

# 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 " $\geq 28.4$  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,

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