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

Randi J. Bertelsen, PhD[1,2], **Anne Lise Brantsæter, PhD**[3], **Maria C. Magnus**[4,2], **Margaretha Haugen, PhD**[3], **Ronny Myhre, PhD**[5], **Bo Jacobsson, MD PhD**[5,6], **Matthew P. Longnecker, MD ScD**[2], **Helle M. Meltzer, PhD**[3], and **Stephanie J. London, MD DrPH**[2]

[1]Department of Food, Water and Cosmetics, Norwegian Institute of Public Health, N-0403 Oslo, Norway

[2]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, RTP, NC 27709, USA

[3]Department of Exposure and Risk Assessment, Norwegian Institute of Public Health, Oslo, N-0403 Oslo, Norway

[4]Department of Chronic Diseases, Norwegian Institute of Public Health, N-0403 Oslo, Norway

[5]Department of Genes and Environment, Norwegian Institute of Public Health, N-0403 Oslo, Norway

[6]Department of Obstetrics and Gynecology, Sahlgrenska Academy, Gothenburg, Sweden

Abstract

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

Objectives—To assess whether consumption of probiotic milk products protects against atopic eczema, rhinoconjuctivitis, 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, rhinoconjuctivitis, and asthma in 40,614 children. Relative risks (RR) were calculated using general linear models, adjusted for potential confounders.

Results—Consumption of probiotic milk in pregnancy was associated with a slightly reduced risk [(adjusted RR (aRR)] of atopic eczema at 6 months aRR=0.94 (95% CI: 0.89, 0.99) and of rhinoconjuctivitis between 18 and 36 months, aRR=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 mother (during pregnancy) and infant (after 6 months of age) had consumed probiotic milk, the adjusted relative risk of rhinoconjunctivitis was aRR=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.

Corresponding author: Randi J. Bertelsen, Department of Food, Water and Cosmetics, Division of Environmental Medicine, Norwegian Institute of Public Health, P.O. Box 4404 Nydalen, N-0403 Oslo, Norway. randi.jacobsen.bertelsen@fhi.no, phone: + 47 21076327..

Conclusions—In this population-based cohort, consumption of probiotic milk products was related to a reduced incidence of atopic eczema and rhinoconjuctivitis, but no association was seen for incidence of asthma by 36 months of age.

Keywords

allergy; asthma; eczema; microbiome; MoBa; probiotics; rhinoconjunctivitis

Introduction

The development of allergic diseases in childhood is influenced by factors that stimulate the immune system. Intestinal microbes influence immunological maturation in infants[1]. The fecal flora has been found to differ between infants who later develop allergic diseases and those who do not[2-4]. The composition of intestinal microbiome is determined by exposure to maternal vaginal inoculum at birth, diet, and other factors[5, 6]. Manipulation of the intestinal microbiome in infants may 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'[7]. One meta-analysis of clinical trials concluded that probiotics, given as supplements in pregnancy or infancy, may reduce the risk of atopic eczema in infants[8]. Most of the trials have been conducted among high-risk infants[8-10]. 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[11-13]. In a large European birth cohort the timing of infantile intestinal colonization was not associated with early childhood atopic eczema or food allergy[14]. Thus, even if probiotic supplementation may provide some beneficial effect, the timing of probiotic supplementation and whether continued supplementation in infancy is necessary is still unclear[9, 10]. 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[12].

Data from clinical trials are the gold standard for establishing causality, but also have limitations[15, 16]. In the case of probiotics supplementation and infant eczema, the trials have been relatively modest in size (median 175, range 69 to 925 infants in the 13 studies included in the meta-analysis[8])[12]. Further, 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[17, 18]; in the US new formulations of probiotic dietary supplements and foods are introduced almost daily[19]. 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.

Methods

We analyzed data from subjects in the Norwegian Mother and Child Cohort Study (MoBa), initiated and maintained at the Norwegian Institute of Public Health[20]. 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 questionnaires at regular intervals[21]. The study was approved by The Regional Committee for Medical Research Ethics in South-Eastern Norway. Informed consent was obtained from each MoBa participant upon recruitment.

The present study was based on version 6 of the quality-assured data files released in 2011. The schedule for completion of questionnaires was: 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 months, 18 months, and 36 months. We also used information collected by the Medical Birth Registry of Norway (MBRN). The version of the FFQ that includes questions on probiotic milk and yogurt consumption during pregnancy has been in use from March 1 2002[22] and thus we included mothers who enrolled in the study after this date (n=76,218 eligible, Figure E1). Among these 76,218, 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), and 4,325 (10.6%) contributed more than one pregnancy.

Outcomes

"Eczema" was classified based on mothers' responses to a question about "atopic eczema (childhood eczema)" asked on both the 6-month 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, e.g. 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 and/or beta-2 agonists (Table E1). These are the main medication dispense 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 (page 5 of the FFQ, available from: http://www.fhi.no/dokumenter/011fbd699d.pdf). The probiotic items queried were Biola milk (Tine SA), 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 *L. rhamnosus* (LGG), and Cultura milk contained *L. acidiophilus* 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[23, 24] and higher bifidobacteria colonization have been reported among non-atopic as compared to atopic children[25]. Reported pregnancy consumption across all probiotic milk products was categorized into one dichotomous variable for any intake versus no intake, and one three level variable based on intake in mL/day categorized into "none", "13.0-28.3 mL/day" and "≥28.4 mL/day". 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 four groups of probiotic milk consumption: no intake, intake reported for the child only, for the mother only, and for both 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 and/or rhinoconjuctivitis), probiotic-containing supplements, and breast-feeding (full or partial) for at least 6 months. The data retrieved from the MBRN were marital status, parity, maternal age at delivery, delivery by cesarean section or vaginally, infant's gender, and birth weight in grams.

Statistical analyses

We used generalized linear models with a log-link for binary data which gives relative risks (RR) as association measures. Robust variance estimations with cluster adjustments were used to account for siblings. In the multivariate analyses, 94-95% of the observations were available in the analyses of atopic eczema, rhinoconjuntivitis, and asthma. Covariates were selected based on a directed acyclic graph (DAG)[26]. The minimal sufficient adjustment set for estimating the total effect of maternal consumption of probiotic milk for allergic disease in the child was: pre-pregnancy 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 (MJ/day), mode of delivery (cesarean section versus vaginal), breast-feeding, parity, and infant's gender. Maternal age, dietary fiber intake, and total energy intake are reported in categories in Table 1, 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, rhinoconjuntivitis 18-36 months, and current asthma with asthma medication at 36 months. We also did stratified analyses by maternal history of allergic disease, mode of delivery, and gender.

P-values ≤ .05, 2-sided, were considered statistically significant. Data were analyzed using Stata 12.1 (Stata Corporation, College Station, Texas).

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 one of the probiotic milk or yogurt products (Table 1), and approximately 50% of these women also gave their child Biola milk after 6 months age. Only 0.4% of the mothers reported taking probiotic-containing supplements (such as in capsule form) in pregnancy. Maternal consumption of probiotic milk and yogurt in pregnancy was more common among the higher educated women, women who did not smoke in pregnancy, in primiparous women, in older women, in women who breast-fed the infants for at least 6 months, in women with normal pre-pregnancy BMI, and in the women with the highest daily fiber intake during pregnancy (Table 1). Compared with the underlying MoBa cohort of women who had entered the study after February 2002, the study population had a slightly lower proportion of women with less than 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 the Online Repository). 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, 3.6% had experienced rhinoconjuctivitis symptoms between 18 and 36 months age, and 5.7% had current asthma with asthma medication at 36 months.

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 relative risk 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 2). However, in analysis considering both during pregnancy and childhood intake, consumption by both mother during pregnancy and by the child after 6 months of age, compared with no intake by either mother or child, was associated with slightly reduced risk of current eczema at 18 months of age (aRR=0.93, 95% CI 0.86, 1.00) (Table 3). For rhinoconjuncitivis between 18 and 36 months the adjusted relative risk for probiotic intake during pregnancy compared with no intake during pregnancy was 0.87 (95% CI: 0.78, 0.98) (Table 2) and aRR=0.80 (0.95% CI: 0.68, 0.93) in analyses incorporating pregnancy and childhood intake compared with no intake during either period (Table 3). The results from the models with the DAG-selected covariates and the additionally adjusted models were essentially the same (Table 2).

No association was seen for consumption of probiotic milk products in pregnancy and asthma with asthma medication at 36 months (Table 2). When we use a less stringent definition of current asthma at age 36 months that does not restrict to those using medication in the past 12 months, we have 2,556 cases compared with 2,260 with medication use. Results are 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 the current asthma with medication use (0.99, 95% CI: 0.91, 1.08 (Table 2)). We found no evidence of a monotonic relation across the three categories of consumption of probiotic milk and yogurt (none, 13.0 −28.3 mL/day, ≥28.4 mL/day) for any of the outcomes (see Table E3 in the Online Repository).

Sensitivity analyses

The estimates for atopic eczema and rhinoconjuctivitis were similar to our main results reported in Tables 2 and 3 after controlling for maternal income, gestational age, day-care, variables considered as surrogates for antibiotic use in pregnancy: reported use of medication due to upper respiratory tract infections, lower respiratory tract infections, and urinary tract infections, and variables considered as surrogates for paracetamol use in pregnancy: reported use of medication due to headache/migraine, fever, and common cold/flu (Tables E4-E6 in the Online Repository).

Stratified analyses

In stratified analyses, maternal history of allergic disease did not notably influence our findings. The adjusted relative risk was below one in both strata for both atopic eczema and rhinoconjuctivitis. While the relative risk was slightly lower in the much larger group of children (74%) whose mothers did not have allergic disease (Table 4), the differences by strata were not statistically significant (Interaction P=.5 for atopic eczema at 6 months and P=.2 for rhinoconjuctivitis).

Upon 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 rhinoconjuctivitis at 18-36 months in the larger group (86% of subjects) born via vaginal delivery (Table 5). 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 gender (*P*>.3 for all outcomes).

Discussion

Intake of probiotic containing milk products in pregnancy was associated with a reduced relative risk of atopic eczema and rhinoconjuctivitis in children. While 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%) consists of children without maternal history of allergic disease. The association between probiotics and rhinoconjuctivitis appeared to be enhanced if both the mother (during pregnancy) and the child (after 6 months of age) had consumed these products, as compared with no consumption or consumption only by 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[8, 9, 13]. 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 due to the substantial heterogeneity between the studies and the excess losses in patient follow-up[11-13].

The preventive effects of probiotics have usually been seen in clinical trials that have used a combination of prenatal and postnatal supplementation[8, 27] and it is hard to draw conclusions regarding the relative importance of intake during the two periods[8]. Probiotic intake during pregnancy may modulate the maternal vaginal bacterial inoculum[28] 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[2, 29]. Probiotic supplementation is assumed to be of particular importance during the first few months after birth[2, 30], and continuous supplementation has been claimed to be necessary to achieve beneficial effects later in childhood[9, 10]. Consistent with this assertion, in our study, 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 outcomes might be regarded as an argument against causality. However, the variability in consumption may not have been sufficient to detect a trend. Our highest category starts at only one 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 rhinoconjuctivitis at 18-36 months when both 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 (full 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[31]. Human breastmilk contains both viable bacteria and a large range of bacterial DNA signatures, some of gut origin[32, 33]. Thus, manipulation of the maternal gut microbiota via probiotics could influence bacteria and bacterial products found in breastmilk. Probiotic supplementation in pregnancy, in particular by the strain LGG which is contained in the Biola milk consumed by study subjects, has been found to increase the levels of IL-10 in breastmilk[32, 34]. IL-10

has anti-inflammatory effects and is involved in pathways of downregulation of IgE synthesis[35]. This mechanism of transmission of bacterial components or cytokines via 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 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[36-38]. In a trial from Norway, where women were given the same Biola product examined here, a statistically significant effect on atopic dermatitis was seen only in children without family history of allergic disease[36]. Another randomized controlled trial reported reduced incidence of eczema in both high- and low-risk infants after probiotic mothers' supplementation during breast-feeding[38]. Although the differences were not statistically significant, the relative risks for atopic eczema and rhinoconjunctivitis were slightly lower in the larger group of children without a family history of allergic disease as compared to 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 developing 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 child consumption of probiotic milk, the children with maternal (pregnancy) consumption only, appeared to be at slightly increased risk of current atopic eczema at 18 months. We saw no increase risk from maternal consumption during pregnancy when ignoring child consumption. Mothers of children with early signs of atopic eczema may 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 the clinical trials. We found a reduced relative risk of rhinoconjuctivitis at 18-36 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 rhinoconjuctivitis at 42 months of age than the placebo group[39]. However, since most of the trials were designed to assess atopic eczema, the infants were usually only followed up until 1-2 years of age and therefore too young to have developed rhinoconjuctivitis symptoms or sensitization to inhaled allergens. We assessed rhinoconjuctivitis 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, rhinoconjuctivitis is a condition that is mainly based on symptoms rather than on examination and thus may be more accurately captured by questionnaires than other allergic disease outcomes where objective clinical examinations are preferred. The overall prevalence of rhinoconjuctivitis symptoms among the children at 18- 36 months was 3.6% which does not suggest over reporting by the mothers[40]. The prevalence was higher among children of mothers with allergic disease as compared to children of mothers without allergic disease, 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 the MoBa study, most of the studies of children ascertained this condition only by maternal report on questionnaire. Despite this limitation, replicable novel genetic loci were

ascertained[41]. Self-reported atopic eczema may include a substantial amount of nonatopic disease and more detailed information about the distribution of the rash in e.g. flexures might have provided more specificity. However, in Norway mothers bring children for frequent visits to public health nurses for free during the first six months of life. Thus, mothers who notice 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 explain an inverse association.

Some cases of reported asthma at 36 months may represent transient wheezing illness that may resolve by school age. In this cohort however, while 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 the MoBa study and showed high validity when the reported medications were compared to the Norwegian Prescription Database[42].

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 may occur. However, we controlled for factors related to healthy lifestyle by adjusting for maternal education, pre-pregnancy BMI, total fiber intake, smoking in pregnancy, and maternal age.

Conclusions

In this large population-based pregnancy cohort study, the mothers were asked specifically about consumption of two 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 developing 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 may be beneficial for the prevention of atopic eczema and rhinoconjuctivitis in the general population of children who mostly have no genetic predisposition for allergic disease development.

Material and methods

Dietary information and exposure assessment

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

Dietary fiber intake in gram per 10 MJ of total energy intake per day (g/10 MJ) 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[E4]. In the MoBa study, dietary fiber intake reflects intake of fruits, vegetables, and whole grains and is a good reflection of a healthy dietary pattern[E5, E6].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
DAG	Directed Acyclic Graph
FFQ	Food Frequency Questionnaire
LGG	Lactobacillus rhamnosus
MBRN	Medical Birth Registry of Norway
MoBa	The Norwegian Mother and Child Cohort Study
RR	relative risk

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Clinical implications

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

Table 1

Demographic and perinatal characteristics by maternal probiotic intake of 40,614 children enrolled in the Norwegian Mother and Child Cohort Study between March 2002 and November 2008, who had completed all questionnaires up to the 36-months questionnaire

	N with characteristic	Percent of total (n=40,614)	% of probiotic consumers by levels of characteristic[a]
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 years of college	17,692	44	38
> 4 years of college	9,512	23	46
Pre-pregnancy body mass index, kg/m,^{2}			
<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, years			
<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	n.a
13 – 28.3mL/day	6,644	16	n.a
≥ 28.4 mL/day	8,398	21	n.a
Total energy intake, MJ/d			

	N with characteristic	Percent of total (n=40,614)	% of probiotic consumers by levels of characteristic[a]
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			
<2500	1,094	3	35
2500-2999	3,455	9	37
3000-3499	11,831	29	38
3500-4000	15,490	38	37
>4000	8,744	21	36
Breast-feeding for at least 6 months			
No	8,601	21	31
Yes	32,013	79	39
Gender			
Boys	20,725	51	37
Girls	19,899	49	37

http://www.fhi.no/dokumenter/1f32a49514.pdf and prenatal questionnaire 3 available from

http://www.fhi.no/dokumenter/7b6b32b0cd.pdf

[a] All *P*-values from chi-squared tests for differences in characteristics between non-consumers and consumers were <.05 except for marital status, gender, and birth weight. Information missing for marital status (n=110), smoking (n=368), parity (n=27), prepregnancy body mass index (n=890), and maternal education (n=149). Prenatal questionnaire 1 available from:

Table 2

Association between maternal probiotic milk and yogurt consumption in pregnancy and atopic eczema, rhinoconjuctivitis, and asthma among 40,614 children in MoBa whose mothers had completed the 6, 18, and 36 months postnatal questionnaires

	Cases n	Cases %*	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)	Adjusted[b] RR (95% CI)
Atopic eczema 6 months	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 18 months	5,440	13.6	0.99 (0.94, 1.04)	1.00 (0.94, 1.05)	1.00 (0.95, 1.05)
Rhinoconjuctivitis 18-36 months	1,425	3.6	0.85 (0.76, 0.95)	0.90 (0.81, 1.00)	0.87 (0.78, 0.98)
Current asthma 36 months 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)

[a] Adjusted for maternal age, smoking in pregnancy, maternal education, pre-pregnancy BMI, dietary fiber intake (g/10 MJ).

[b] Additional adjustment for total energy intake (MJ/day), breast-feeding, maternal history of allergic disease, parity, infant's gender, and mode of delivery (Cesarean section versus vaginal).

* Missing outcome data for: atopic eczema 6 months (2.1%), current atopic eczema 18 months (1.3%), rhinoconjuctivitis 18-36 months (2.9%), and current asthma 36 months with asthma medication (2.6%). The case percent is calculated with the total N in the denominator with no missing information

Table 3

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

		Current atopic eczema 18 months		Rhinoconjunctivis 18-36 months		Current asthma with asthma medication 36 months	
Probiotic milk products	**N**	**Cases %**	**Adjusted[a] RR (95% CI)**	**Cases %**	**Adjusted[a] RR (95% CI)**	**Cases %**	**Adjusted[a] RR (95% CI)**
No intake (ref)	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)

[a]Adjusted for maternal age, smoking in pregnancy, maternal education, pre-pregnancy BMI, dietary fiber intake (g/10 MJ), total energy intake (MJ/day), breast-feeding, maternal history of allergic disease, parity, infant's gender, and mode of delivery.

Table 4

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 history of asthma and allergy

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

[a] Adjusted for maternal age, smoking in pregnancy, maternal education, pre-pregnancy BMI, dietary fiber intake (g/10 MJ), total energy intake (MJ/day), breast-feeding, parity, infant's gender, and mode of delivery

Table 5

Association between maternal intake of probiotic containing milk and yogurt in pregnancy and atopic eczema, rhinoconjuctivitis, and asthma for children delivered vaginally or by cesarean section

	Vaginal delivery N=35,057		Cesarean section N=5,557	
	Cases %	Adjusted[a] aRR (95% CI)	Cases %	Adjusted[a] aRR (95% C1)
Atopic eczema by 6 months	12.2	0.94 (0.88, 1.00)	12.5	0.93 (0.80, 1.09)
Current atopic eczema 18 months	13.7	1.00 (0.95, 1.06)	12.7	0.97 (0.83, 1.13)
Rhinoconjuctivitis 18-36 months	3.5	0.86 (0.76, 0.98)	4.4	0.92 (0.70, 1.22)
Current asthma with asthma medication 36 months	5.5	0.99 (0.90, 1.09)	7.4	1.01 (0.82, 1.24)

[a]Adjusted for maternal age, smoking in pregnancy, maternal education, pre-pregnancy BMI, dietary fiber intake (g/10 MJ), total energy intake (MJ/day), breast-feeding, maternal history of allergic disease, parity, and infant's gender.