

Correspondence

Probiotics cannot be generally recommended for primary prevention of atopic dermatitis

To the Editor:

In a recently published meta-analysis, Lee et al¹ concluded that a prenatal and postnatal regimen of probiotics is “an effective option for pregnant women with risk factors for atopic disease to help prevent persistent PAD in their children.” We would like to add the following comments on difficulties arising from their study selection.

First, 3 of 6 studies included in the meta-analysis refer to the same study population. Kalliomäki et al^{2,3} recruited a birth cohort supplemented with probiotics or placebo and reported the prevalence of atopic dermatitis (AD) as the primary outcome at the age of 2 and 4 years. Moreover, Rautava et al⁴ published data of a subgroup of this cohort showing the reduction of TGF- β levels in mother's milk. However, the clinical data indicating a lower prevalence of AD at 2 years of age in this subgroup are also included in this meta-analysis. Because these 3 publications represent only 1 study population, allowing a 39.83% effect on the whole meta-analysis in the prevention section is therefore not justified. Basically, only the follow-up data at 2 or 4 years should be considered in this meta-analysis.

Second, the largest clinical trial in the meta-analysis is the study of Kukkonen et al,⁵ reporting positive effects of a combination of prebiotics and probiotics. However, in contrast to all the other included studies that used different lactobacilli strains as a single probiotic, this study used a mixture of 4 strains of probiotics combined with 1 prebiotic. Because it is yet unclear whether and which prebiotic or probiotic might yield any effect, it is at least questionable to include this trial in the meta-analysis.

Third, the significance of the effect of probiotics in the meta-analysis is in part caused by not including a randomized clinical trial in which a negative result was obtained after a postnatal-only supplementation period.⁶ The authors conclude that these data indicate that the timing of the supplementation is of major importance. They disregard that in all included trials the timing of the supplementation is completely different, ranging from 0 to 6 weeks before and from 6 to 12 months after delivery.¹ Up to now, no direct comparison of the administration and efficacy of 1 probiotic during different periods is available. Thus the conclusion should be that the timing of supplementation of prebiotics or probiotics is still unclear.

These comments are now becoming even more important because the only trial that used a nearly identical study design of the original Kalliomäki study by our group⁷ showed no effect in reduction of AD frequency at the age of 2 years. Taken together, the selection of the most beneficial probiotic strain or the composition of different probiotics, prebiotics, or both; the timing of supplementation; and the optimal dose and means of delivery still need to be determined. Thus far, an allergen-preventive effect of various probiotics for the prevention of AD could not be consistently established. Therefore, probiotics cannot be generally recommended for primary prevention.

Peter Salfeld, MD
Matthias V. Kopp, MD

From the Centre for Pediatrics and Adolescent Medicine, University of Freiburg, Freiburg, Germany. E-mail: matthias.kopp@uniklinik-freiburg.de.

Disclosure of potential conflict of interest: M. V. Kopp has received research support from Novartis Pharma GmbH, Nurnberg, Germany. P. Salfeld has declared that he has no conflict of interest.

REFERENCES

1. Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 2008;121:116-21.
2. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357:1076-9.
3. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361:1869-71.
4. Rautava S, Kalliomäki M, Isolauri E. Probiotics during pregnancy and breastfeeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol* 2002;109:119-21.
5. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119:192-8.
6. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007;119:184-91.
7. Kopp MV, Hennemuth I, Dietschek A, Goldstein M, Ihorst G, Heinzmann A, et al. A randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical or immunological effects of *Lactobacillus* GG supplementation. *Pediatrics* 2008;121:e850-6.

doi:10.1016/j.jaci.2009.02.038