Probiotic Administration in Early Life, Atopy, and Asthma: A Meta-analysis of Clinical Trials

BACKGROUND AND OBJECTIVE: Probiotics may reduce the risk of atopy and asthma in children. However, results from clinical trials have been conflicting, and several of them may have been underpowered. We performed a meta-analysis of randomized, placebo-controlled trials to assess the effects of probiotic supplementation on atopic sensitization and asthma/wheeze prevention in children.

METHODS: Random-effects models were used to calculate pooled risk estimates. Meta-regression was conducted to examine the effect of potential factors on probiotics efficacy.

RESULTS: Probiotics were effective in reducing total immunoglobulin E (IgE) (mean reduction: −7.59 U/mL [95% confidence interval (CI): −14.96 to −0.22]; P = .044). Meta-regression showed that the reduction in IgE was more pronounced with longer follow-up. Probiotics significantly reduced the risk of atopic sensitization when administered prenatally (relative risk: 0.88 [95% CI: 0.78 to 0.99]; P = .035 for positive result on the skin prick test and/or elevated specific IgE to common allergens) and postnatally (relative risk: 0.86 [95% CI: 0.75 to 0.98]; P = .027 for positive result on skin prick test). Administration of Lactobacillus acidophilus, compared with other strains, was associated with an increased risk of atopic sensitization (P = .002). Probiotics did not significantly reduce asthma/wheeze (relative risk: 0.96 [95% CI: 0.85 to 1.07]).

CONCLUSIONS: Prenatal and/or early-life probiotic administration reduces the risk of atopic sensitization and decreases the total IgE level in children but may not reduce the risk of asthma/wheeze. Follow-up duration and strain significantly modified these effects. Future trials for asthma prevention should carefully select probiotic strain and include longer follow-up.

WHAT IS KNOWN ON THIS SUBJECT: The intestinal microbiome may play a role in immune system maturation, and it has been postulated that early-life probiotic administration may reduce the risk of allergies and asthma in childhood. To date, however, results from clinical trials have been inconsistent.

WHAT THIS STUDY ADDS: In this meta-analysis, administration of probiotics in early life may reduce total immunoglobulin E level and protect against atopic sensitization but do not seem to protect against asthma/wheeze. Future trials should carefully select probiotic strains and include longer follow-up.

KEY WORDS atopic sensitization, childhood asthma, childhood atopy, meta-analysis, intestinal microbiome, probiotics, total IgE

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
Worldwide prevalence of allergic diseases such as asthma, atopic dermatitis, and allergic rhinoconjunctivitis are significant and has increased over the past few decades. Currently, an estimated 20% of the population worldwide suffers from some form of allergic disorder. The hygiene hypothesis, formulated as a probable explanation for the rise in the prevalence of allergic diseases, suggests that increased cleanliness, reduced family size, and decreased childhood infections have lowered our exposure to microbes, which play a crucial role in the maturation of the host immune system during the first years of life.

The intestinal microbial flora, or microbiome, may contribute to the pathogenesis of allergic diseases due to its substantial effect on mucosal immunity. Exposure to a normal microbial flora early in life allows for a change in the lymphocyte T-helper 1 (Th1)/lymphocyte T-helper 2 (Th2) balance, favoring a Th1 cell response. Atopic diseases, on the contrary, involve Th2 responses to allergens; abnormal allergic responses are thought to arise in the absence of a normal gut microbiome while the immune system is still developing, producing a shift of the Th1/Th2 cytokine balance toward a Th2 response, and consequent activation of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, as well as increased production of immunoglobulin (Ig) E.

Probiotics, defined as “live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host” by the World Health Organization, can potentially modulate the immune response, resulting in stimulation of Th1 cytokines that can suppress Th2 responses. Several studies were therefore designed to examine the efficacy of probiotics in many allergic disorders. However, the results on atopy and asthma have been conflicting, and several of these reports may have been underpowered. In the current study, we performed a meta-analysis of randomized controlled trials to assess whether probiotic administration during pregnancy and/or after birth decreases the incidence of atopy and asthma in young children compared with placebo.

METHODS
A protocol for this meta-analysis is registered in PROSPERO (registration number: 42013004176) (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004176).

Data Sources
We searched Medline, Highwire, Cumulative Index to Nursing and Allied Health Literature, Web of Knowledge, and The Cochrane Central Register of Controlled Trials (Central) for randomized trials evaluating the effect of probiotic supplementation on allergic diseases in children up to March 2013. In all the databases, we used the following key words: “probiotics” in association with “asthma,” “wheeze,” “rhinitis,” “atopy,” “allergy,” “immunoglobulin,” “IgE,” “sensitization,” or “eczema.” In Medline, we searched for the following Medical Subject Headings: Probiotic AND (Asthma OR Wheeze OR Rhinitis OR Hay Fever OR Atopy OR Allergy OR Immunoglobulin OR IgE OR Sensitization OR Eczema). The search was restricted to children using the limits “Humans” and “Child: birth–18 years.” In addition, we manually screened references in the selected articles for additional relevant studies.

Study Selection
All of the studies retrieved from the different databases by using the aforementioned search strategies were imported to a Web-based reference management program (Refworks [Pro-Quest, Ann Arbor, MI]), and duplicates were removed. Studies on probiotics that met the following predefined criteria were included in the meta-analysis.

Study Design
Double-blinded, randomized, placebo-controlled trials published in English (or in languages other than English, when able to translate into English by using online translation services) were included. Randomization was considered adequate when a study was described as randomized, even if the precise randomization method was not reported. Trials were included if the intervention (probiotic supplementation) was directed at the child and/or the pregnant mother. Crossover studies were considered only if analysis was performed separately for the first half of the study, and results were available.

Population
Children in whom outcomes were measured between birth and age 18 years, without atopic diseases at the time of probiotic supplementation, were included. Children with atopic diseases were considered only for the outcome “total IgE.”

Intervention
Bacterial probiotics (single strain or mixture) administered prenatally and/or postnatally within the first year of life for the prevention of atopic diseases were assessed. The use of probiotics after the first year was only considered for the outcome “total IgE” when evaluating the effect of probiotics on total IgE in both atopic and nonatopic children.

Control
Control subjects were children who received a placebo.

Outcomes
The outcomes included total IgE level, atopic sensitization, and asthma/wheeze. Total IgE levels were measured...
by using immunoassay. Atopic sensitization was defined as a positive result on a skin prick test (SPT) and/or elevated specific IgE (>0.35 kU/L) to any food or inhalant allergen. When data were separately reported on positive SPT and elevated IgE, data on positive SPT were selected. Asthma/wheeze was defined as parental report of physician diagnosis or direct diagnosis by a physician participating in the trial.

Two authors (Drs Elazab and Mendy) independently screened all references according to the selection criteria. Initial selection after removal of duplicates was based on title and abstract screening, and the final selection was performed by using full texts. Exclusion criteria were: (1) ineligible study design (ie, nonrandomized, placebo-controlled trials, observational studies, crossover studies without separate analysis of the first half); (2) ineligible population (eg, animal studies, studies including adults aged >18 years); (3) ineligible intervention (eg, administration of products other than probiotics or association of probiotics with any other products such as prebiotics); (4) ineligible outcome, which included outcomes other than allergic diseases.

In the final selection, based on full-text screening, the criterion for exclusion was ineligible intervention or outcomes (study on allergic diseases that did not include data on asthma, wheeze, total IgE, or atopic sensitization after follow-up). When possible, authors who measured the outcomes of interest after follow-up but did not report the results were contacted for additional information. Differences of opinion for inclusion were resolved by agreement.

Data Extraction

Using a uniform data extraction form, two of the authors (Drs Elazab and Mendy) independently retrieved from full-text articles data on references (first author, year of publication), timing of probiotic supplementation (prenatal and/or postnatal), strain of probiotic administered, dose and duration of supplementation, age of participants at baseline and after follow-up, outcome definitions, total number of participants, number of participants and cases in the intervention and control groups, mean total IgE levels, and corresponding SD or confidence interval (CI) (Table 1). When studies used the same population, we retained the 1 with the longest follow-up time for the appropriate analysis. Disagreements on data extraction between the 2 authors were resolved through mutual discussion and, if needed, by consulting a third author (Dr Forno). Agreement between the reviewers on study selection was determined by using the Cohen $\kappa$ statistic ($\kappa$).

Quality Assessment

The methodologic quality of the individual randomized clinical trials was evaluated by using the Jadad scale.\textsuperscript{10} It is calculated by using 3 items assessing randomization, blinding, and withdrawals, resulting in a total score between 0 (lowest quality) and 5 (highest quality). Scores of 3 to 5 were considered as high quality.

Analysis

Collected data were pooled to generate summary estimates, and each study was weighted by its inverse effect size variance.\textsuperscript{11} To evaluate the effect of probiotics, we calculated relative risks (RRs) for the development of asthma and atopic sensitization and weighted mean differences (WMDs) for total IgE between intervention and control groups, using DerSimonian and Laird random-effects methods. Random-effects analysis not only weights each study by its inverse variance but also includes the within- and between-studies variances; it is more conservative than fixed-effects models, providing wider CIs when there is between-study heterogeneity.\textsuperscript{12} We tested for heterogeneity in results across studies by using a Cochran Q statistic. Given the low test power, the significance level was defined as $P < .10$. The $I^2$ was used to quantify the extent of true heterogeneity.\textsuperscript{13} An assessment of publication bias was performed with the Egger test, based on the funnel plot and the regression of the standardized effect estimate on a measure of precision.\textsuperscript{14,15} Subgroup analyses by timing of probiotics administration, age group, outcome definition (SPT or elevated specific IgE for atopic sensitization; asthma or wheeze for asthma/wheeze), and meta-regression analyses were conducted to explore potential sources of heterogeneity and test the effects of different factors such as probiotic strain(s), baseline age of participants, dose administered, duration of supplementation, and duration of follow-up on the efficacy of probiotics, as well as maternal supplementation of probiotics during lactation versus direct infant supplementation. All analyses were performed in Stata version 11 (Stata Corp, College Station, TX), and a $P$ value of .05 was considered to be statistically significant.

RESULTS

A total of 1081 articles were identified (Fig 1): 355 articles from PubMed, 44 from Cumulative Index to Nursing and Allied Health Literature, 518 from Web of Knowledge, 73 from Highwire, and 91 from the Cochrane Central Register of Controlled Trials. Of these, 25 studies were included in the meta-analysis for 20 cohorts with a total of 4031 participants.\textsuperscript{16–40} There was complete agreement on 697 of the 778 articles (after exclusion of duplicates) after title and abstract screening (interreader agreement: $\kappa = 79.2\%$) and on 62 of 68 articles after full text screening (interreader agreement: $\kappa = 81.8\%$). Excluded studies are listed in Supplemental Table 2.
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<th>References</th>
<th>Strain(s)</th>
<th>No. of Participants</th>
<th>Pre and/or Postnatal Intervention</th>
<th>Baseline Age (mo)</th>
<th>Daily Dose (×10^9 CFU)</th>
<th>Duration (mo)</th>
<th>Follow-up (mo)</th>
<th>Outcome(s)</th>
<th>Quality Score</th>
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<td>3 (B lactis)</td>
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<td>98</td>
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<td>0</td>
<td>Total IgE</td>
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</table>

CFU, colony-forming unit; —, if administration began prenatally to mothers.

* Baseline age.
* Represents cohort from Wickens 2008 and 2012.
Studies that were included were published between 2001 and 2012. Trials were performed mainly in Europe\textsuperscript{16,17,19,20,22,23,32,33,35–37,39,40} but also in Asia,\textsuperscript{21,24,25,34} Australia,\textsuperscript{18,26} and New Zealand.\textsuperscript{31} Probiotics were administered prenatally (to pregnant mothers) in 2 trials,\textsuperscript{18,24} prenatally to pregnant mothers and postnatally directly to children in 10 trials,\textsuperscript{16,17,19–23,26,39,40} and only postnatally to children in 9 studies.\textsuperscript{25,30–33,35–37,41} Ten trials used \textit{Lactobacillus}\textsuperscript{16,18,20,22,24,26,33,35,37,40} and 8 used probiotic mixtures.\textsuperscript{17,19,21,23,25,32,39,40} Wickens et al,\textsuperscript{31} Rautava et al,\textsuperscript{39} and Gore et al\textsuperscript{52} used separate \textit{Lactobacillus} and \textit{Bifidobacterium} arms compared with 1 placebo group. All but 2 studies\textsuperscript{32,37} had a Jadad score between 3 and 5 and were considered of good methodologic quality.

Atopic sensitization was defined as positive SPT result and/or IgE level $\geq 0.35$ kU/L to any food or inhalant allergen (eg, cat, dog, dust mite, egg white, cow milk, peanut, birch pollen, grass) in the majority of studies that assessed atopic sensitization.\textsuperscript{16–20,23–27,39,40} One tested only for food allergens\textsuperscript{21} and another only for inhalant allergens.\textsuperscript{22} Asthma/wheeze was only reported by parents using a questionnaire.\textsuperscript{18,20,25,27,36,37}

Total Serum IgE

Nine studies\textsuperscript{20–25,32–35} representing cohorts from 9 trials were included (1103 children). Overall, probiotics were effective in reducing total IgE (WMD: $-7.59$ U/mL [95% CI: $-14.96$ to $-0.22$]; $P = .044$), with no significant heterogeneity across studies ($I^2$ null, Cochran’s $Q$ test, $P = .573$) (Fig 2). In subgroup analyses, the effect of probiotics on total IgE was significant among children with atopy (WMD: $-35.12$ U/mL [95% CI: $-69.82$ to $-0.42$]; $P = .047$) but not in nonatopic children with family history. By age, the effect of probiotics was found significant in children aged $\geq 2$ years (WMD: $-12.74$ U/mL [95% CI: $-24.55$ to $-0.93$]; $P = .035$).

Multivariate meta-regression analyses, including baseline age, age at follow-up, gender, treatment length, daily and total dose, and duration of follow-up, showed that length of follow-up modified the effect of probiotics on total IgE: the reduction in IgE was more pronounced with longer follow-up (correlation coefficient $\beta$: $-1.95$ [95% CI: $-3.69$ to $-0.21$]; $P = .028$) (Fig 3). Funnel plot and Egger test showed no evidence of publication bias ($P = .23$) (Fig 4).

Atopic Sensitization

Twenty-one studies\textsuperscript{16–31,38–40} characterizing 14 trials were included ($N = 2797$).
Overall, probiotics had a partially significant effect in reducing the risk of atopic sensitization, defined as positive SPT result and/or elevated specific IgE (RR: 0.90 [95% CI: 0.80 to 1.00]; \(P = .060\)). The reduction was significant when probiotics were administered prenatally and postnatally (RR: 0.88 [95% CI: 0.78 to 0.99]; \(P = .035\)) but not when given only postnatally (\(P = .825\)) (Fig 5). Subgroup analysis by definition of atopic sensitization showed a significant protective effect of probiotics against positive result on SPT to common allergens when administered prenatally and postnatally (RR: 0.86 [95% CI: 0.75 to 0.98]; \(P = .027\)) (Supplemental Figure 7). The overall protective effect against atopic sensitization was close to significance (RR: 0.88 [95% CI: 0.78 to 1.00]; \(P = .059\)) when defined as positive result on SPT but not significant when defined as elevated specific IgE level.

Multivariate meta-regression showed that the administration of *Lactobacillus acidophilus* was associated with an increased risk of atopic sensitization (\(\beta = 0.45 [95\% \text{ CI}: 0.16 \text{ to } 0.74]; \(P = .002\)). Funnel plot and Egger test showed no evidence of publication bias (\(P = .57\)).

**Asthma/Wheeze**

Fourteen studies from 10 trials were included (\(n = 3143\)).
Probiotics did not significantly reduce asthma/wheeze (RR: 0.96 [95% CI: 0.85 to 1.07]) (Fig 6). No significant association was found in subgroup analyses according to age group, treatment length, follow-up duration, probiotic strain, dose administered, or outcome definition (wheeze ever, recurrent asthma/wheeze, atopic asthma/wheeze). Funnel plot and Egger test showed no evidence of publication bias (P = .25).

**DISCUSSION**

The results of our meta-analysis indicate that the administration of probiotics early in life is effective in reducing IgE levels and the risk of atopic sensitization in young children but not the risk asthma or wheeze. There was no difference based on timing of administration (prenatally to mothers plus postnatally versus only postnatally) with regard to IgE, but the decrease in the risk of atopy was
significant only when probiotics were started during pregnancy and continued after birth. Meta-regression analysis results showed that the effect of probiotics in decreasing total IgE level was more pronounced with longer follow-up periods, and that their effect in decreasing risk of atopic sensitization may depend on the specific strains administered.

These results are consistent with the hygiene hypothesis, which proposes that a relative lack of microbial exposure during infancy and early childhood may result in an imbalance between Th1- and Th2-type immune responses and may induce the development of IgE-mediated allergic responses. It has been postulated that early exposure to commensal bacteria plays a crucial role in Th1/Th2 polarization and maturation of proper immune regulatory mechanisms. The gut is the most important source of postnatal microbial stimulation of the immune system, and atopic children may have different gut microbiome compared with their nonatopic peers; such differences have been found between cases of eczema and healthy controls, as well as between countries with high and low incidence of atopic diseases. Probiotic administration early in life may promote a healthier gut microbiome, which in turn modulates the maturation of the immune response. Allergic disorders are associated with a shift of the Th1/Th2 cytokine balance toward a Th2 response. This action leads to activation of Th2 cytokines such as IL-4, IL-5, and IL-13, as well as increased IgE production. Probiotics may modulate toll-like receptors and the proteoglycan recognition proteins of enterocytes, leading to activation of dendritic cells and a Th1 response; the resulting stimulation of Th1 cytokines can suppress Th2 responses. Pediatric studies suggest that the use of probiotics in children with atopic disorders, such as food allergies or atopic dermatitis, results in enhancement of interferon-γ production (a Th1 cytokine), decreased IgE, and decreased secretion of antigen-induced tumor necrosis factor-α, IL-5, and IL-10. In animal models of ovalbumin (OVA)-induced allergy, probiotics (L acidophilus AD031 and Bifidobacterium lactis AD011) significantly decrease serum levels of OVA-specific IgE, IgA, and IgG1; up-regulate interferon-γ and IL-10; and down-regulate IL-4.

Probiotics may also prevent atopy via low-grade systemic or local inflammation: increased plasma C-reactive protein concentrations have been found in children with eczema and cow's milk allergy who were treated with...
probiotics. Higher C-reactive protein levels in infants at risk for allergy at 6 months of age were associated with lower risks for eczema and allergic disease at 2 years of age after treatment with probiotics in combination with prebiotics. Probiotics can induce fecal inflammatory markers, such as α1-antitrypsin, tumor necrosis factor-α, and calprotectin, which have been associated with higher fecal IgA levels and lower risk of IgE-associated allergic disease, suggesting minimal intestinal inflammation may play a role in their mechanism of action.

Although our pooled analyses found a significant effect of probiotics on total IgE and risk of atopic sensitization, we did not find a similar significant risk reduction for asthma and wheeze, which is consistent with previous studies in adults. Animal studies with probiotics have shown decreased inflammatory response to single but not repeated allergen challenge: in murine models of asthma sensitized with OVA, administration of *Lactobacillus reuteri* ATCC 25272, *Lactobacillus rhamnosus* GG, or *B. lactis* Bb-12 significantly decreased airway hyperactivity and reduced inflammatory cells in bronchoalveolar lavage fluid after intranasal OVA challenge. *L rhamnosus* GG and *B lactis* also increase natural regulatory T cells in the lungs of asthmatic mice. However, MacSharry et al reported that the inhibition of certain components of allergen-induced airway inflammation by *Bifidobacterium longum* administration was overcome after repeated allergen exposure.

Based on the results of our meta-regression analysis for IgE and atopic sensitization, we speculate that the lack of effect of probiotics in reducing the risk of asthma/wheeze may have been due to the specific combinations of strains used in these trials or due to insufficient length of follow-up; these theories will need to be tested prospectively. Animal studies suggest that the effects of probiotics on allergen-induced airway responses may be sensitive to the organism used: *L reuteri*, but not *Lactobacillus salivarius*, has been shown to inhibit allergic airway responses in sensitized mice, and a recent study by Hougee et al demonstrated *Bacillus brevis* has strain-dependent immunomodulatory effects. The duration and timing of feeding are also determinants of anti-inflammatory efficacy; Forsythe et al found that a period of feeding of at least 9 days was required for significant inhibition of airway eosinophilia and airway hyperreactivity in mice. To be most effective, the bacterial species used as probiotics must be resistant to acid and bile to survive and make the transit through the upper gastrointestinal tract, and even the most resilient strains can be cultured in stool for only 1 to 2 weeks after ingestion; thus, regular intake is vital.

There are several potential limitations to our study. We included only articles published in English or with abstracts in English with sufficient information, which may not be representative of all studies conducted on the topic. Another important limitation in any meta-analysis is the variability among studies; although we used random-effects models to try to account for this variability and we performed meta-regression analysis to detect significant effect modifiers, we can only analyze covariates that are available to us from the original manuscripts. Finally, we cannot completely exclude the risk of publication bias, although funnel plots and Egger test analyses showed no evidence of such bias for any of our outcomes.

**CONCLUSIONS**

We found that the administration of probiotics in early life may reduce total IgE and protect against atopic sensitization but does not appear to protect against asthma and wheeze. Therefore, carefully selected probiotics administered during pregnancy and early infancy may have a role in the primary prevention of atopic diseases, particularly in high-risk infants. Future trials should consider specific strains of probiotics, longer follow-up times, and perhaps association with oligosaccharides, particularly when assessing the effects of probiotics on the reduction of risk of asthma and wheeze later in life.

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Pediatrics 2013;132:e666
DOI: 10.1542/peds.2013-0246 originally published online August 19, 2013;
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