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Editorial

Placebo-controlled Trial of the Probiotic Lactobacillus Rhamnosus

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INTRODUCTION

This study aimed to investigate whether supplementation with the probiotic Lactobacillus rhamnosus HN001 reduced the build-up of stress, reduced symptoms of anxiety, and improved psychological wellbeing in university students leading up to examinations.

The study design was a randomized, double-blind, placebo-controlled trial.

The New Zealand university system operates on two semesters per year, with examinations for a paper held at the end of a semester. Participants were undergraduate students at the University of Auckland enrolled in semester one of 2020. Exclusion criteria were: currently taking a regular probiotic supplement, taking immunosuppressant's, e.g., chemotherapy, or current participation in another research trial.

All consent and data collection was through an online web interface. Students registered for the study and completed the questionnaires using their mobile phones, tablet, or computer. Fonterra Co-Operative Group Limited managed the randomization schedule and was not involved with the recruitment, collection of data, or analysis of results. Both participants and the researchers were blind to the randomization schedule. As students completed baseline consent and registration information, they were assigned the following available sequential study number and provided with the corresponding bottle of capsules according to the study number.

Fonterra Cooperative Group Limited supplied capsules containing the probiotic Lactobacillus rhamnosus HN001 (6×109 colony forming units) manufactured to pharmaceutical grade. Placebo capsules identical in appearance and smell to the probiotic contain corn-derived maltodextrin. Both probiotics and placebo capsules are lactose-free and gluten-free. Previous studies have safely used the probiotic L. rhamnosus HN001 (6 X 109 cfu) in previous studies conducted in New Zealand, including in pregnant women and infants.

Instructions to students were to take one capsule a day from when they enrolled in the study and received the capsules until two days before the commencement of university examinations for the semester.

The Perceived Stress Scale is a 10 item questionnaire that asks about stress and coping in the previous month. Scores range from 0-40, with higher scores being indicative of higher levels of stress. Scores from 0-13 represent low stress, 14-26 indicate moderate stress, and 27-40 indicate high stress.

State Trait Anxiety Inventory 6 item version (STAI6): The STAI6 is a short 6 item scale validated as an anxiety screening questionnaire based on the more extended State Trait Anxiety Inventory. Clinically significant anxiety was defined as a score above a cut-off of score >15.

The World Health Organisation - Five Well-Being Index (WHO-5) is a five-item, positively worded measure of psychological wellbeing with scores ranging from 0 to 25. Higher scores represent better wellbeing. Scores of 13 or lower indicate low levels of psychological wellbeing. A systematic review of the WHO-5 concluded that it was a widely used and sensitive measure of depression.

Intent-to-treat analysis was conducted in SAS 9.4 using a two-sample t-test. Change in stress, anxiety, and psychological wellbeing was calculated by subtracting post-intervention scores from baseline scores for each of the three measures. The findings are reported according to the CONSORT statement.

Of the 483 participants initially enrolled in the trial, 391 (81.0%) completed the end-of-intervention questions. Figure 1 shows the CONSORT flow diagram for the trial. There was no significant difference between respondents and non-respondents to the end of intervention questions in the intervention group (p=0.66), sex (p=0.91), ethnicity (p=0.51), study paper (p=0.65), or year of study (p=0.42).

The probiotic supplemented, and placebo groups did not significantly differ in demographic factors or measures of psychological health.

It shows the outcome measure results according to study group assignment. Overall there were no significant differences between groups for measures of stress, anxiety, or psychological wellbeing. For the group as a whole there was a significant improvement in stress (mean change=1.70; SED=6.10, p<0.0001), anxiety (mean change =0.87; SD=6.88, p=0.001) and psychological wellbeing scores (mean change=0.49; SD=4.49, p=0.03) between baseline and post-intervention.

In this randomized, double-blind, placebo-controlled trial of the probiotic Lactobacillus rhamnosus HN001, we found no significant difference in stress, anxiety, and psychological wellbeing in university students between the placebo and probiotic intervention

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groups. Although there is promising evidence that probiotic supplementation may improve the stress-induced suppressed immune function in students, these previous trials have also not shown a significant difference in psychological symptoms of stress, anxiety, or depression in university participants. In a previous trial of L. rhamnosus JB-1 in healthy volunteers, there was no significant difference between placebo and probiotic groups on stress, depression, and anxiety or physiological measures, including HPA-axis function, neurocognitive and inflammatory markers, despite preclinical evidence in a mouse model showing promising results for this strain of probiotic. This finding highlights the difficulties in translating promising preclinical evidence into human populations

It is well understood in the probiotic field that benefits for health conditions associated with probiotics are strain-specific. While the HN001 strain did not benefit psychological outcomes in our study where other strains may have, we have previously demonstrated that the HN001 strain significantly lower depression and anxiety scores in postpartum mothers. Furthermore, a recent trial showed improvements in psychological wellbeing associated with HN001 probiotic supplementation in prediabetic adults on an intermittent fasting diet.

The potential impact of COVID-19 on this research requires discussion. The university semester this study was conducted in was interrupted by government-led restrictions that forced the closure of the university campus and a complete shift to online learning, studying, and assessment for the university campus semester. The COVID-19 pandemic is often assumed to increase stress and anxiety; however, the opposite was true for our cohort of university students, and this may have influenced our study results. New Zealand has been one of the most successful countries worldwide in containing and eliminating COVID-19. During the university semester of this study, New Zealand moved from Alert Level 4 (complete lockdown) to Alert Level 1 (no restrictions except on international travel). Our lockdown was one of the most restrictive in the western world. Stay at home instructions asked people to restrict outings to essential personal movement, travel was severely limited, gatherings were cancelled, and all public venues closed, businesses were closed except for essential services, and all educational facilities were closed. Many students returned home where they may have been more supported by family.

Furthermore, students may have experienced a reduction in stress before their examinations due to a significant improvement in eliminating COVID-19 from the community that resulted in a shift down to Alert Level 1 during the semester. In addition, examinations for students were online and uninvigilated, and this may also have resulted in a reduction of stress for students leading up to examinations in direct contrast to previously reported increase in pre-examination stress in studies conducted before COVID-19. Literature indicates that some students find online examinations less stressful.