# PROBIOTICS IN PRIMARY PREVENTION OF ATOPIC DISEASE: A RANDOMISED PLACEBO-CONTROLLED TRIAL

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***Abstrakt:*** *This article provides information on probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial*

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Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in Western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of Lactobacillus GG (which is safe at an early age and effective in treatment of allergic inflammation and food allergy). Methods In a double-blind, randomised placebo-controlled trial we gave Lactobacillus GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint. Findings Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0·51 [95% CI 0·32□0·84]). The number needed to treat was 4·5 (95% CI 2·6□15·6). Interpretations Lactobacillus GG was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators

and probiotics, for prevention of atopic disease.

Introduction Allergy, in the form of atopic diseases such as atopic eczema, allergic rhinitis, and asthma, is a chronic disorder of increasing importance in economically more-developed countries.1 The International Study of Asthma and Allergies in Childhood2,3 included 11607 Finnish children aged 13□14 years; 10□20% of the children had symptoms of asthma, 15□23% allergic rhinitis, and 15□19% atopic eczema. Proof of an inverse association between infections early in life and atopy has led to renewed interest in the hygiene hypothesis devised by Strachan4 a decade ago. The recent rapid rise in atopy might be a result of improved hygiene and reduced family size. Recent epidemiological studies have yielded results both for,5□7 and against,8 such a hypothesis. We propose that specific microbes in the commensal gut microflora are more important than sporadic infections in atopic disease prevention. Gastrointestinal microflora promote potentially antiallergenic processes: (1) T-helper1-type immunity;9 (2) generation of transforming growth factor , 10,11 which has an essential role in suppression of T-helper-2-induced allergic inflammation12 and induction of oral tolerance;13 and (3) IgA production,14 an essential component of mucosal immune defence. The gut microflora might therefore be a major postnatal counterregulator of the universal T-helper-2-skewed immune system in fetuses and neonates. Confrontation between microbes and their antigens in the gastrointestinal tract begins instantly after birth, and the viable cells of fully established gut microflora outnumber those of the human host by a factor of ten.15 Consequently, commensal gastrointestinal microbes are the earliest and biggest stimulus for development of gut-associated lymphoid tissue. Probiotics are cultures of potentially beneficial bacteria of healthy gut microflora15 and one such strain, Lactobacillus rhamnosus (Lactobacillus GG, American Type Culture Collection 53103), has proved safe at an early age and effective in treatment of allergic inflammation11 and food allergy.16 In a double-blind randomised placebo-controlled trial of prevention of atopic disease, we gave Lactobacillus GG prenatally to mothers and postnatally for 6 months to their infants at high risk of these diseases. Methods Participants and study design The

only inclusion criterion was a family history of atopic disease□ie, one or more family members (mother, father, or older sibling) with atopic eczema, allergic rhinitis, or asthma. Families were recruited in antenatal clinics in Turku, Finland (population 170 000) between February, 1997, and January, 1998, to avoid the effect of birth month on atopic sensitisation. On the basis of our sample-size calculation before the study, 159 mothers were randomly assigned by computer to receive two capsules of placebo (microcrystalline cellulose) or 1 1010 colony-forming units of Lactobacillus GG (Valio Ltd; Helsinki, Finland) daily for 2□4 weeks before expected delivery. After delivery, breastfeeding mothers could take the capsules, otherwise children received the agents; in the latter case, capsule contents were mixed with water then given by spoon. Both these modes of administration have resulted in similar amounts of Lactobacillus GG in infant faeces.16 Lactobacillus GG and placebo capsules and contents looked, smelled, and tasted identical. Capsules were taken postnatally for 6 months. Treatment codes were kept by the supplier until data had been collected and analysed□ie, until March, 2000. Children were examined during the neonatal period and on study visits to a department of paediatrics at ages 3, 6, 12, 18, and 24 months. The outcome measure was atopic disease at 2 years. Since chronic recurring atopic eczema is the main sign of atopic disease in the first years of life,17 it was the primary study endpoint. Children were grouped as having this disorder (children with atopic eczema) or not (healthy children). The study was approved by the Committees on Ethical Practice in Turku University Hospital and the Health Office of Turku. Written informed consent was obtained from children□s parents. Procedures The physician (MK) who did the physical examinations, diagnoses of atopic disease, and antiasthma treatments was unaware of the contents of the capsules until March, 2000, when all data had been obtained and analysed. Physical examination included inspection of eyes, ears, nose, and skin, auscultation of heart and lungs, palpation of abdomen, and assessment of growth and neurological development. Parents were asked about their child□s signs and symptoms that were possibly related to atopic disease: redness, dryness, oozing,

and scratching (itch) of skin; redness, discharge, sneezing, and rubbing (itch) of eyes and nose; and cough, wheeze, and shortness of breath. Sensitisation to common dietary and respiratory antigens was measured by: skin-prick tests at ages 6, 12, and 24 months; and by total and antigen-specific IgE assays in umbilical cord blood and at ages 3, 12, and 24 months. Atopic eczema was confirmed by pruritis, facial or extensor involvement, or both, and chronic relapsing course.17 This last criterion was fulfilled if the child had had eczema for 1 month or longer at the 24-month study visit and on at least one previous visit. The SCORAD index18 was used to assess eczema severity. Allergic rhinitis was diagnosed if the baby had on most days two or more of: nasal discharge, blockage, sneezing, and itching. For diagnosis, temporal relations had to be established between these symptoms of allergic rhinitis, symptoms with allergen exposure, relief of symptoms by antihistamine treatment, and evidence of atopic sensitisation (ie, positive skin-prick test or positive radioallergosorbent assay, or both). Asthma diagnosis was based on an algorithm created by an international paediatric asthma concensus group.19 Asthma was diagnosed if an infant had chronic or recurrent cough, wheeze or shortness of breath, or both, suggestive of asthma, and if other diagnoses were excluded and trial antiasthma treatment was effective. Assays for serum total IgE and specific IgE antibodies to milk, egg, cat, and house-dust mite were done with the Pharmacia CAP FEIA immunoassay on a UniCAP 100 automatic analyser (Pharmacia and Upjohn; Uppsala, Sweden) in accordance with manufacturer□s instructions. An antigen-specific IgE value of more than 0·35 kU/L was classed as increased. Skin-prick tests were done as previously described,20 and antigens tested included: milk; wheat and rye flours, both diluted 1/10 (weight/volume) with 0·9% (weight/volume) sodium chloride; gliadin diluted 1/1000 (weight/volume) with 0·9% (weight/volume) sodium chloride; banana, potato, and carrot (all three by prick-prick technique), egg white, cod, soya bean, birch, six local grasses, cat, dog, and Dermatophagoides pteronyssimus allergen Der p1 (ALK; Abellò, Denmark); and latex (Stallergens; Marseille, France). Statistical analysis The anticipated frequency of atopic disease in the placebo group was 50%. With at

least 56 individuals in each group, a reduction of 25% in the frequency of atopic disease could be detected at a 5% level of significance with 80% power. Normally distributed data are expressed as means with 95% CI, and skewed data as geometric means with 95% CI after logarithmic transformation. Values were compared between the groups by unpaired t test. 2 test was used to compare proportions between the groups. Relative risk and the number needed to treat, both with 95% CI, were used to describe the treatment effect of Lactobacillus GG.21 The proportion (and 95% CI) of children with atopic disease in both groups was calculated with the formulas devised by Gardner and Altman.22 Total IgE concentration was rated as high if it were greater than the geometric mean concentration of total IgE plus 1 SD in children without atopic disease.23 A p value less than 0·05 was regarded as statistically significant.

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