Respiratory Medicine (2007) **101**, 1123–1131

ELSEVIER

respiratoryMEDICINE

Allergy in marathon runners and effect of *Lactobacillus* GG supplementation on allergic inflammatory markers ☆

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Received 11 September 2006; accepted 16 November 2006
Available online 29 December 2006

KEYWORDS
Allergy;
Athletes;
Eosinophil cationic protein;
IgE;
Lactobacillus GG

Summary
Objective: We studied the prevalence of asthma and allergy in non-elite marathon runners and investigated the effects of probiotic supplementation on allergic inflammatory markers.
Methods: Asthma and allergies were surveyed by questionnaire, and blood eosinophils, serum eosinophil cationic protein (ECP), total IgE, and Phadiatop® were measured in 141 Finnish marathon runners who took part in the Helsinki City Marathon. They were also randomized to receive either *Lactobacillus* GG (LGG) or placebo during the 3 months of the pollen season prior to the marathon.
Results: Lifetime prevalence of physician-diagnosed asthma was 4.3% (six out of 139 athletes), of allergic rhinitis 17.3% (24/139), of food allergy 5.0% (7/139), and of atopic eczema 4.3% (6/139). Prevalence of atopy was 31% (35/112), and 21% (24/112) of the athletes were sensitized to birch pollen. Asthma or allergy medication was used by 20% (28/139) of the athletes. During pollen season, serum ECP increased significantly in all athletes, and total IgE and Phadiatop® in atopics. The marathon induced a significant eosinopenia but had no effect on serum ECP or total IgE. No differences in changes were seen between groups receiving LGG or placebo.

☆Sources of support: André Moreira holds a Grant from the Finnish Center for International Mobility and a Fellowship Award from the European Academy of Allergy and Clinical Immunology.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2006.11.015

Conclusion: Non-elite marathon runners have asthma and allergies similar to Finnish general population. LGG supplementation did not prevent the increase of allergic markers during the pollen season, or the eosinopenia induced by the marathon.

Background

Evidence suggests an increased risk of asthma and bronchial hyperresponsiveness in elite athletes.[1–3] Plausible biological explanations include type of sports, training environment and athlete's atopic background.[4–6]

Strenuous exercise, such as a marathon run, can lead to a temporary immunosuppression, with impairment of both innate and acquired immune responses.[7] Several nutritional countermeasures to this immunosuppression have been tried without success.[8] Probiotic lactic acid bacteria can be defined as ''a live microbial food ingredient that is beneficial to health''.[9] In addition to the effects on non-immunologic gut defence these bacteria promote both innate and acquired immune responses, and their protective role in allergy development has also been recently suggested.[10,11]

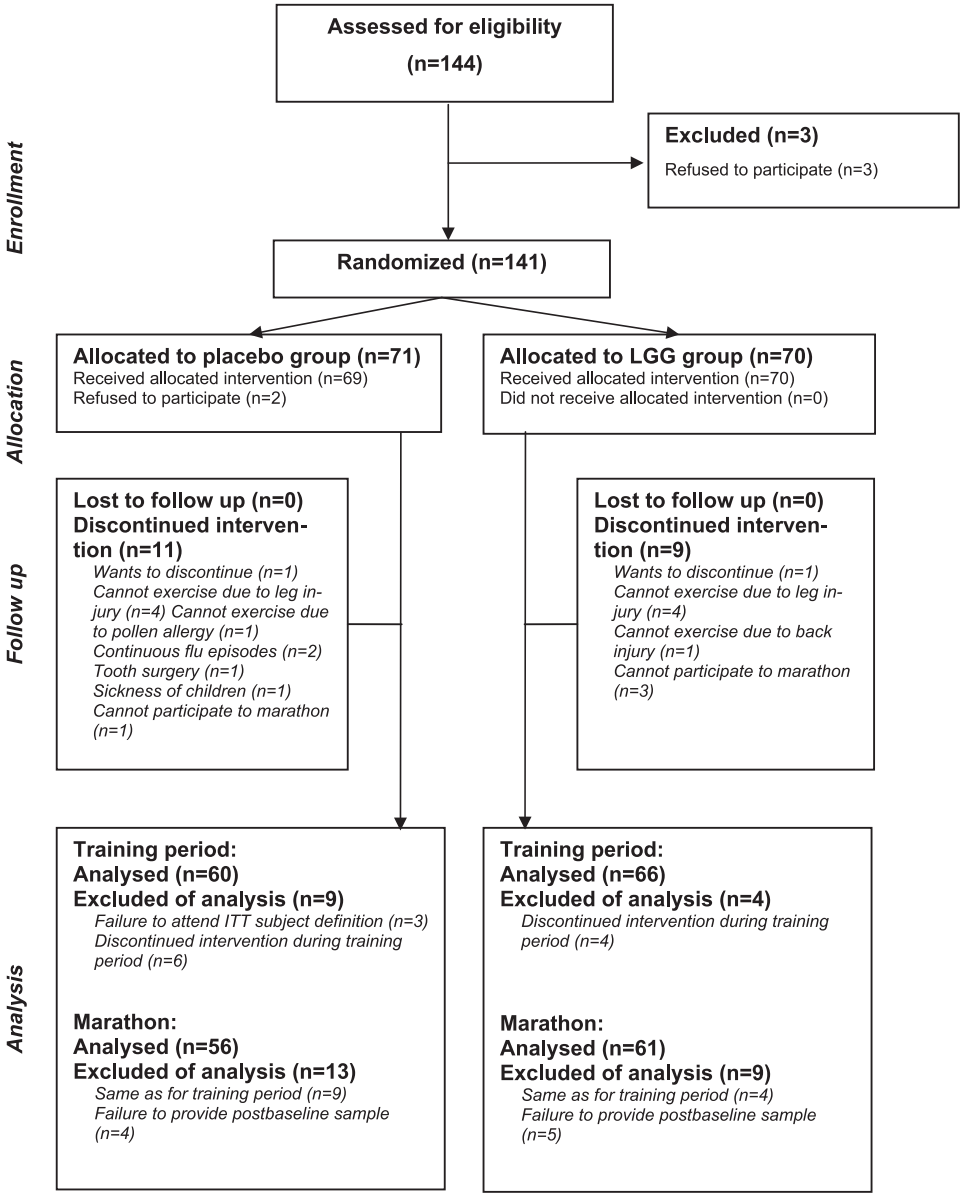

Figure 1 Flow diagram of subjects through each stage of the study.

We studied the prevalence of atopic sensitization and related clinical conditions in marathon runners and investigated the effects of probiotic supplementation during pollen season and during the marathon.

Methods

Participants

Marathon runners planning to attend the 2003 Helsinki City Marathon (HCM) were recruited through an invitation letter sent to the former HCM participants and a call on a national runner's magazine. Runners were included if their personal best marathon time for women was less than 3 h 40 min and for men less than 3 h 30 min. Exclusion criteria included use of antibiotics 2 months prior to the study, pregnancy, lactation, gastrointestinal diseases and medication for them and acute gastrointestinal disorders 2 months prior to the study. All provided informed consent and the study was approved by the Ethics Committee of Hospital District of Helsinki and Uusimaa.

Athletes answered to a structured questionnaire that included specific allergy and asthma questions. Athletes were considered to suffer from asthma, rhinitis, conjunctivitis, atopic dermatitis or food allergy, if the diagnosis had been made by a physician. Atopy was defined by specific IgE to any of the allergens tested (see below).

Intervention

The study was a randomized, double-blind, placebo-controlled trial, which took place between April and August 2003. After a 4-week run-in period, subjects were allocated according to computer-generated block randomization, to receive either *Lactobacillus rhamnosus* GG (LGG) (ATCC53103) or placebo containing milk-based fruit drink supplied by Valio Ltd., Helsinki, Finland. LGG drink contained LGG $3.0 \times 10E8$ cfu/ml. Subjects were asked to drink two 65 ml bottles of LGG or placebo drink per day. The

Table 1 Baseline characteristics of the 139 marathon runners.

	Placebo *n = 69*	*Lactobacillus* GG *n = 70*	Total *n = 139*
Demographic			
Age (years)	40 (10)	39 (9)	39 (9)
Sex (female:male)	8:61	8:62	16:123
Running distance last month (km)	42 (24)	47 (38)	44 (32)
Training experience (years)	7 (7)	7 (6)	7 (6)
Marathon personal best time (min)	190 (21)	188 (19)	189 (20)
Total marathons completed, *n*	11 (14)	12 (13)	12 (14)
Diagnosis			
Asthma: *n* (%)	3 (4.3)	3 (4.3)	6 (4.3)
Allergic rhinitis: *n* (%)	7 (10.1)	17 (24.3)	24 (17.3)
Allergic conjunctivitis: *n* (%)	1 (1.4)	3 (4.3)	4 (2.9)
Food allergy: *n* (%)	5 (7.2)	2 (2.9)	7 (5.0)
Atopic eczema: *n* (%)	4 (5.8)	2 (2.9)	6 (4.3)
Any allergy: *n* (%)	14 (20.3)	23 (32.9)	37 (26.6)
Medication			
Inhaled β_2-agonists: *n* (%)	1 (1.4)	3 (4.3)	4 (2.9)
Inhaled corticosteroids: *n* (%)	2 (2.9)	2 (2.9)	4 (2.9)
Anti-histamines: *n* (%)	7 (10.1)	15 (21.4)	22 (15.8)
Nasal corticosteroids: *n* (%)	4 (5.8)	1 (1.4)	5 (3.6)
Allergen specific IgE			
Positive Phadiatop®: *n*/total	15/55	20/57	35/112
Specific IgE to:			
Betula verrucosa: n (%)	10 (18.2)	14 (24.6)	24 (21.4)
Phleum pratensis: n (%)	6 (10.9)	9 (15.8)	15 (13.4)
Dog: *n* (%)	8 (14.5)	7 (12.3)	15 (13.4)
Cat: *n* (%)	7 (12.7)	6 (10.5)	13 (11.6)
Artemisia vulgaris: n (%)	5 (9.1)	5 (8.8)	10 (8.9)
Dermatophagoides pteronyssinus: *n* (%)	3 (5.5)	2 (3.5)	5 (4.5)
Horse: *n* (%)	3 (5.5)	2 (3.5)	5 (4.5)
Cladosporium herbarum: *n* (%)	2 (3.6)	1 (1.2)	3 (2.7)

Data are presented as mean (SD) unless otherwise indicated. No significant differences between groups were found.

subject was given a possibility to use LGG ($5.0 \times 10E9$ cfu/capsule) or placebo capsules (two per day) in specific occasions, for example during trips abroad. The needed amount of capsules were asked and given by the study coordinator. Twenty-seven subjects in the LGG group (3–49 days) and 28 subjects in the placebo group (3–36 days) used the capsules. The intervention continued for 3 months until the 2003 HCM. Compliance with the intervention was assessed by questionnaire. During the intervention, athletes were instructed to restrain intake of food containing probiotics. The 2003 HCM was held on the 2nd of August at sea level.

Outcome measurements

Blood samples were collected at (1) baseline (Train 1) 3 months before the marathon, (2) 1 week prior to the marathon (Train 2), (3) just before the marathon (Run 1), and (4) after completing the marathon (Run 2). Blood samples at Train 1 and Train 2 were collected after an overnight fasting, and Run 1 and Run 2 collected in the Olympic Stadium and immediately transported to the laboratory. Eosinophil cationic protein (ECP), serum total IgE levels, and Phadiatop® test were determined by Pharmacia CAP system (Pharmacia Diagnostics, Uppsala, Sweden) according to manufacturers instructions. When Phadiatop® was positive, quantitative IgE antibodies against *Phleum pratensis*, *Betula verrucosa*, *Artemisia vulgaris*, *Cladosporium herbarum*, *Dermatophagoides pteronyssinus*, and horse, cat and dog dander were determined. Measuring range was 2–200 μg/L for serum ECP, and 0.35–100 kU_A/l for serum Phadiatop® and specific IgE.

Statistical analysis

All analyses were conducted using the "intention-to-treat" approach, including all randomized athletes who took at least one dose of the study preparation and who had at least one postbaseline efficacy variable measurement. The ITT analyses were used for all efficacy measures. Missing data for those who withdrew from the study before its completion or from whom data was missing for reasons unrelated to treatment were estimated using an expectation-maximization algorithm. Overall, data was imputed in 5.9% (70/1182) of the samples (60/644 for the training period and 10/538 for the marathon). Because of their skewed distributions, all comparisons were made after logarithmic transformation. To permit analysis in the log scale, a constant (0.1) was added to each value of the percent eosinophil count to eliminate 0 values. Baseline characteristics were compared using Fisher exact test for categorical variables or Student's test for numeric variables; changes within groups were compared using paired *t*-test and differences between placebo and LGG groups were compared by analysis of covariance (ANCOVA) with baseline value (Train 1 or Run 1) as covariate. Values of $p < 0.05$ were regarded as significant. No adjustment was made for multiple testing, but this information can be obtained by multiplying the actual *p* value by the number of comparisons made.

Table 2 Changes of blood eosinophils, ECP, total IgE and Phadiotop® before (Train 1) and after (Train 2) the 3 month training period for athletes supplemented with *Lactobacillus* GG or placebo.

	Placebo				*Lactobacillus* GG				Total				Placebo vs. *Lactobacillus* GG
	n	Train 1	Train 2	Change*	*n*	Train 1	Train 2	Change*	*n*	Train 1	Train 2	Change*	*p*-value†
B-Eos (%)	60	3.9 (2.4)	3.8 (2.3)	−0.1(−0.5,0.3)	66	3.6 (2.2)	3.7 (2.2)	0.1 (−0.3,0.5)	126	3.7 (2.3)	3.7 (2.2)	0.0 (−0.3,0.3)	0.59
ECP (mcg/L)	60	7.8 (4.9)	10.0 (6.5)	2.2 (0.6,3.7) $p = 0.0050$	66	8.0 (6.4)	12.0 (8.3)	4.0 (2.3,5.8); $p < 0.001$	126	7.9 (5.7)	11.1 (7.5)	3.1 (2.0,4.3); $p < 0.001$	0.15
Total IgE (kUA/L)	15	220 (152)	243 (181)	24 (−3,51)	20	168 (216)	198 (255)	30 (9,50); $p = 0.015$	35	190 (190)	217 (225)	2 (0,4); $p < 0.001$	0.26
Phadiatop® (kUA/L)	15	17 (26)	18 (23)	0 (−2,3)	20	11 (13)	14 (16)	3 (1,5); $p = 0.001$	35	14 (20)	16 (20)	27 (12,43); $p = 0.0050$	0.13

Values are shown as mean (SD) or mean differences (IC 95%) were appropriate.
ECP: eosinophil cationic protein; B-Eos: blood eosinophils.
*Paired samples *t*-test.
†Analysis of covariance, baseline value as covariate.

Results

Of the 144 volunteers recruited to the study, 141 fulfilled the entry criteria and were randomized. Two subjects withdrew before starting the intervention and were excluded from the analysis (Fig. 1).

Prevalence of asthma and allergy

Physician-diagnosed asthma was reported by 6 (4.3%) and allergic rhinitis by 24 (17.3%) athletes (Table 1).

Five of the six athletes with asthma, and 13 of the 24 athletes (62%) with rhinitis were atopic according to the Phadiatop® result. Twenty-eight athletes (20%) reported current use of asthma or allergy medication. Eight athletes, however, did not provide medical diagnosis justifying the medication use.

Phadiatop® was positive in 35 of the 112 athletes tested (31%); 21.4% were sensitized to birch pollen, 13.4% to timothy pollen, 13.4% to dog and 11.6% to cat. Nineteen of the sensitized runners (54%) did not, however, report any symptoms. Phadiatop®-positive athletes (defined here as atopics) had higher serum total IgE compared with Phadiatop®-negative athletes (geometric mean, 112 vs. 32 kU_A/L; $p<0.001$), but blood eosinophils numbers or serum ECP values were not different. When athletes were categorized by their running performance, no differences in atopy prevalence were observed.

Effect of LGG during 3-month training

Training period occurred during the pollen season. In 2003, the highest pollen counts were observed between May and July.[12] In all runners, blood eosinophil numbers did not change, but serum ECP increased. No differences in changes of blood eosinophil numbers, serum ECP, total IgE and Phadiatop® were observed between the LGG or placebo groups (Table 2, Fig. 2) or between the atopic (Phadiatop®-positive) or non-atopic runners during the training period (Table 3). In the 35 atopic runners, total serum IgE and Phadiatop® increased but blood eosinophil numbers or serum ECP did not change.

Effect of LGG during 1 week prior to and during marathon run

In all runners, the number of blood eosinophils and serum ECP levels decreased significantly during the week preceding the run. In atopic runners, total IgE increased significantly. No differences in changes were observed between the LGG or placebo groups during 1 week before the run (Table 4).

In all runners, the marathon run induced a significant eosinopenia, but serum ECP did not change. In atopic runners, similar eosinopenia was observed as in the whole group. The marathon run did not affect total IgE of the atopic runners. The responses to the marathon run were similar in the LGG and placebo groups (Table 5, Fig. 2).

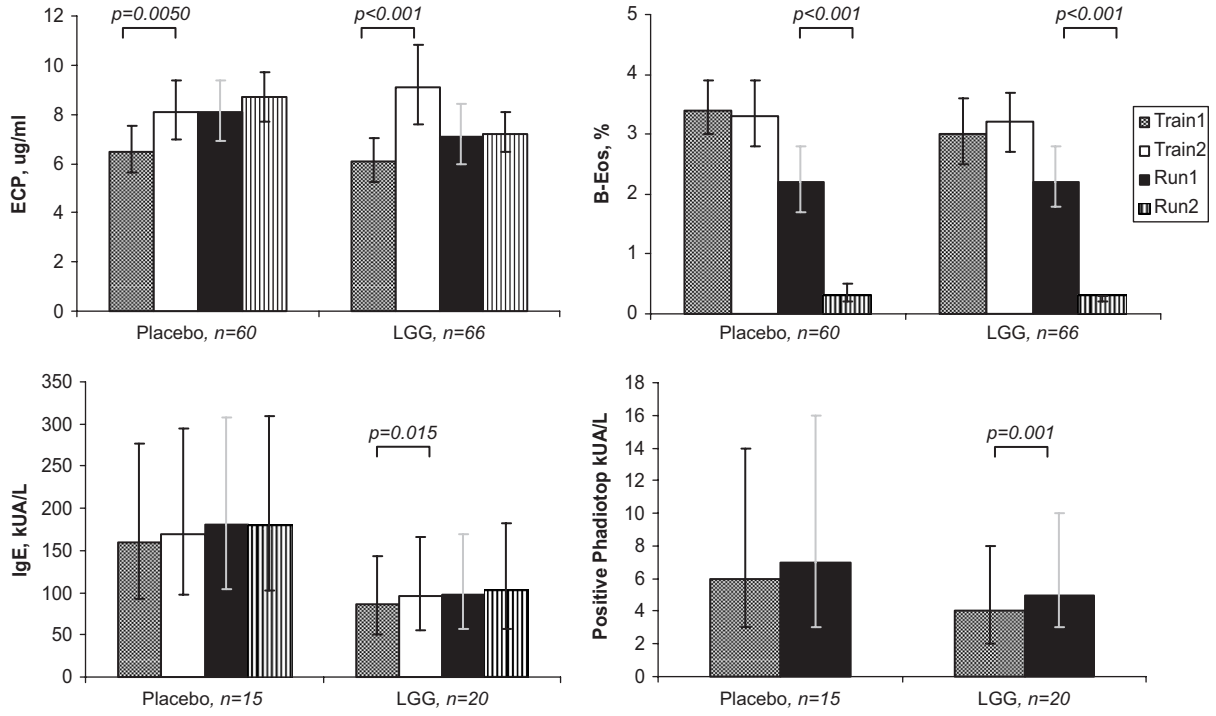

Figure 2 Eosinophil cationic protein (ECP, mcg/L), blood eosinophils (B-Eos, %), total IgE (kUA/L) and Phadiotop® (KUA/L) before and after the training period (Train1 and Train2), and before and after the marathon run (Run1 and Run2). Results are expressed as geometric means (95% CI).

Table 3 Changes of blood eosinophils, ECP and total IgE for atopic (positive Phadiatop) vs. non atopic athletes before (Train 1) and after (Train 2) the 3 month training period.

	Atopic athletes				Non-atopic athletes				
	n	Train 1	Train 2	Change*	*n*	Train 1	Train 2	Change*	*p*-value†
B-Eos (%)	35	3.9 (2.5)	4.0 (2.3)	0.2 (−0.4,0.7)	77	3.7 (2.4)	3.6 (2.1)	−0.1 (−0.5,0.3)	0.57
ECP (mcg/L)	35	8.6 (6.5)	10.7 (8.7)	2.0 (−0.3,4.3)	77	7.3 (5.6)	10.8 (7.1)	3.5 (2.0,5.0); $p<0.001$	0.16
Total IgE (kUA/L)	35	190 (32)	217 (225)	27 (12,43); $p = 0.0050$	77	53 (53)	53 (49)	0 (−3,4)	0.15

Values are shown as mean (SD) or mean differences (IC 95%) were appropriate.
ECP: eosinophil cationic protein; B-Eos: blood eosinophils.
*Paired samples *t*-test.
†Analysis of covariance, baseline value as covariate.

Table 4 Changes of blood eosinophils, serum ECP, and total IgE a week before (Train 2) and just before (Run 1) the Helsinki City Marathon in athletes supplemented with *Lactobacillus* GG or placebo.

	Placebo				*Lactobacillus* GG				Total				Placebo vs. *Lactobacillus* GG
	n	Train 2	Run 1	Change*	*n*	Train 2	Run 1	Change*	*n*	Train 2	Run 1	Change*	*p*-value†
B-Eos (%)	56	3.8 (2.3)	2.9 (2.0)	−1.0 (−1.3, −0.7); $p<0.001$	61	3.6 (2.2)	2.9 (2.3)	−0.7 (−1.2, −0.3); $p<0.001$	117	3.7 (2.3)	2.9 (2.1)	−0.9 (−1.1, −0.6); $p<0.001$	0.50
ECP (mcg/L)	56	10.0 (6.6)	9.6 (5.9)	−0.4 (−2.1,1.3)	61	12.0 (8.4)	8.9 (6.4)	−3.1 (−5.4, −0.9); $p = 0.010$	117	11.1 (7.6)	9.2 (6.1)	−1.8 (−3.3,−0.4); $p = 0.043$	0.069
Total IgE (kUA/L)	15	243 (181)	260 (201)	16 (3,29); $p = 0.017$	20	198 (255)	203 (269)	5 (−6,16)	35	218 (225)	227 (240)	10 (2,18); $p = 0.0030$	0.10

Values are shown as mean (SD) or mean differences (IC 95%) were appropriate.ECP: eosinophil cationic protein; B-Eos: blood eosinophils.
*Paired samples *t*-test.
†Analysis of covariance, Train 2 value as covariate.

Table 5 Changes of blood eosinophils, serum ECP, and total IgE before (Run 1) and after (Run 2) the Helsinki City Marathon in athletes supplemented with *Lactobacillus* GG or placebo.

	Placebo				*Lactobacillus* GG				Total				Placebo vs. *Lactobacillus* GG
	n	Run 1	Run 2	Change*	*n*	Run 1	Run 2	Change*	*n*	Run 1	Run 2	Change*	*p*-value†
B-Eos (%)	56	2.9 (2.0)	1.0 (2.5)	−1.9 (−2.7, −1.1); $p<0.001$	61	2.9 (2.3)	0.4 (0.6)	−2.5 (−3.0, −1.9); $p<0.001$	117	2.9 (2.1)	0.7 (1.8)	−2.2 (−2.7, −1.7); $p<0.001$	0.35
ECP (mcg/L)	56	9.6 (5.9)	9.8 (6.1)	0.2 (−1.2,1.6)	61	8.9 (6.4)	8.0 (3.8)	−0.9 (−2.3,0.5)	117	9.2 (6.1)	8.9 (5.1)	−0.4 (−1.4,0.6); $p=0.38$	0.062
Total IgE (kUA/L)	15	260 (201)	258 (193)	−2 (−9,6)	20	203 (269)	242 (349)	39 (−34,111)	35	227 (240)	249 (289)	21 (−19,62); $p=0.49$	0.29

Values are shown as mean (SD) or mean differences (IC 95%) were appropriate.
ECP: eosinophil cationic protein; B-Eos: blood eosinophils.
*Paired samples *t*-test.
†Analysis of covariance, pre-marathon value as covariate.

Discussion

Asthma is diagnosed more frequently in elite athletes than in the general population.[4,13–16] Atopy and type of sports appear to be the two major risk factors; atopic long distance runners had a 42-fold increased risk of asthma compared to non-atopic non-athletes.[17] We observed a 4.3% prevalence of physician-diagnosed asthma in non-elite athletes. This is close to asthma prevalence in the Finnish general population (between 5.5% and 6.6%).[18,19] Of the runners, 88% were male, and asthma prevalence of 5.1% of Finnish males has been reported.[18] In a sample of 71 Finnish long distance runners, 7.0% had asthma.[17] Of 108 endurance athletes supported by the Finnish National Olympic Committee, and of 103 athletes from Finnish national teams, 22.2%[20] and 16%, respectively, had asthma.[13] The increased figures of asthma prevalence in high level competitive athletes have been attributed to an irritant-induced airway inflammation and bronchial hyperreactivity,[2,6,21] which have attenuated after discontinuing training and competition.[2] The relatively low prevalence of asthma in our athletes may reflect a "healthy runner effect". Our subjects were non-elite runners, and individuals having symptoms suggestive of asthma do not easily continue long-distance running; they may change their hobby to other types of sports. The prevalence of allergic rhinitis in athletes, assessed by the questionnaire has varied from 16.8% to 41%[4,14,15,22–26] while the prevalence of allergic rhinitis in Finnish population ranges from 26% to 36%.[18] The prevalence of allergic rhinitis (17.3%) in the present study is close to the figures of the general population. In contrast, the prevalence of allergic conjunctivitis (2.9%) was low, although similar to another study (3.6%) of athletes.[26] Athletes conjunctivas are not exposed to such an increased amount of airborne allergens than airway mucosa due to a high ventilation rate. The overall prevalence of atopy (31%) was similar to the figure previously reported in Finnish long-distance runners (33.8%).[17] Sensitization rates to birch, timothy, mugwort, *D. pteronyssinus* and *C. herbarum* were almost coincident with those reported for Helsinki adult population,[27] not suggesting an increased risk of sensitization in non-elite runners. In Finland, between 1994 and 2000, the use of asthma medication increased 42% to a figure near 5% of the general population.[28] However, the use of asthma medication has been four times more frequent (22%) in Finnish elite long-distance runners.[17] In the present study, the frequency of reported asthma medication (2.9%) was close to figures in the general population.

During the training period, the main pollen season in Finland, we observed: (1) an increase of serum ECP in all athletes, and of total IgE and Phadiatop® in the atopics, and (2) LGG intake had no effect on this variation neither in atopic nor in non-atopic athletes.

Higher levels of ECP during the birch pollen season in healthy subjects have been reported but remain unexplained.[29] Exposure to pollen proteases in vitro causes concentration-dependent detachment of airway epithelial cells.[30] Disruption of the epithelial barrier by proteases in pollens might thus occur in some subjects when training outdoor, with high ventilation rates during the pollen season, contributing to a low-grade systemic inflammation.

Although probiotic supplementation may have a role in prevention and management of allergic eczema,[10,11,31] only

a few trials have addressed its effects on IgE responses in established allergic sensitization. In animal models, the administration of *Lactobacillus plantarum* L-137 to mice fed with a casein diet suppressed the elevation of casein-specific IgE levels by an anti-casein IgG1mechanism.[32] In a food allergy model, the intraperitoneal injection of *Lactobacillus casei* strain Shirota to OVA-TCR-Tg mice-induced suppression of IgE, IgG1 and systemic allergic reactions.[33] *L. casei* induced IFN-gamma, but inhibited IL-4 and IL-5 secretion, and markedly suppressed total and antigen-specific IgE secretion by OVA-stimulated splenocytes obtained from OVA-primed BALB/c mice.[34] Probiotics may regulate IL-4 and IL-5 expression[35] and affect eosinophil development and activation. In human studies, a trend to decrease blood eosinophils was noticed after *L. acidophilus* supplementation to asthma patients.[36,37] Our findings do not support probiotic supplementation during pollen season in reducing the seasonal increase of IgE response in runners, but do not rule out possible beneficial effects of probiotics in other type of sports, e.g. in cold air sports or swimming.

Pre-competitive stress and stop of heavy training during the week preceding the marathon could play a major role in the decrease of ECP and blood eosinophils. Acute exercise has increased numbers of neutrophils and monocytes and decreased lymphocytes in cell counts.[7] Changes in eosinophils after marathon or strenuous exercise have been reported with conflicting results. Nieman et al.[38] reported eosinopenia in 10 marathoners after a 3 h run in a laboratory setting; the eosinopenia was maintained for at least 21 h. In another study, cell counts and ECP from seven athletes swimming 5-km were unaffected.[39] Increase in serum cortisol levels seen after a marathon may have a role in the observed marathon-induced eosinopenia.[7] LGG did not prevent the eosinopenia.

We conclude that in non-elite long-distance runners, prevalence of allergic diseases is similar to the general population. LGG did not affect the allergic markers during the training period or the marathon race.

Acknowledgments

We thank Salme Järvenpää for statistical advice and comments during manuscript preparation. We also thank all athletes for their participation. This study was supported by Valio Ltd., Helsinki, Finland.

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