

The Effect of Probiotics on Respiratory Infections and Gastrointestinal Symptoms During Training in Marathon Runners

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Heavy exercise is associated with an increased risk of upper respiratory tract infections. Strenuous exercise also causes gastrointestinal (GI) symptoms. In previous studies probiotics have reduced respiratory tract infections and GI symptoms in general populations including children, adults, and the elderly. These questions have not been studied in athletes before. The purpose of this study was to investigate the effect of probiotics on the number of healthy days, respiratory infections, and GI-symptom episodes in marathon runners in the summer. Marathon runners ($N = 141$) were recruited for a randomized, double-blind intervention study during which they received *Lactobacillus rhamnosus* GG (LGG) or placebo for a 3-mo training period. At the end of the training period the subjects took part in a marathon race, after which they were followed up for 2 wk. The mean number of healthy days was 79.0 in the LGG group and 73.4 in the placebo group ($P = 0.82$). There were no differences in the number of respiratory infections or GI-symptom episodes. The duration of GI-symptom episodes in the LGG group was 2.9 vs. 4.3 d in the placebo group during the training period ($P = 0.35$) and 1.0 vs. 2.3 d, respectively, during the 2 wk after the marathon ($P = 0.046$). LGG had no effect on the incidence of respiratory infections or GI-symptom episodes in marathon runners, but it seemed to shorten the duration of GI-symptom episodes.

Key Words: *Lactobacillus rhamnosus* GG, athletes, exercise

Epidemiological studies suggest that strenuous acute or chronic exercise is associated with an increased risk of upper respiratory tract infections (15, 17, 20, 23, 26, 27). The risk appears to be especially high during the 2-wk period after a marathon-type race event (19). It is also known that during training periods with heavy exercise the risk of respiratory tract infection is increased (4, 6, 36), but moderate training seems to protect from respiratory tract infections (13, 16). Continuous heavy exercise suppresses certain immunological parameters such as neutrophil

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function, serum and mucosal immunoglobulin levels, macrophage antigen presentation, macrophage and lymphocyte cytokine production, lymphocyte proliferation in response to mitogens, and possibly also natural killer-cell cytotoxic activity (14, 44). This has led to a theory that an “open window” of impaired immunity exists in which viruses and bacteria are more likely to take over and increase the risk of subclinical and clinical infection. It is known that acute strenuous exercise causes many gastrointestinal symptoms such as diarrhea and heartburn (28, 33). Relatively little is known, however, about gastrointestinal symptoms during training periods. Upper respiratory tract infections and gastrointestinal symptoms can seriously impair an athlete’s ability to train, and it is therefore extremely important for athletes to stay healthy during training periods.

Probiotics are defined as living micro-organisms that have beneficial effects for human health. Documented health effects in human intervention trials include treatment of acute diarrhea in children, reduced risk of antibiotic-associated symptoms, relief of milk allergy/atopic dermatitis in infants, reduction in the risk of atopic diseases and respiratory infections, relief of irritable bowel syndrome and rheumatoid arthritis symptoms, suppression of *Helicobacter pylori*, and modulation of the immune response (reviewed in 31). There is increasing interest in the effect of probiotics on the incidence of respiratory tract infections and the common cold. *Lactobacillus rhamnosus* GG (LGG) has reduced respiratory tract infections and the need for antibiotic treatments in children (8). In children *Lactobacillus casei* (DN-114001) had no effect on the duration or incidence of respiratory infection or gastrointestinal symptoms (2). In infants *Lactobacillus reuteri* (ATCC 55730) or *Bifidobacterium lactis* Bb-12 did not have an effect on incidence and duration of respiratory illnesses but, compared with placebo, the probiotic groups had fewer and shorter episodes of diarrhea (42). The *L. reuteri* group had also a decrease in the number of days, with fewer clinic visits, childcare absences, and antibiotic prescriptions (42). In adults a probiotic drink (Tribion harmonis with *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, and *Bifidobacterium bifidum* MF 20/5 bacteria) has been shown to reduce the incidence (43), duration (40, 41), and severity of symptoms (40, 41) during common cold infections. *L. reuteri* (ATCC 55730) has reduced the absence from work in adults (37). In the elderly *L. casei* DN-114001 has reduced the duration of infections during wintertime (38). A probiotic drink containing LGG has also lowered the nasal colonization of potentially harmful bacteria (5). It has been shown that LGG is effective in the treatment of acute diarrhea in children (35, 39) and in reducing the risk of symptoms associated with antibiotic therapy in children and adults (3, 18, 32). Probiotics have also reduced the amount of gastrointestinal symptoms expressed as a total symptom score for abdominal pain, distension, flatulence, and borborygmi in patients with irritable bowel syndrome (12).

Probiotic treatment might therefore help athletes reduce the incidence of upper respiratory tract infections and gastrointestinal symptoms. As far as we know, only 2 probiotic intervention trials have been conducted in athletes. *L. casei* DN-114001 fermented milk prevented a decrease in NK cells after an exercise stress test (29). In another trial *Lactobacillus acidophilus* (LAFTI L10) significantly increased the secretion of IFN- γ from T-cells in fatigued athletes and increased the concentration of IFN- γ in the saliva of healthy athletes (1). Neither of the trials assessed the effect of the probiotic on infections.

The aim of this clinical trial was to study the effect of probiotic LGG on the number of healthy days, incidence of upper respiratory tract infections, and gastrointestinal symptoms in marathon runners during a training period and during the 2 wk after a marathon race.

Subjects and Methods

Subjects

The subjects were recruited from among those planning to participate in the Helsinki City Marathon in August 2003 through an advertisement in a national runners' magazine and using a recruitment letter sent to previous Helsinki City Marathon participants. Subjects were eligible for the study if they were healthy and not participating in any other study and their personal-best marathon time was less than 3 h 45 min for women and less than 3 h 30 min for men. Exclusion criteria included use of antibiotics for 2 months or less before the study, acute gastrointestinal disorders 2 months before the study, gastrointestinal diseases and related medication, pregnancy, and lactation. The subjects gave their informed consent before entering the study. The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. A total of 144 subjects were recruited for the study, of whom 141 (16 women, 125 men) were randomized according to sex and personal-best marathon time (Table 1).

Study Design and Intervention

The study was a randomized, double-blind, placebo-controlled, parallel-group intervention study. Before the intervention period there was a 4-wk run-in period in April, after which the subjects were randomized, stratified according to the personal-best marathon time (<median marathon time, ≥median marathon time, no previous marathons), to receive either *Lactobacillus rhamnosus* GG (LGG) or placebo. The subjects received LGG or placebo for 3 months (training period) from the beginning of May until the day of the Helsinki City Marathon (August 2). During the marathon the subjects were permitted to ingest fluids and food freely. After the marathon there was a 4-wk follow-up period until the end of August. The subjects were instructed to refrain from eating food containing probiotics throughout the entire study.

Products

LGG was given in the form of a milk-based fruit drink containing LGG (ATCC 53103) bacteria 3.0×10^8 colony-forming units (cfu)/mL (Valio Research Center, Helsinki, Finland). The placebo drink was similar but without LGG bacteria. The subjects were asked to drink two 65-mL bottles of LGG or placebo drink per day for 3 months. The two LGG bottles provided a total of 4×10^{10} bacteria. The subjects were allowed to take the study products as capsules if they wished, for example, when traveling abroad. The LGG capsules contained 5.0×10^9 cfu/capsule, and placebo capsules were otherwise similar but without LGG bacteria. The subjects were asked to take 2 capsules per day—a daily total of 1×10^{10} LGG bacteria. The

Table 1 Baseline Characteristics of the Subjects

Characteristic	Placebo, <i>n</i> = 71	LGG, <i>n</i> = 70
Age	40 (23–69)	40 (22–58)
Female	8 (11)	8 (11)
Male	63 (89)	62 (89)
Weight, kg	69 (51–88)	71 (49–98)
Height, cm	178 (158–190)	177 (160–200)
Body-mass index, kg/m ²	22 (19–26)	22 (18–26)
Subjects with respiratory tract infections 6 months before the study	26 (37)	33 (47)
Subjects with gastrointestinal-symptom episodes 6 months before the study	16 (23)	16 (23)
Diseases		
heart disease	1	0
elevated blood pressure	2	2
cancer	1	0
lactose intolerance	5	2
atopic eczema	4	2
allergy	9	17
asthma	3	3
other chronic disease	3	5
Use of nutritional supplements	34	41
Use of sports supplements	15	16
Smokes occasionally	2	4
Exercise habits		
years of marathon training	7 (0–35)	8 (0–30)
marathons participated in	11 (0–60)	13 (0–71)
best marathon time, h:min	3:11 (2:23–3:40)	3:10 (2:35–3:42)

Values are expressed as number (%) of subjects or mean (range). At the baseline there were no statistically significant differences between the groups (Pearson chi-square or *t*-test).

number of capsules used was recorded. Twenty-seven subjects in the LGG group (mean 14 d, range 3–49 d) and 28 subjects in the placebo group (mean 9 d, range 3–36 d) used the capsules. The subjects reported no adverse effects on health associated with consumption of either LGG or the placebo drink.

Blood Samples, Symptom Diaries, and Exercise Diaries

Venous blood samples were taken from the antecubital vein at baseline, 1 wk before the marathon (after the 3-month training period), and on marathon day just before and after the race. The samples were taken into two 10-mL standard serum tubes and two 7-mL EDTA tubes. The blood samples obtained at baseline and 1 wk before the marathon were taken in a laboratory after an overnight fast. Samples before and after the marathon were taken at Helsinki's Olympic Stadium and sent immediately to the laboratory. Hematological parameters were determined using

an electronic counter (Coulter MAXM hematology analyzer, Beckman Coulter, Fullerton, CA). Throughout the study period from run-in to follow-up the subjects were asked to fill in a diary questionnaire with ready-made questions. Each day they scored their health status (healthy or sick) and recorded whether they had had any upper respiratory tract infection symptoms (fever, rhinitis, sore throat, cough, wheezing, earache), gastrointestinal symptoms (diarrhea, vomiting, stomachache), or any other symptoms or took medication during the day. The subjects also recorded their adherence to the intervention in the diary. They were also asked to keep an exercise diary in which they reported their running in kilometers and minutes and other exercise in minutes. Symptom diaries were received from all subjects, and exercise diaries, from 114 subjects.

Outcome Measures

The main outcome measures were the number of healthy days and the number of upper respiratory tract infections and gastrointestinal-symptom episodes. Subjects were considered to have had a respiratory tract infection if they suffered from any respiratory tract infection symptom for at least 2 d in a row and if there were at least 3 d until the next symptoms of respiratory tract infection symptoms appeared; otherwise they were considered to be suffering from the same respiratory tract infection. The criteria for gastrointestinal-symptom episode were a duration of at least 1 d and at least 3 d before the next gastrointestinal symptom appeared.

Statistical Analyses

All outcome analyses were performed by intention to treat, according to random allocation. For the dropouts, the number of healthy days, symptoms, respiratory tract infections, and gastrointestinal-symptom episodes were imputed by calculating according to the length of each subject's follow-up time. The results were expressed as mean, standard deviation, and range. The most important descriptive values were expressed with a 95% confidence interval (CI). A continuous statistical comparison between the groups was made using a *t*-test, analysis of covariance (ANCOVA), or Mann–Whitney test (with Monte Carlo *P*-value). Measures with a discrete distribution are expressed as counts (%) and analyzed using the chi-square or Fischer's exact test. 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. The α level was set at 0.05 for all tests. The statistical analyses were performed using SPSS version 13.0 software (SPSS, Inc., Chicago.).

Results

Adherence to the intervention was good. The self-reported mean consumption of LGG was 84/89 d and of placebo was 76/89 days ($P = 0.93$). Of 141 subjects, 119 successfully completed the study. Of the 22 subjects who dropped out of the study, 5 refused to continue and 17 could not take part in the marathon because of injury or illness. A flowchart for the participants is presented in Figure 1.

During the 6 months before entering the study, 47% of the subjects in the LGG group and 37% of the placebo group had had a respiratory tract infection (P

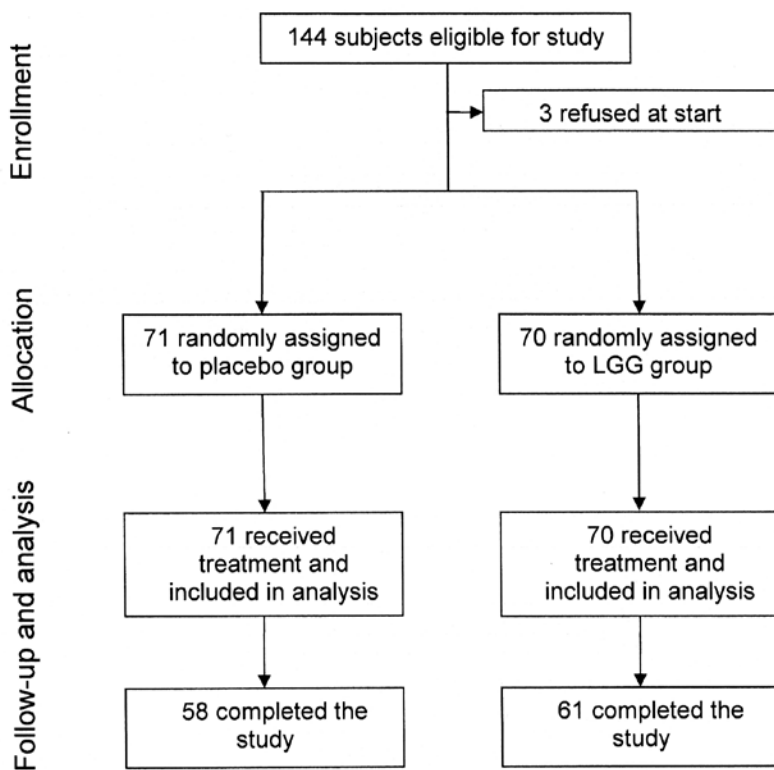


Figure 1 — Flowchart for the participants in the study.

= 0.41), and 23% in both study groups had experienced a gastrointestinal-symptom episode ($P = 0.79$).

During the 3-month training period the mean number of healthy days was 79.0 in the LGG group and 73.4 in the placebo group (Table 2), and there was no statistical difference between the groups ($P = 0.82$). Forty-six percent of the LGG group and 39% of the placebo group had a respiratory tract infection, and 27% and 32%, respectively, experienced a gastrointestinal-symptom episode during the training period. The mean number of respiratory tract infections was 0.7 in the LGG group and 0.5 in the placebo group ($P = 0.32$), and of gastrointestinal-symptom episodes, 0.4 and 0.6 ($P = 0.48$), respectively. The duration of the gastrointestinal-symptom episode was 33% shorter in the LGG group than in the placebo group (2.9 vs. 4.3 d, $P = 0.35$).

During the 2 wk after the marathon there were no differences between the groups in the number of respiratory tract infections or gastrointestinal-symptom episodes. During the same period, however, the duration of a gastrointestinal-symptom episode was 57% shorter in the LGG group than in the placebo group (1.0 vs. 2.3 d, $P = 0.046$).

Table 2 The Number of Healthy Days and Episodes of Upper Respiratory Tract Infection (URTI) and Gastrointestinal (GI) Symptoms During the 3-Month Training Period and 2 Wk After the Helsinki City Marathon

	Placebo	LGG	<i>P</i> -value ^a
During training period			
number of healthy days	73.4 (26.1)	79.0 (15.9)	0.82
number of sick days	3.9 (5.9)	5.3 (6.8)	0.13
subjects with URTI episodes (%)	26 (37)	32 (46)	0.52
number of URTI episodes ^b	0.5 (0.7)	0.7 (0.9)	0.32
duration of URTI episode (d)	6.3 (4.3)	7.9 (7.1)	0.69
subjects with GI-symptom episodes (%)	21 (30)	19 (27)	0.62
number of GI-symptom episodes ^c	0.6 (1.1)	0.4 (0.8)	0.48
duration of GI-symptom episode (d)	4.2 (5.1)	2.9 (3.2)	0.35
During 2 wk after marathon			
subjects with URTI episodes (%)	5 (7)	7 (10)	0.61
number of URTI episodes ^b	0.1 (0.3)	0.1 (0.3)	0.61
duration of URTI episode (d)	4.2 (2.2)	5.1 (2.9)	0.55
subjects with GI-symptom episodes (%)	4 (6)	4 (6)	0.94
number of GI-symptom episodes ^c	0.1 (0.3)	0.1 (0.3)	0.94
duration of GI-symptom episode (d)	2.3 (1.0)	1.0 (0.0)	0.05

^aMann–Whitney test (Monte Carlo *P*-value) or Pearson chi-square. ^bAt least 2 d with URTI symptoms and at least 3 d apart from another URTI episode. ^cAt least 1 d with GI symptoms and at least 3 d apart from another GI-symptom episode.

Values are expressed as number of subjects or mean (SD).

Hematological parameters were measured to assess the health status of the subjects, and they remained within normal range during the whole study. The changes of the hematological parameters during the study are reported in Tables 3A and 3B.

Subjects in the LGG group exercised (running and other exercises) more often than those in the placebo group during the training period (4.8 vs. 4.4 times weekly, *P* = 0.024). The number of running exercises per week was 4.3 in the LGG group and 4.0 in the placebo group (*P* = 0.25), and the weekly average distance covered was 54.7 km (range 18–114 km) in the LGG group and 53.0 km (range 22–88 km) in the placebo group (*P* = 0.96). Of the 119 subjects who ran in the marathon, 111 completed the distance (56 in the LGG group and 55 in the placebo group) and 8 had to pull out before the finish (5 in the LGG group and 3 in the placebo group). The mean time for the 2003 Helsinki City Marathon was 3 h 32 min (range 2 h 24 min to 4 h 35 min) for the LGG group and 3 h 30 min (range 2 h 52 min to 4 h 19 min) for the placebo group (no significant difference between the treatment groups).

Table 3A Hematological Parameters at Baseline and Change After the 3-Month Training Period

	Placebo		LGG		<i>P</i> ^a
	Baseline, mean (SD)	Change after 3 months, mean (95% CI)	Baseline, mean (SD)	Change after 3 months, mean (95% CI)	
Erythrocytes ($\times 10^{12}/L$)	4.7 (0.4)	-0.02 (-0.08 to 0.04)	4.7 (0.4)	-0.05 (-0.1 to 0.01)	0.52
Hemoglobin (g/L)	145 (9)	-2 (-4 to -0.7)	145 (11)	-3 (-4 to -1)	0.64
Hematocrit (%)	44 (3)	-0.3 (-0.3 to 0.9)	43 (4)	0.5 (-0.08 to 1)	0.79
MCV (fl)	93 (4)	1 (1 to 2)	92 (4)	2 (2 to 3)	0.015 ^b
MCH (pg)	31 (1)	-0.4 (-0.6 to -0.2)	31 (1)	-0.3 (-0.5 to -0.1)	0.52
MCHC (g/L)	334 (8)	-8 (-11 to -5)	334 (7)	-10 (-12 to -8)	0.20
Thrombocytes ($\times 10^9/L$)	226 (52)	-14 (-23 to -4)	241 (58)	-17 (-26 to -8)	0.51

^aANCOVA, baseline as covariable.

^bTreatment effect for mean cell volume (LGG-placebo) = 1.00 (95% CI: 0.28-1.74).

SD indicates standard deviation; CI, confidence interval; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

Table 3B Hematological Parameters Before the Marathon and Change After the Marathon

	Placebo		LGG		<i>P</i> ^a
	Before marathon, mean (SD)	Change after marathon, mean (95% CI)	Before marathon, mean (SD)	Change after marathon, mean (95% CI)	
Erythrocytes ($\times 10^{12}/L$)	4.7 (0.4)	0.09 (0.04 to 0.1)	4.7 (0.4)	0.01 (-0.04 to 0.06)	0.031 ^a
Hemoglobin (g/L)	145 (10)	1 (-0.3 to 3)	145 (10)	-0.3 (-2 to 1)	0.13
Hematocrit (%)	43 (3)	0.7 (0.2 to 1)	43 (3)	0.1 (-0.3 to 0.6)	0.056
MCV (fl)	92 (4)	-0.03 (-0.3 to 0.2)	92 (4)	0.08 (-0.2 to 0.4)	0.88
MCH (pg)	31 (2)	-0.1 (-0.3 to 0.03)	31 (1)	-0.2 (-0.3 to 0.05)	0.74
MCHC (g/L)	336 (6)	-2 (-4 to -1)	335 (4)	-0.1 (-2 to 0.5)	0.074
Thrombocytes ($\times 10^9/L$)	217 (45)	39 (32 to 46)	223 (49)	35 (27 to 43)	0.42

^aTreatment effect for erythrocytes (LGG-placebo) = 0.08 (95% CI: 0.01-0.15).

SD indicates standard deviation; CI, confidence interval; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

Discussion

The present clinical trial was the first study to examine the effects of probiotics on the incidence of respiratory tract infections and gastrointestinal-symptom episodes during a training period and after a marathon race in marathon runners. The effect of probiotic LGG was studied in a randomized, double-blind, placebo-controlled manner. The intervention lasted 3 months during a training season in the summertime, and compliance with the intervention was very good. Even though the subjects were not elite athletes, they were used to marathon-type physical stress, were exercising regularly, and intended to take part in the marathon. Presumably, therefore, they would have been more likely to suffer from infections during the training period and after the marathon (15, 17, 19, 20, 26).

The respiratory tract infections and gastrointestinal symptoms experienced were monitored carefully by means of a daily symptom diary, a method used in a previous study in our group by Hatakka et al. (8). There is no consensus on the criteria for the respiratory tract infection. In this study subjects were considered to have had a respiratory tract infection if they had suffered from any symptom of respiratory tract infection for at least 2 d in a row and if there were at least 3 d until the next symptoms of respiratory tract infection appeared; otherwise they were considered to be suffering from the same respiratory tract infection. It is reported that intensive exercise increases the risk of upper respiratory tract infections and that the risk is especially high 2 wk after a competitive race (15, 19). The number of subjects experiencing an upper respiratory tract infection during the training period was higher in this study than in previous studies (43% vs. 27%) (22). This might be because of the longer follow-up period in the present study. During the 2 wk after the marathon race the number of subjects with a respiratory tract infection was lower in this study than in earlier studies (10% vs. 17% and 26%) (21, 22). The average number of respiratory tract infections during the 3-month training period was 0.6, and the corresponding figure for the 2-wk period after the marathon was 0.1. This gives the same average number of respiratory tract infections as in the previous study, in which the number was 1.2 (9). There were no differences in the number of upper respiratory tract infections between the intervention groups, but the number of healthy days during the intervention was slightly higher in the subjects receiving LGG. Previous probiotic intervention studies aiming at reducing the number of respiratory tract infections have been carried out in wintertime (8, 38, 40, 41, 42, 43) or in high-risk groups (2, 8, 38, 42). The fact that the adult athletes in our study were healthy and the lack of seasonality of colds and flu in that the study was performed during the summer might have counteracted any small beneficial effects the probiotics might have had on the variables measured.

The effect of probiotics on gastrointestinal symptoms in athletes has not been studied before. LGG shortened the duration of gastrointestinal-symptom episodes by 33% during the training period and by 57% during the 2 wk after the marathon as compared with placebo. This supports previous observations that probiotics can reduce gastrointestinal symptoms in risk groups (3, 12, 42). Athletes, especially long-distance runners, are known to suffer from gastrointestinal disturbances (30, 33), and probiotic treatment could thus help diminish their gastrointestinal problems. It is known that long-distance running can affect the integrity of the gastric and intestinal mucosa and increase their permeability (24, 34). LGG has had beneficial

effects on mucosal permeability in animal studies (10, 11, 25) and in 1 clinical trial (7). Because markers of intestinal permeability such as urinary excretion of orally administered sugars were not measured, no conclusions can be made as to whether the integrity of the mucosa and permeability would explain the effects seen in reducing gastrointestinal symptoms.

It is concluded that *L. rhamnosus* GG had no effect on the incidence of upper respiratory tract infections or gastrointestinal-symptom episodes in healthy marathon runners, but LGG seemed to shorten the duration of gastrointestinal-symptom episodes. The effect of probiotics on upper respiratory tract infections in athletes should be studied during the winter. In addition, the effect of probiotics on the integrity of the intestinal mucosa in endurance athletes should be further studied.

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