

A randomized, double-blind, placebo-controlled

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INTRODUCTION

Lactose and lactase

Studies suggest that bioactive compounds such as probiotics may positively influence psychological health. This study aimed to determine whether supplementation with the probiotic *Lactobacillus rhamnosus* HN001 reduced stress and improve psychological wellbeing in university students sitting examinations.

The study was a randomized, double-blind, placebo-controlled design, in which 483 undergraduate students received either the probiotic *L. rhamnosus* HN001, or placebo, daily during a university semester. Students completed measures of stress, anxiety, and psychological wellbeing at baseline and post-intervention before examinations. T-tests compared the change in psychological outcomes between groups.

The 483 students, 391 (81.0%) completed the post-intervention questions. There was no significant difference between the probiotic and placebo supplemented groups in psychological health outcomes. The COVID19 pandemic restrictions may have influenced the typical trajectory of stress leading up to examinations.

These findings further reinforce the difficulty of translating preclinical evidence into probiotic mediated health improvements for humans.

The microbiota in the human gut is a colony of microbes (bacteria, viruses, and fungi) that play an essential role in physiological and biochemical processes in the body. The microbiota-gut-brain axis refers to multidirectional signaling pathways that communicate between the microbes in the gut and the central nervous system, including the hypothalamic-pituitary-adrenal (HPA) axis, which modulates stress response and the immune system, both pathways linked to the experience of stress, anxiety, and depression.

Disruption to the gut microbial balance influences the biochemical metabolites produced in the gut, thereby altering neurotransmitter synthesis and modulating regulation of the HPA axis. Stress, in turn, can alter the balance of microbiota in the gut. A recent review concluded that although there is substantial evidence from preclinical studies showing the gut microbiota influence the physiological stress response, further work in human populations is needed to realize the potential benefits of positively influencing

the gut microbiota to manage stress.

Promising preclinical studies using mice have suggested that probiotics (defined as live microorganisms that, when ingested in sufficient quantity, confer a health benefit) may improve the mental health of human participants by enhancing the gastrointestinal microbial environment. In one of the foundational studies in the field, germ-free mice, who have no commensal microbiota, displayed exaggerated responses to stress which improved with probiotic supplementation. Understanding the therapeutic role of probiotics in humans is far less well elucidated, in part due to the incredible complexity of human physiology and psychology. A systematic review of the evidence for the benefit of probiotics on subclinical symptoms of psychological stress concluded that probiotic supplementation could reduce depression, anxiety, and perceived stress in healthy volunteers. However, small sample sizes were a limitation of most of these studies.

Conversely, in their systematic review and meta-analysis of 10 randomized controlled probiotic trials for depression and anxiety, suggested there was limited evidence that probiotics could reduce depression and anxiety. Six of the reviewed studies were in healthy volunteers. Of those, two studies found statistically significant improvements in depression or anxiety attributable to probiotic supplementation. The need to translate preclinical research into therapeutic benefits for people with psychiatric or stress-related conditions remains. With the prevalence of stress and its impact on physical and psychological health, probiotic supplementation trials are critical to advancing the potential utility of probiotics in humans.

University students experience increased stress associated with examinations. A study of Japanese medical students found that stress increased over eight weeks before a national examination peaking the day before and then decreased to baseline two weeks later. The same study found that those students supplemented with *Lactobacillus casei* (strain Shirota) had fewer gastrointestinal, cold, or flu-like symptoms. A study of stressed American university students reported similar results, those supplemented with *Bifidobacterium bifidum* reported fewer days of cold and flu symptoms and more healthy days than those who received a placebo. A previous study of 155 university students randomly allocated students to receive either a multispecies probiotic containing *Lactobacillus casei* DN 114001, *Lactobacillus delbrueckii* subsp.

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Bulgaricus, and *Streptococcus salivarius* subsp. *Thermophilus* or placebo daily for six weeks which included three weeks leading up to examinations and three weeks during the examination period. They found that scores on the State Trait Anxiety Inventory increased for all students, but there were no significant differences between probiotic and placebo groups. However, the probiotic supplemented group showed a statistically significant increase in

markers of immune function.

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