3,412	8	38
Day care			
No day care by 18 mo	11,086	28	33
Day care at 6 mo	596	1	34
Started day care by 12 mo	5,271	13	38
Started day care by 15 mo	17,144	43	39
Started day care by 18 mo	5,922	15	38

Information is missing for day care (n = 595) and maternal income (n = 1,184).

Medication use because of the various conditions was derived from prenatal questionnaires at gestational weeks 18 and 30 and from the 6-month postnatal questionnaire, which queried about the women's medical conditions during the last part of pregnancy. The women were asked the following: "Have you experienced any of the following illnesses or problems during this pregnancy?": "throat infection," sinusitis/ear infection, "influenza/common cold," "pneumonia/bronchitis," "urinary tract infections," "fever," or "migraine/other headache." For each of the conditions, the women were asked whether she had taken any medication. We defined medication use because of the various conditions if the women had reported use of medication in the prenatal questionnaires, the 6-month postnatal questionnaire, or both.

*LRTI*, Lower respiratory tract infection; *URTI*, upper respiratory tract infection; *UTI*, urinary tract infection.

\**P* values were less than .05 for maternal income, medication use because of common cold/flu and fever in pregnancy, gestational age, and day care.

†Upper respiratory tract infection includes tonsillitis, sinusitis, and/or otitis.

‡Lower respiratory tract infection includes pneumonia, bronchiolitis, or both.

**TABLE E5.** Association between maternal probiotic milk and yogurt consumption in pregnancy and atopic eczema, rhinoconjunctivitis, and asthma among 40,614 children in MoBa whose mothers had completed the 6-, 18-, and 36-month postnatal questionnaires

	Cases (no.)	Cases (%)*	Unadjusted RR (95% CI)	Adjusted† RR (95% CI)
Atopic eczema at 6 mo	4,849	12.2	0.94 (0.89-1.00)	0.93 (0.88-0.99)
Current atopic eczema at 18 mo	5,440	13.6	0.99 (0.94-1.04)	1.00 (0.95-1.06)
Rhinoconjunctivitis at 18-36 mo	1,425	3.6	0.85 (0.76-0.95)	0.87 (0.78-0.98)
Current asthma at 36 mo and asthma medication	2,260	5.7	0.96 (0.88-1.04)	1.00 (0.92-1.10)

\*Outcome data were missing for atopic eczema at 6 months (2.1%), current atopic eczema at 18 months (1.3%), rhinoconjunctivitis at 18 to 36 months (2.9%), current asthma at 36 months, and asthma medication (2.6%). The case percentage is calculated with the total N in the denominator with no missing information.

†Adjusted for maternal age; smoking in pregnancy; maternal education; prepregnancy BMI; dietary fiber intake (grams per 10 MJ); breast-feeding; maternal history of allergic disease; parity; infant's sex; mode of delivery (cesarean section vs vaginal); total energy intake (MJ per day); gestational age; maternal income; use of medication in pregnancy because of fever, headache/migraine, upper respiratory tract infection, lower respiratory tract infection, urinary tract infection, and common cold/flu; and day care (for outcomes reported at 18 mo or later).

**TABLE E6.** Association between consumption of probiotic milk products by the child only, mother only (in pregnancy), and both the mother and child and atopic eczema, rhinoconjunctivitis, and asthma among 40,614 children in MoBa who had completed all of the follow-up questionnaires

Probiotic milk products	No.	Current atopic eczema at 18 mo		Rhinoconjunctivitis at 18-36 mo		Current asthma at 36 mo and asthma medication	
		Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted RR (95% CI)
No intake (reference)	18,572	13.6	1	3.9	1	5.8	1
Child intake only	7,000	13.6	1.02 (0.94-1.09)	3.7	0.96 (0.82-1.11)	5.9	1.10 (0.98-1.24)
Mother intake only	7,437	14.6	1.07 (1.00-1.15)	3.6	0.92 (0.79-1.07)	5.3	0.98 (0.87-1.10)
Mother and child intake	7,605	12.5	0.93 (0.86-1.00)	3.0	0.80 (0.68-0.94)	5.8	1.09 (0.97-1.22)

\*Adjusted for maternal age; smoking in pregnancy; maternal education; prepregnancy BMI; dietary fiber intake (grams per 10 MJ); breast-feeding; maternal history of allergic disease; parity; infant's sex; mode of delivery; total energy intake (MJ per day); gestational age; maternal income; use of medication in pregnancy because of fever, headache/migraine, upper respiratory tract infection, lower respiratory tract infection, urinary tract infection, and common cold/flu; and day care.