Randomized control trials

Probiotic supplementation for respiratory and gastrointestinal illness symptoms in healthy physically active individuals☆

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1. Introduction

Upper respiratory tract and gastrointestinal illnesses are associated with substantial economic, productivity and personal costs. Upper respiratory tract illnesses, referred to as the common cold, are the most prevalent infectious condition in developed countries and the most common new presentation to general practitioners.1 In general, most adults contract two to three colds annually while the elderly and the young typically experience four to six colds a year.2 Consistent with such prevalence, respiratory illnesses are estimated to cost $AUD7 billion annually in Australia through absenteeism.3 According to Australia’s most recent notifiable diseases report, gastrointestinal diseases are the third most prevalent notifiable disease.4 Reducing respiratory and gastrointestinal illnesses would have clinical benefits to both individuals and the broader community.

Probiotic supplementation has been reported to reduce the incidence, severity and duration of respiratory and gastrointestinal illness.5 It is, however, well established that the beneficial effects of probiotic supplements are both strain- and dose-specific.6 Given

Keywords: Healthy adults Respiratory illness Gastrointestinal illness Probiotics

Bifidobacterium animalis Subsp. lactis BL-04 Lactobacillus acidophilus NCFM

Bifidobacterium animalis Subsp. lactis BI-07

Abbreviations: URTI, upper respiratory tract illness; GI, gastrointestinal; BMI, body mass index; CFU, colony forming units.

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the diverse composition of the GI microbiota there is interest in the use of multi-strain probiotic supplements over traditional single-strain probiotic supplements. The use of a multi-strain probiotic reduced antibiotic associated diarrhoea more than the use of a single strain probiotic supplement. The mutualistic relationship between probiotic strains may confer additive beneficial health effects. Such an effect has been demonstrated with regard to cold and influenza-like symptoms in healthy children aged three to five, in which the combination of NCFM & Bi-07 compared to placebo significantly reduced fever, coughing incidence and rhinorrhea to a greater extent that NCFM alone.

Evidence for the efficacy of probiotics for respiratory illness has been shown in various population sub-groups, including the elderly, the young, healthy sedentary and highly trained athletes. No research on whether probiotic supplementation is of clinical benefit for respiratory illness in healthy, physically active adult males and females has yet been conducted. Individuals who undertake frequent moderate exercise are often more health conscious than their sedentary counterparts and have the lowest rates of respiratory illness in the population. Furthermore, they consume a range of functional foods, inclusive of probiotics. This deliberate use of functional foods makes this cohort a primary target group for the functional food market. Determining whether probiotics reduce susceptibility to respiratory illnesses in this health-conscious population will inform the development of evidence-based guidelines for supplementation.

The aim of this study was to examine the effect of daily supplementation with a single strain (Bifidobacterium lactis subsp lactis BI-04) probiotic and double strain (Lactobacillus acidophilus NCFM and Bifidobacterium animalis subsp. lactis Bi-07) on respiratory and gastrointestinal illness in healthy active individuals. The choice of the probiotics was made on the basis of previous data showing effects on immune-related outcomes in adults and in children.

2. Materials and methods

2.1. Design of the study

A randomised double blind placebo-controlled parallel trial was conducted over 164 d to examine the effect of probiotic supplementation on episodes of respiratory and gastrointestinal illness, cold medication usage and doctor visits. The first phase consisted of a 14 d wash out period in which participants ceased consumption of probiotic/prebiotic supplements and fortified foods to allow previously ingested probiotics to wash out of the system. Participants were also provided detailed instructions on use of the internet-based physical activity and illness questionnaire had their height and body mass recorded, and provided with their supplement following group allocation. Participants then completed a 150 d supplementation phase in which either a sachet of the probiotic or placebo supplement was consumed. Participants completed a Web-based physical activity and illness questionnaire over the entire duration of the supplementation period. At day 0, day 75 and day 150 participants completed the Connor-Davidson Resilience Scale questionnaire. A cohort of the participants (n = 45 in each group) provided blood, saliva and faecal sample at day 0 and day 150 for assessment of the effects of probiotics on faecal microbiology and immunology. The study was conducted over the Autumn to Spring timeframe.

Participants for the study were recruited from the local community of Canberra, Australia by advertising in local media, attendance at research staff at local gyms to promote the study, and circulation of emails to local sporting groups. Both male and female participants aged between 18 and 60 y were recruited. Inclusion in the study was based on an individual’s history of undertaking a minimum of three 30 min sessions per week of physical activity in the previous three months. Exclusion criteria at the time of enrolment were: less than three sessions of physical activity a week, a history of asthma or allergies, use of immune-modulating medications, active respiratory or gastrointestinal illness at time of recruitment, or use of antibiotics in the four weeks prior to the study. Participants were also required to refrain from consumption of non-study probiotic or prebiotic supplements or foods during the study. Physical activity levels ranged from recreationally active (including walking) to athletes competitive at a regional level. All participants were fully informed of the study procedures and provided written informed consent. Ethics approval was obtained from the Griffith University Human Research Ethics Committee and the Australian Institute of Sport Human Research Ethics Committee.

2.2. Evaluation of illness symptoms

Patterns of illness and physical activity were determined via a Web-based questionnaire, as described previously. Briefly, subjects recorded the type of exercise, exercise duration and exercise intensity on a 10-point Likert scale to characterise physical activity patterns. The signs and symptoms of URTI included a scratchy or sore throat, sneezing, stuffy nose or runny nose. A diagnosis of URTI was made when two or more symptoms were recorded for three or more consecutive days. A GI illness was defined when two or more of the following signs and symptoms were present: diarrhoea, constipation, stomach rumbles, bloating, nausea and abdominal pain. Symptoms separated by less than two days were recorded as the same episode. Episodes of URTI and GI illness were collated during the data analysis and this was defined as an illness event as per the study registration. The severity of URTI and GI illness signs and symptoms were self-rated as mild, moderate or severe based on their impact on physical activities for that day: mild — no change to physical activity, moderate — a reduction in physical activity volume and/or intensity, and severe — total cessation of physical activity on that day. The duration and severity of episodes were also calculated. Illness and physical activity data was examined on a weekly basis and individuals were contacted when the requested information had not been submitted.

Participants consumed one sachet daily of either 2.0 × 10^9 CFU per day of Bifidobacterium animalis subsp. lactis BI-04 (Bl-04; Danisco USA, Madison, WI) or L. acidophilus NCFM and Bifidobacterium animalis subsp. lactis Bi-07 (Danisco USA) 1.0 × 10^10 CFU per day (5.0 × 10^9 CFU of each strain) in a 1 g sucrose base or placebo powder (sucrose base without the probiotic bacteria) dissolved in a cold non-alcoholic beverage during the intervention period of 150 days. The placebo was identical in packaging, appearance and taste to the probiotic supplement but did not contain any probiotic cells. Subjects were provided with a list of probiotic and prebiotic products in the local market and instructed not to consume these products. Participants were also provided a list of fermented dairy products not containing probiotics, which were permitted during the study. Subjects were asked to record any dietary supplements consumed during the study, including the study products. Subject data was examined on a weekly basis and individuals were contacted in the event information on activity and illness signs and symptoms was missing. Unused sachets were returned to investigators during the final visit. Compliance was determined based on the daily supplement record and the number of unused sachets.

2.3. Statistical methods

The study design was a three-arm double-blind randomised controlled trial with participants centrally allocated to a group by
simple randomisation.\textsuperscript{20} The annual incidence of respiratory tract illness in this population is \(~45\%\) with an expected rate of two to four episodes per year.\textsuperscript{16,21} The pre-specified primary outcome was the incidence (proportion of subjects experiencing illness and the rate of illness events), severity and duration of URTI or GI illness.

Based on previous research by our group the anticipated base rate of the incidence of URTI was estimated to be 30\% during the study, and a minimum 14\% absolute reduction in the incidence of symptom episodes was deemed clinically worthwhile.\textsuperscript{18} As such, 145 participants per group would provide at least 80\% power with 95\% confidence to detect this difference. The statistical approach was modified under blinded conditions during the data analysis to be time to URTI and GI illness episode event rather than the incidence of illness. This was due to the URTI episode illness rate being almost double that anticipated in the study design. A time to illness event analysis provides more statistical power by modelling the occurrence of illness over time.\textsuperscript{22} Due to the low number of GI illness episodes (placebo \(n = 1\), Bl-04 \(n = 3\), NCFM & Bi-07 \(n = 4\)) over the study period a separate illness analysis was based on a comparison of hazard ratios on time to URTI only.

As participants may experience multiple URTI illness episodes during the course of the study, recurrent event analysis was undertaken\textsuperscript{23} to model the risk of the first, second, and third episodes of URTI over time with episodes combined over time as described previously.\textsuperscript{24} Time to episode curves were described using Kaplan–Meier method.\textsuperscript{25} The total duration of illness measured in days was compared using a t-test with the square root of the duration as a variance stabilising transformation for the Poisson distribution. Other comparisons (doctor visits and medication usage) were performed using the chi-squared distribution for discrete variables and linear models (on appropriately transformed data) for continuous variables. Sub-group analysis was undertaken using age, sex, and body mass. Precision of estimation was indicated with 95\% confidence intervals. All P-values are two-sided with a nominal 5\% level considered statistically significant. Data were analysed using SAS V9.x and ACCoRD (Analysis of Censored and Correlated Data) v2.

3. Results

3.1. Participants

Of the 465 people recruited to the study 161 individuals were allocated to the Bl-04 group, 155 people to the NCFM & Bi-07 group and 149 individuals to the placebo group. The characteristics of the participants at supplement allocation are shown in Table 1. The supplement groups were well matched on age, body mass index (BMI), sex and emotional resilience. The flow of participants through the study is shown in Fig. 1. One participant withdrew with headaches (NCFM & Bi-07 group) and three participants (placebo \(n = 1\), Bl-04 \(n = 2\)) withdrew because of uncomfortable GI symptoms after the onset of supplementation. Participants that withdrew before experiencing an illness episode or reaching 150 days did so due to travel and other undisclosed reasons. There were no substantial differences between the groups in dietary habits (inclusive of other probiotic containing foods), alcohol consumption or resilience values at the mid-point and end of study (data not shown).

4. Outcome measures

4.1. URTI and GI illness

The effect of supplementation on the risk of URTI using recurrent event analysis is shown in Table 2. There was a significant risk reduction of 27\% in any URTI episode in the Bl-04 group (\(P = 0.02\)) and a non-significant 19\% lower risk reduction in the NCFM & Bi-07 group (\(P = 0.12\)). This difference between the groups remained consistent throughout the study duration (Fig. 2). The median time to first URTI was 3.2 months in the Bl-04 group, 3.4 months in the NCFM & Bi-07 group and 2.5 months in the placebo group, a difference of \(\approx 0.7–0.9\) of a month. The proportion of participants experiencing a moderate to severe URTI did not differ significantly between the groups.

There was a total of 59 single episodes and 43 recurrent events of URTI in the Bl-04 group, 55 single episodes and 55 recurrent episodes in the NCFM & Bi-07 group and 67 single episodes and 60 recurrent episodes in the placebo group during the study (Table 3). The proportion of participants experiencing URTI was a non-significant 8\% lower in the Bl-04 group and 10\% lower in the NCFM & B-07 group compared to placebo. The URTI illness episode rate in both probiotic groups was a non-significant 10\% lower than in the placebo group (Table 3). Analysis of the effects of supplementation on GI illness (Table 3) was precluded by the low number of GI illness episodes (\(n = 8\)). Analysis of URTI and GI illness as a combined illness event as per the trial registration found a non-significant 24\% reduction in both probiotic groups compared to the placebo group (Bl-04 v placebo \(P = 0.12\); and NCFM & Bi-07 and placebo \(P = 0.13\)).

4.2. Duration of illness

Comparisons were performed on the total duration of illness for subjects experiencing at least one episode of illness at least three days duration. As the distribution of the duration was very skewed the square root transformation was employed (thus increasing the symmetry of the distribution) to compare the probiotic groups with the placebo group. The median duration (untransformed) for upper respiratory tract illness was 6.3 days for the Bl-04 group, 7.0 for NCFM & Bi-07 group and 7.4 days for the placebo group. This difference was not statistically significant between either the Bl-04 and placebo groups (\(P = 0.25\)) or between the NCFM & Bi-07 and placebo groups (\(P = 0.82\)).

Multivariate analyses examining the impact of body mass, height, age and sex were conducted with URTI. None of these variables were univariately predictive of URTI outcome and this was also the case in the multivariate analysis.

4.3. Physical activity patterns

Physical activity patterns in the groups over the supplementation period are presented at Table 4. In the NCFM & Bi-07
compared to placebo group the mean intensity of physical activity was a significant 0.13 of a step lower ($P < 0.01$) while average weekly duration was approximately 30 min more per week ($P < 0.01$). These differences between the placebo and NCFM & Bi-07 group resulted in a significantly higher level of physical activity load (duration x intensity) undertaken in the NCFM & Bi-07 group during the study ($P < 0.01$). No significant differences were observed between the Bl-04 and placebo group. On average, the supplement groups were undertaking four exercise sessions per week, indicating that participants were moderately active.

### Table 2

<table>
<thead>
<tr>
<th>Episode number</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bl-04</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>0.75 (0.53–1.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>Second</td>
<td>0.76 (0.43–1.35)</td>
<td>0.35</td>
</tr>
<tr>
<td>Third</td>
<td>0.6 (0.27–1.34)</td>
<td>0.21</td>
</tr>
<tr>
<td>Fourth</td>
<td>0.63 (0.18–2.22)</td>
<td>0.47</td>
</tr>
<tr>
<td>Overall</td>
<td>0.73 (0.55–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>NCFM &amp; Bi-07</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>0.76 (0.52–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Second</td>
<td>1.03 (0.58–1.80)</td>
<td>0.93</td>
</tr>
<tr>
<td>Third</td>
<td>0.58 (0.24–1.39)</td>
<td>0.23</td>
</tr>
<tr>
<td>Fourth</td>
<td>0.93 (0.25–3.49)</td>
<td>0.92</td>
</tr>
<tr>
<td>Fifth</td>
<td>1.09 (0.27–4.39)</td>
<td>0.90</td>
</tr>
<tr>
<td>Overall</td>
<td>0.81 (0.62–1.08)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

4.4. Medication usage and doctor visits

Details on visits to a general practitioner and medication usage during a URTI episode are presented in Table 5. No statistically significant differences were observed in visits to general practitioners between the supplement and placebo groups. However, there was a trend towards fewer medications being prescribed in the supplement groups, particularly for the Bl-04 group.

**Fig. 1.** Flow of participants through the study.

**Fig. 2.** Kaplan–Meier time to event for upper respiratory tract illness. The median time to illness was 3.2 months in the Bl-04 group, 2.4 months in the placebo group and 3.4 months in the probiotic group. PLA, Bl-04, NCFM & Bi-07.
Table 3
The effect of supplementation on single URTI and GI illness episodes using risk ratio analysis over five months of supplementation.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>BI-04</th>
<th>Difference</th>
<th>NCFM &amp; BI-07</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>URTI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with an illness (%)</td>
<td>67 (45%)</td>
<td>59 (37%)</td>
<td>P = 0.14</td>
<td>55 (35%)</td>
<td>P = 0.09</td>
</tr>
<tr>
<td>Rate of illness episodes per month</td>
<td>0.035%</td>
<td>0.026%</td>
<td>RR: 0.74</td>
<td>0.026%</td>
<td>RR: 0.74</td>
</tr>
<tr>
<td>% of participants with severe illnesses*</td>
<td>20</td>
<td>19</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants with an illness</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR: relative risk reduction.

* Severity at time of illness rated as moderate or above.

The main finding in this study was that daily BI-04 supplementation was associated with a statistically significant 27% reduction in the risk of any URTI episode compared to placebo supplementation. While not statistically significant, there was also a reduction in URTI illness risk in the NCFM & BI-07 group. The reduction in the risk of URTI in the probiotic groups corresponded to a delayed interval to URTI illness of approximately 0.8 months between the probiotic groups and the placebo group. With only eight total GI illness episodes between the groups, no analysis could be conducted separately on this outcome. Over the duration of the study over 30% of participants experienced recurring URTI, which is consistent with other probiotic research. While not significant there was a consistent benefit in the reduction of URTI illness risk by approximately 25–40% for recurrent URTI in the BI-04 group. A similar observation is evident across other measures of URTI (Table 3), where the mean effect in the probiotic group was larger compared to the placebo group, with the exception for severity in the NCFM & BI-07 group. Both probiotic supplements were associated with a non-significant 24% reduction in the risk of an illness event, which could be either a URTI or GI illness episode. This study provides some evidence that probiotic supplementation has benefits in relation to URTI in otherwise healthy adults.

Differences in the time to onset of illness between the two probiotic groups and the placebo group became apparent after approximately two weeks of supplementation, as depicted in the Kaplan–Meier plots. This pattern of response is consistent with general understanding that probiotics typically take between 10 and 14 days to colonise the GI tract. Beyond this point, the Kaplan–Meier survival curves for the two probiotic arms are similar over the course of the study and show a continuous delay in time to the first illness episode compared with the placebo group (Fig. 2). Further to this, the difference in the episode rate between the two probiotic groups and the placebo group widens through to the third month of the study. Beyond this the power of the study falls below a level in which differences can be estimated reliably, evidenced by the change in the intervals plotted on the graph, which represents the occurrence of an event. In the context of a seasonal illness like the common cold, a delay in the occurrence of illness indicates a positive clinical benefit from supplementation in that if the delay is long enough the higher risk of illness associated with the winter period may be reduced.

The overall effect of probiotic supplementation on the rate of URTI illness episodes (absolute difference in the rate being 9%) was less than planned in the study design. Our trial was designed to detect an absolute difference of 14%. The smaller effect observed in this study is most likely attributable to the underlying characteristics of the study cohort. In a relatively fit, healthy, exercising cohort, the risk of URTI is low, particularly in relation to other population cohorts studied in previous probiotic research.

Despite this, daily supplementation with both probiotic supplements was associated with reductions in almost all illness parameters in comparison to the placebo group. These differences corresponded to a significant reduction in the hazard ratio, or risk of illness, in the BI-04 group. Hazard ratios calculate the difference in illness rates as a function of the study duration. In comparison, rate ratios are purely a measure of the difference in the number of events. The acknowledged limitations of examining rate ratios include the choice of the point in the study to examine differences between the groups, and dealing with differences in compliance to the study protocol. Further to this, no adverse events were observed during the study. Given the economic and productivity losses and personal costs associated with URTI, the significant risk reduction and findings from this study are promising for healthy physically active individuals in relation to URTI.

An interesting observation in the study was the significantly lower self-reported level of exercise intensity but substantially higher exercise duration and exercise training load observed in the NCFM & BI-07 group. The lower intensity of exercise undertaken by the NCFM & BI-07 group is easily explained; the longer duration of exercise undertaken diluted the training intensity. To overcome the issue of assessing a multitude of training outcomes we examined the effect of supplementation on training load, computed as the product of exercise duration and intensity. Physical activity patterns were monitored to ensure participants complied with the inclusion criteria of being physically active. URTI may lead to a reduction or the complete cessation of participation in physical activity, particularly competitive sport. The negative impact of URTI on exercise is the basis for a substantial body of research that has attempted to identify markers of increased risk of illness in athletes and strategies to prevent contraction of an illness episode.

The reason for the greater amount of physical activity undertaken by those in the NCFM & BI-07 group may have been through the delayed time to illness. The findings from the current study indicate that NCFM & BI-07 supplementation may be a useful nutritional adjunct to reduce the negative effects of illness on patterns of physical activity.

In the context of the literature, this study adds important new information regarding the effects of probiotic supplementation for respiratory illness. The positive effects of probiotic...
supplementation appear to extend beyond individuals considered to have a higher susceptibility to illness. Scientific investigation of probiotic supplements has traditionally focused on individual strains, particularly given the need to quantify effects on specific physiological and clinical endpoints. Given evidence that probiotic strains differentially alter various neuroendocrine, immune and metabolic parameters, interest has grown in the use of multi-strain probiotics. Defined as supplements with more than one bacterial strain, multi-strain probiotics are designed to reduce antagonistic effects between strains, promote synergistic and additive effects, and are tailored toward specific conditions.220 Multi-strain probiotics have clinical benefit in relation to respiratory illnesses,30 with the combination of *L. acidophilus* NCFM and *B. lactis* Bi-07 showing promise in reducing rhinorrhoea and cough in children.8 A number of limitations that are consistent with this being a free living community study of a food ingredient/functional food rather than a medicinal product also need to be recognised. Community-based studies rely on participants to comply with the requirements of the study. The research team undertook two processes to determine compliance to the dosing regimen. Participants indicated on their daily questionnaire whether they had consumed the supplement, and the boxes containing the study sachets were collected from the cohort who provided a sample. Based on this, participant compliance to the dosing regimen was considered excellent with 95% (±7%) of the sachets consumed. On the basis of the detailed instructions given to participants, consumption of other prebiotic or probiotic foods at the mid-point and end of study indicates that consumption of restricted foods was similar in all three groups. The study also relied on self-reported illness data. The ecological validity of the study was high as the effect of supplementation was examined in a real life situation, where missed servings and intake of other food ingredients/functional foods are likely to occur.

In conclusion, probiotic supplementation had positive effects in relation to URTI in a healthy active cohort. BI-04 significantly reduced the risk of URTI by 27% and both probiotic supplements were associated with a delay in the time to URTI of ~0.8 of a month. There were too few GI illness episodes for analysis. The greater level of physical activity undertaken in the NCFM & Bi-07 indicates that the delay in illness may have ameliorated the negative impact of illness on activity patterns, which will be of interest to those involved in competitive sport.

### Statement of authorship

The experimental protocol was developed by all authors. The recruitment, experimental work and statistical analysis were undertaken by the non-industry authors. All authors contributed to the final manuscript.

### Sources of funding

The study was funded by Danisco Sweeteners Oy, now part of DuPont.


### Conflict of interest

Sampo Lahtinen is an employee of Danisco Sweeteners Oy. Allan Criggs is the recipient of research funding from Danisco Sweeteners Oy. There are no other conflicts of interest to declare.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at [http://dx.doi.org/10.1016/j.clnu.2013.10.002](http://dx.doi.org/10.1016/j.clnu.2013.10.002).

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