Probiotics: Myths or facts about their role in allergy prevention

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Abstract

Background. The hygiene hypothesis proposed by Strachan in the 1980s clearly emphasized the role of microorganisms in atopy prevention.

Objectives. The study objective was to assess the preventive role of probiotics in patients with allergic rhinitis, bronchial asthma, atopic dermatitis, and/or food allergy.

Material and methods. The methods used in the study were the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires for 6–7- and 13–14-year-olds and the European Community Respiratory Health Survey II (ECRHS II) questionnaire targeted for the 20–44 age group. The study was conducted as part of the cross-sectional Epidemiology of Allergic Diseases in Poland study conducted in 9 Polish regions (8 urban: Warszawa, Lublin, Białystok, Gdańsk, Poznań, Wrocław, Katowice, Kraków, and the rural regions of Zamojski and Krasnostawski counties). The study material was a group of patients diagnosed with food allergy (n = 407), atopic dermatitis (n = 311), allergic rhinitis (n = 1.353), bronchial asthma (n = 505), and healthy volunteers (n = 2,403).

Results. Genetic factors play an important role in the allergy development. A family history positive for chronic skin disorders increased the risk of atopic dermatitis and food allergies (OR = 1.456, CI = 1.14–1.85, p = 0.002; and OR = 1.378, CI = 1.05–1.81, p = 0.02, respectively). The consumption of products containing live bacterial cultures showed no preventive effects in any of the evaluated disorders in early childhood. Conversely, over the age of 14 years, probiotic formulations exhibit health-promoting effects and may lower the risk of allergic diseases.

Conclusions. The use of probiotics in the Polish population showed no protective effect in the first years of life. The changes in dietary habits introduced during late adolescence demonstrated significantly greater preventive effects of live bacterial cultures against the development of allergic diseases.

Key words: probiotics, prevention, allergy

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The prevalence of allergic diseases poses a serious problem in the field of modern medicine and public health. Estimates suggest that nearly 40% of the general population suffers from some form of allergy.[1] Measures such as primary and secondary prophylaxis are crucial in allergy prevention and contribute to health improvement. Recent decades saw an increased interest in diet supplementation with live bacterial cultures (*Lactobacillus rhamnosus GG, Lactobacillus acidophilus, Lactobacillus reuteri*, and mixed cultures) which – apart from having protective gastrointestinal effects – modulate the immune system (the intestinal microflora regulates the Th1/Th2 ratio and stimulates IL10).[2,3]

The objective of this study was to assess the rates of probiotic use in the Polish population as well as to detect any probiotic-induced protection against allergic diseases, including atopic dermatitis (AD), food allergies (FA), allergic rhinitis (AR), and bronchial asthma (BA).

Material and methods

Study group

A total of 22,454 respondents took part in the questionnaire survey, of whom the quality verification process was passed by 18,617 people in the age ranges: 6–7 years (n = 4510; 24.2% of all the subjects); 13–14 years (n = 4721; 25.4%); and 20–44 years (n = 9386; 50.4%). There were 10,011 (53.8%) women and 8,606 (46.2%) men altogether in the survey. The percentage distribution of respondents in individual research centers in Poland was similar: Białystok – 3,411 (18.3%); Katowice – 2,434 (13.1%); Lublin – 2,422 (13.0%); Warszawa – 2,281 (12.3%); Zamość – 2,055 (11.0%); Gdańsk – 1,837 (9.9%); Kraków – 1,642 (8.8%); Wrocław – 1,317 (7.1%), and Poznań – 1,218 (6.5%). The selection of the group was based on purposive (nonprobability) sampling, and within the surveyed centers, the subjects were randomly selected with their personal identification number (PESEL) used as the sampling frame (the PESEL system is administered and maintained by the Ministry of the Interior and Administration). For the purposes of sampling in the research centers, the following 3 criteria were taken into account: geographical location, the number of inhabitants, the level of air pollution. From among the entire population from the 1st stage of the study, 30% (4,783) of all the respondents were qualified on an outpatient basis for further analysis. They were in 3 age ranges: children (6–7 years; 29.5%); adolescents (13–14 years; 28.0%); and adults (20–44 years; 22.7%). The study involved subjects who had been diagnosed with AR (n = 1,353), BA (n = 505), AD (n = 311) and/or FA (n = 407), and 2,403 healthy controls (HC) (Fig. 1). The diagnoses were verified based on the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria, Global Initiative for Asthma (GINA) criteria, and according to Hanifina and Rajka. The patients underwent additional complementary skin prick tests (16 environmental allergens), a spirometry test, an assessment of specific IgE (sIgE) antibodies, and had their nasal patency measured by peak nasal inspiratory flow (PNIF).

Methods

The assessment tools used in the study were the European Community Respiratory Health Survey II (ECRHS II) and the International Study of Asthma and Allergies in Childhood (ISAAC); the latter had been adapted to European conditions. The project involved the use of the innovative Computer-Assisted Personal Interviewing (CAPI) technique and Personal Digital Assistant (PDA) equipment, which was employed to ensure quality control of the survey questionnaire. Furthermore, after the interview had been completed, all the data was transferred via GPRS to the central office and exported to the project database. This cross-sectional study was part of the project "Implementation of a System for the Prevention and Early Detection of Allergic Diseases in Poland" (No. 6 PO5 2005 C/06572), conducted on the residents of 8 large Polish cities (Gdańsk, Wrocław, Poznań, Katowice, Kraków, Lublin, Białystok, Warszawa) and rural areas of Zamojski and Krasnostawski counties. The study was approved by the Ethics Committee at Medical University of Warsaw (KB/206/2005).

Table 1. Coinheritance factors for allergic diseases

Food allergy (FA)	OR	CI	p-value
Genetic factors – mother*	1.850	1.44–2.38	1.64e-06
Genetic factors – father*	2.058	1.56–2.72	3.45e-07
Chronic skin disorders in the family**	1.456	1.14–1.85	0.00227
Atopic dermatitis (AD)			
Genetic factors – mother*	1.831	1.38–2.43	2.84e-05*
Genetic factors – father*	1.822	1.33–2.50	0.000192*
Genetic factors – paternal grandfather	1.896	1.16–3.09	0.010303
Chronic skin disorders in the family**	1.378	1.05–1.81	0.021048
Allergic rhinitis (AR)			
Genetic factors – mother*	1.277	1.07–1.53	0.00751
Genetic factors – father*	1.767	1.44–2.17	4.23e-08*
Genetic factors – siblings	1.300	1.10–1.53	0.00160
Bronchial asthma (BA)			
Genetic factors – father*	1.386	1.05–1.84	0.02338
Genetic factors – siblings	1.275	1.01–1.61	0.03968
Genetic factors – maternal grandparents*	1.480	1.04–2.10	0.02833
Genetic factors – paternal grandfather	1.946	1.28–2.95	0.00176

Asterisks indicate statistically significant results (Bonferroni-corrected due to a high number of tests); * declared responses according to the ECRHS/ ISAAC standardized questionnaire (Does anyone in the immediate family suffer from allergy?); ** declared responses according to the ECRHS/ ISAAC standardized questionnaire (Is there any history of skin disease in your family?).

Statistical analysis

The odds ratio (OR) for individual risk factors was calculated based on the appropriate logistic regression models. The Wald test was used to determine statistical significance. The 95% confidence intervals (CI) for the OR were also provided. Due to a large number of factors (28 factors from Table 1 and 6 factors from Table 2, stratified by 4 diseases), a total of 136 tests were conducted. Consequently, the standard significance level of 0.05 was divided by the number of tests, which yielded a significance level of 3.7e-4. The results marked with an asterisk (*) in Tables 1 and 2 represent findings that are significant according to this new significance level (with the Bonferonni correction).

Results

Genetic factors (the risk factor analysis included 28 variables; Table 1) significantly increased the risk of allergic diseases, with a higher risk of allergy in children with a family history of paternal atopy. Interestingly, chronic hereditary skin disorders tended to increase the risk of FA and AD. FA manifestation rates were 5-fold (OR = 5.45; p < 2e-16; 95% CI 4.127809–7.185846), AO manifestations were 2-fold (OR = 2.32; p = 2e-8; 95% CI 1.73–3.11), and AR manifestations were 2-fold (OR = 1.85; p = 2.7e-7; 95% CI 1.47–2.35) higher in patients with AD.

The use of probiotics was declared by 80% of patients diagnosed with FA, 79% of patients with AD, 71% of patients with AR, and 78% patients with BA. The most commonly used probiotic products were Lakcid (*Lactobacillus rhamnosus*), Lacidofil (*Lactobacillus rhamnosus, Lactobacillus helveticus*) and Trilac (*Lactobacillus*). The frequency distribution of probiotic use was nearly identical between the groups, with slightly higher rates in the AD and FA groups, with the difference being nonsignificant. Probiotic products used for the purpose of allergy prevention did not exhibit any prophylactic effects in subjects under 14 years of age (1 exception was a case of AR, in which preventive effects were observed from the age of 1 year) (Table 2). Supplements such as kefir (*Lactobacillus kefiri, Leuconostac*) and yogurts (*Streptococcus thermophilus, Lactobacillus*), administered several times a week in late adolescence (above the age of 14 years), showed health-promoting effects in allergic diseases.

Discussion

The effect of environmental changes as well as outdoor and indoor factors play a key role in allergic disease development. The hygiene hypothesis proposed by Strachan

Table 2. Products containing live bacterial

Food allergy (FA)	OR	CI	p-value
Products containing live bacterial cultures	1.902	1.46–2.46	1.27e-06*
Products containing live bacterial cultures, used independently of antibiotic therapy	1.703	1.18–2.44	0.00386
Products containing live bacterial cultures, used until the age of 1 year	1.835	1.17–2.87	0.008012
Products containing live bacterial cultures, used at the age of 3–7 years	1.336	1.01–1.75	0.036345
Products containing live bacterial cultures, used at the age of over 14 years	0.490	0.33–0.71	0.000232*
Yogurts consumed 3 times a week or more at the age of over 14 years	0.311	0.19–0.49	5.14e-07*
Atopic dermatitis (AD)			
Products containing *Lactobacilli*	2.061	1.52– 2.78	2.69e-06*
Products containing live bacterial cultures, used independently of antibiotic therapy	1.610	1.07–2.40	0.0202
Products containing live bacterial cultures, used at the age of over 14 years	0.378	0.23–0.59	3.22e-05*
Kefirs consumed 3 times a week or more at the age of over 14 years	0.389	0.18–0.81	0.0124
Yogurts consumed 3 times a week or more at the age of over 14 years	0.381	0.23–0.60	4.83e-05*
Allergic rhinitis (AR)			
Products containing live bacterial cultures	1.165	1.00–1.34	0.041
Products containing live bacterial cultures, used until the age of 1 year	1.477	1.02–2.13	0.0371
Products containing live bacterial cultures, used at the age of 1–3 years	0.751	0.58– 0.96	0.0277
Yogurts consumed 3 times a week or more at the age of 3–7 years	0.725	0.56–0.92	0.00929
Bronchial asthma (BA)			
Products containing live bacterial cultures	1.850	1.45–2.34	4.09e-07*
Products containing live bacterial cultures, used in combination with antibiotic therapy	0.576	1.12–2.81	0.0141
Products containing live bacterial cultures, used at the age of over 14 years	0.673	0.49–0.91	0.0104
Kefirs consumed 3 times a week or more at the age of 7–14 years	0.399	0.22–0.71	0.00201

Asterisks indicate statistically significant results (Bonferroni-corrected due to a high number of tests).

in the 1980s clearly emphasized the role of microorganisms in atopy prevention.[4] Excessive hygiene or genetic factors lead to disturbances in the intestinal microbiota, which begins forming during the first days of life in a breastfed neonate and reaches its mature composition at the age of 2 years.[5] Due to the disturbances the activity of lymphocytes Th1 is limited. A study by Bjorksten et al. on the relationship between allergic diseases and the composition of intestinal microflora showed considerably lower levels of *Lactobacillus* and *Bacteroides* in the group with a history of allergies as compared to the control group. This clearly indicates the necessity to use probiotic supplementation apart from an elimination diet.[6]

As mentioned before, live bacterial cultures play a distinct role in maintaining good health via their effects on the gastrointestinal tract (the stomach, intestines). Although studies on the health-promoting influence of probiotics showed good therapeutic and preventive effects in animal models, the treatment of allergic diseases in humans showed only moderate effects (most pronounced in atopic eczema).[7,8] Moreover, the World Allergy Organization and McMaster University Guidelines for Allergic Disease Prevention (GLAD-P) panel of experts clearly indicated a lack of robust evidence confirming the effectiveness of probiotics in a group of pregnant or breastfeeding women, or infants at a high risk of atopy.[9]

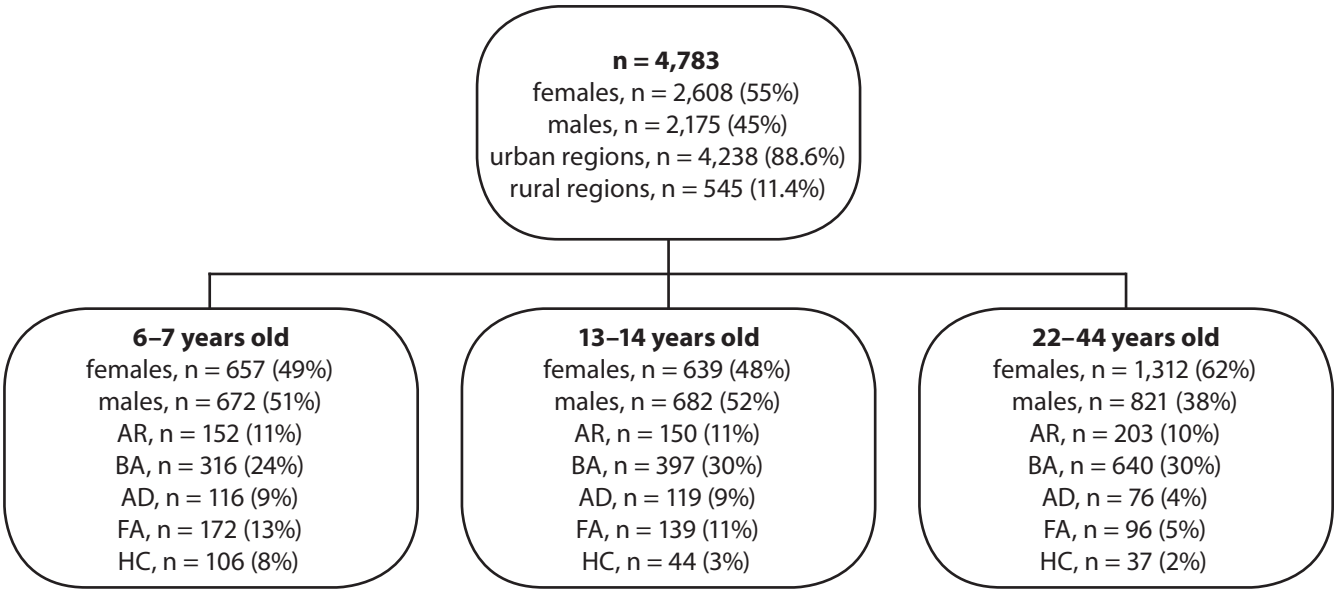

Fig. 1. Study group characteristics

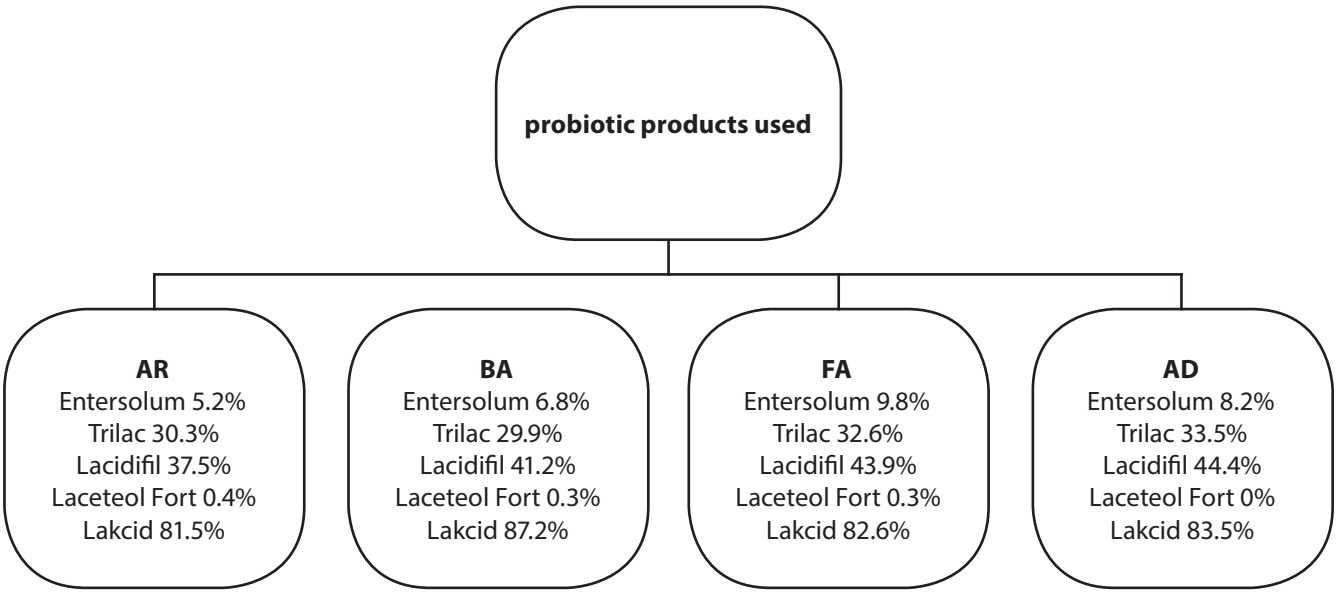

Fig. 2. Probiotic products used by the study population

Despite the fact that a meta-analysis (n = 2,403) by Cuello-Garcia et al., based on the Cochrane Central Register of Controlled Trials, MEDLINE and Embase, documented a preventive effect of probiotics on atopic eczema in a group of women using products containing live bacterial cultures (OR = 0.71; 95% CI 0.60–0.84), in breastfeeding women (OR = 0.57; 95% CI 0.47–0.69) and in neonates (OR = 0.80; 95% CI 0.68–0.94), it did not indicate the necessity of supplementation due to a number of confounding factors.[10] A similar study by Boyle et al. evaluated the effects of *Lactobacillus rhamnosus* (LGG®) supplementation from 36 Hbd until birth as a factor significantly reducing the development of AD in infants; likewise, the use of *Lactobacillus casei DN114001* in neonates for 6 weeks minimized the risk of AD in a group of children under 6 months of age.[11]

The GUSTO cohort study with 3 assessment time points (at 6 months of age, 6–12 months of age, and at consecutive years after the age of 12 months) showed a significantly high risk of developing AD associated with antibiotic therapy (OR = 3.11; 95% CI 1.10–8.76; p = 0.03) during the first 6 months of life and the use of probiotics at the age of 9–12 months (OR = 4.32; 95% CI 1.07–17.45; p = 0.04). Moreover, the risk of developing AD was shown to increase over 20-fold in genetically predisposed patients, with a positive family history (OR = 20.46; 95% CI 2.73–153.15, p < 0.01).[12]

The risk of developing an allergy when one of the parents has an allergy ranges from 35 to 40%; however, when both parents have been diagnosed with atopy, the risk can increase up to 60%. Moreover, a predilection for developing allergies is usually inherited by the son when the father has an allergy and, correspondingly, by the daughter when the mother has an allergy. Scientific literature contains considerably more evidence documenting a higher risk of allergy in the offspring, irrespective of sex, from the affected mother than from the affected father (40% in the case of maternal allergies, approx. 30% in the case of paternal allergies). Conversely, our analysis clearly indicates higher rates of allergies inherited from the father's side. Recent attempts to estimate the risk of developing allergy via hereditary means have been using filaggrin (an amino acid precursor with molecular weight of 35–37 kDA that is a component of a natural moisturizing factor), particularly its mutations in the *2282del4* and *R501X* genes.[13] A study by Ponińska et al. (one of the studies on the role of filaggrin *2282del4* in inheriting allergic diseases), conducted on a population of 3,802, estimated the risk of developing AD (OR = 2.01; 95% CI 1.20–3.36; p = 0.007), AR (OR = 1.69; 95% CI 1.12–2.54; p = 0.011) and atopic asthma (OR = 2.22; 95% Cl 1.24–3.96; p = 0.006) in patients with mutations in this gene.[13] We observed no correlation between the presence of gene mutations and serum sIgE levels. Conversely, Filipowska-Grońska et al. demonstrated filaggrin gene mutations in 11.4% out of all 205 study subjects with AD with concomitantly increased total and specific serum IgE levels.[15]

Subsequent attempts at estimating the effectiveness of probiotic supplementation in patients with AR and BA also yielded inconsistent evidence. A meta-analysis by Zajac et al., including 23 randomized studies conducted on 1,919 subjects to assess the rationale for probiotic use in 3 aspects – Rhinitis Quality of Life (RQLQ), Rhinitis Total Symptom Scores (RTSS) and sIgE levels, demonstrated the preventive effect of probiotics in 17 studies and a protective effect in 6 studies. The probiotics used in the studies significantly improved quality of life (SMD –2.23; p = 0.02), with no effect on rhinitis symptoms or total serum IgE levels (SMD 0.01; p = 0.94). Moreover, we observed a decreasing trend in sIgE levels (SMD 0.20; p = 0.06) vs placebo.[16] Giovannini et al. showed a significant beneficial effect of *Lactobacillus casei* supplementation on the symptoms of AR (n = 131), with a lack of effectiveness on the rates of dyspneic episodes in atopic asthma (n = 119).[17] These finding were consistent with those of Wheeler et al., who evaluated the effect of *Lactobacillus bulgaricus* in a group of 15 patients diagnosed with moderate asthma and demonstrated no significant changes in the assessed lung function parameters and total serum IgE levels.[18]

This first cross-sectional study on probiotic supplementation in the Polish population suggested a need for further prospective, cohort studies. The observed preventive effects of live bacterial cultures in patients aged over 14 years, diagnosed with allergic diseases may be explained by a change in dietary preferences – making own decisions, e.g., to augment one's diet to include cultured dairy products (yogurts, kefirs) with a composition recommended by the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO).

There is no consistent evidence for the effectiveness of consuming live bacterial cultures in the prevention or treatment of allergic diseases, especially in subjects under 14 years of age. Probiotic supplementation while changing dietary habits and full maturation of microbiota may have a protective effect against the development of allergic diseases. Further prospective studies are needed to evaluate the effectiveness of the potential probiotic-induced prevention of allergic diseases.

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