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## Research Digest

### Exclusive Sneak Peek

Issue 8 ♦ June 2015

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# I get by with a little help from my friends: probiotics and depression

*A randomized controlled trial to test  
the effect of multispecies probiotics on  
cognitive reactivity to sad mood* 



# Introduction

For thousands of years, clinicians have observed a connection between the gut, brain, and overall health. Hippocrates is famously quoted as saying “all disease begins in the gut.” This should not come as a surprise to anyone who has ever experienced gastrointestinal (GI) symptoms like diarrhea, indigestion, or abdominal discomfort in response to changes in their emotional state. Studies in both healthy patients and in people with functional bowel disorders have confirmed [connections between emotional state and GI function](#).

The gut and brain [communicate](#) through neural, endocrine and immune pathways. It has become increasingly clear that [interactions with intestinal microbiota](#) are also an important part of this communication. A number of animal and human studies have examined the relationship between gut bacteria and mood symptoms such as anxiety and depression, leading to the idea that probiotic supplementation may be a potential strategy for reducing or preventing depression.

According to the [cognitive theory of depression](#), an individual’s negative and distorted thinking is the basic

psychological problem at the root of depressive syndrome. Cognitive reactivity refers to the activation of dysfunctional patterns of thinking triggered by subtle mood changes. This is a key feature in the development and occurrence of depression, and as such would be a relevant target for interventions. Dysfunctional patterns of thinking can include thoughts of hopelessness, thoughts of hurting oneself or others, ruminating on the causes and consequences of anguish, and a general loss of motivation for life. These responses are thought to come from underlying negative thought patterns that get brought to the surface during times of low mood. Cognitive reactivity appears to be a cause of, rather than simply an association with, depression, since higher cognitive reactivity scores precede and predict the onset of depression, [even in people with no prior incidence](#) of depression.

Considering the vast potential to treat and prevent mood disorders by improving gut health, the objective of this Dutch study was to determine the effects of a probiotic supplement on cognitive reactivity to sad mood, as well as symptoms of depression and anxiety in non-depressed, healthy adults.

“ Cognitive reactivity appears to be a cause of, rather than simply an association with, depression, since higher cognitive reactivity scores precede and predict the onset of depression, even in people with no prior incidence of depression. ”



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**Cognitive reactivity, which involves negative thought patterns triggered by mood change, has been shown to predict the onset of depression. Since the brain and gut communicate through several pathways and the gut microbiome has recently been found to influence this communication, it is possible that probiotic supplementation could affect cognitive reactivity. This is what this study set out to test.**

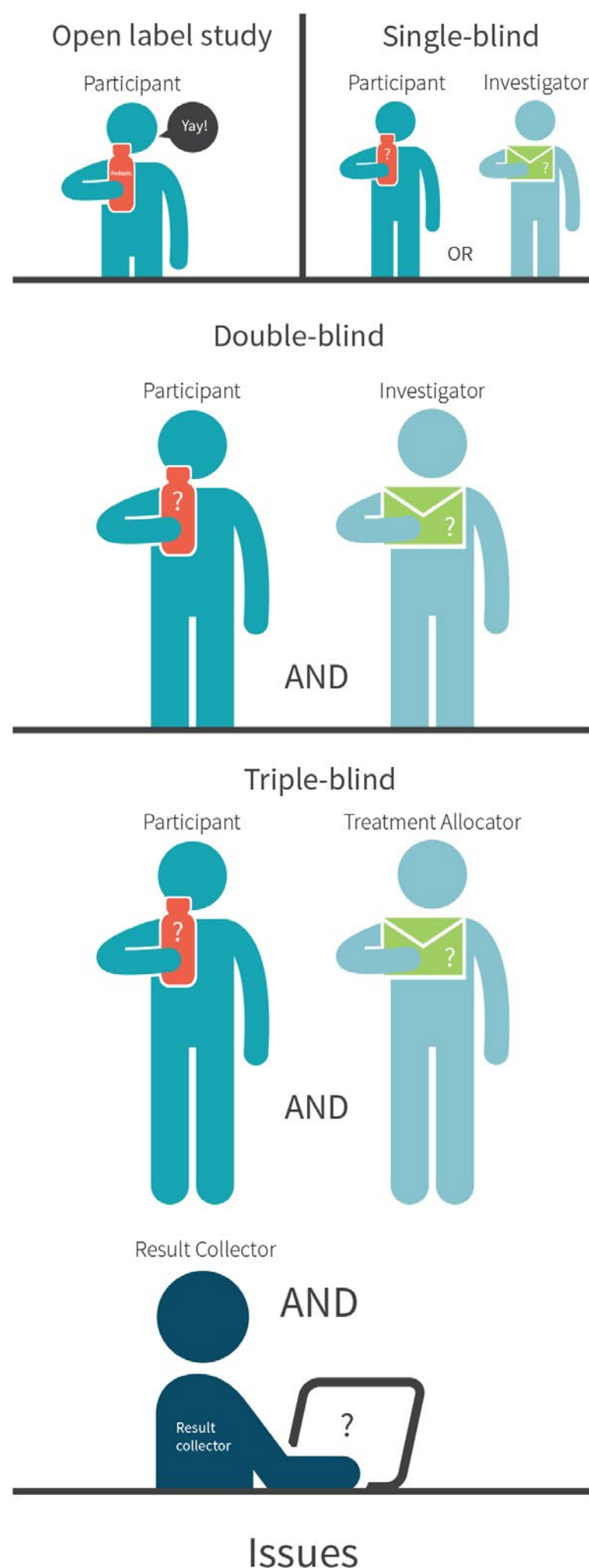
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## Who and what was studied?

Forty healthy, normal weight college-age adults participated in this triple blind study. A triple blind study means neither the participants, researchers, nor the people who organize and analyzed the data knew which group a participant was in. Different types of study blinding are depicted in Figure 1. The participants did not smoke, had no reported medical conditions, food allergies, medications, or drug use, and consumed no more than three to five drinks per week. Participants also did not have any psychiatric or neurological disorders, or any personal or family history of depression or migraines. They were randomly assigned to receive either a probiotic supplement (n=20, five males) or placebo (n=20, three males) for four weeks. The menstrual cycle was not controlled for in the female participants.

Interestingly, all participants were told they were receiving the probiotic supplement. This is different from many other trials, as participants would normally be told they have an equal chance of receiving the supplement being studied or placebo. The probiotic used was a mixture that is commercially available in the Netherlands, containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *L. casei* W56, *Lactobacillus salivarius* W24, and *Lactococcus lactis* (W19 and W58). The participants consumed either supplement or placebo for four weeks.

Figure 1: Triple blinding vs other blinding



\*Definitions are not standard. Sometimes the other blind is an investigator rather than treatment allocator, for example.

\*\*The term "Masking" has been proposed, given the number of people with serious visual impairments (e.g. blindness)

Three different questionnaires were used before and after the intervention period to quantify the outcomes. The [revised Leiden Index of Depression Sensitivity](#) (LEIDS-r) measured the perceived cognitive reactivity to transient changes in sad mood, [which indicates vulnerability to depression](#). The LEIDS-r is made up of 34 questions that assess the extent to which dysfunctional thoughts are activated when someone is experiencing a mild state of dissatisfaction with their life. Example questions include “*when in a low mood, I take fewer risks,*” or “*when in a sad mood, I more often think about how my life could have been different.*” Responses are given on a 5-point scale, with 0 being “does not apply to me” and a score of 5 meaning “very strongly applied to me.” The scale measures vulnerability to depression overall, and consists of six different subscales: regard to aggression, hopelessness/suicidality, acceptance/coping, control/perfectionism, risk aversion, and rumination.

The [Beck Depression Inventory II](#) (BDI-II) is a 21-item questionnaire that assesses the existence and severity of depressive symptoms occurring during the previous

two weeks. Similar to the LEIDS-r, questions are rated on a 4-point scale ranging from 0 to 3 in terms of severity, and the total score is added up to classify the level of depression (minimal, mild, moderate, or severe). The [Beck Anxiety Inventory](#) (BAI) is also a 21-item questionnaire, used to assess the existence and severity of anxiety symptoms occurring during the previous week. Questions are also answered on a 4-point scale ranging from 0 to 3 in terms of severity.

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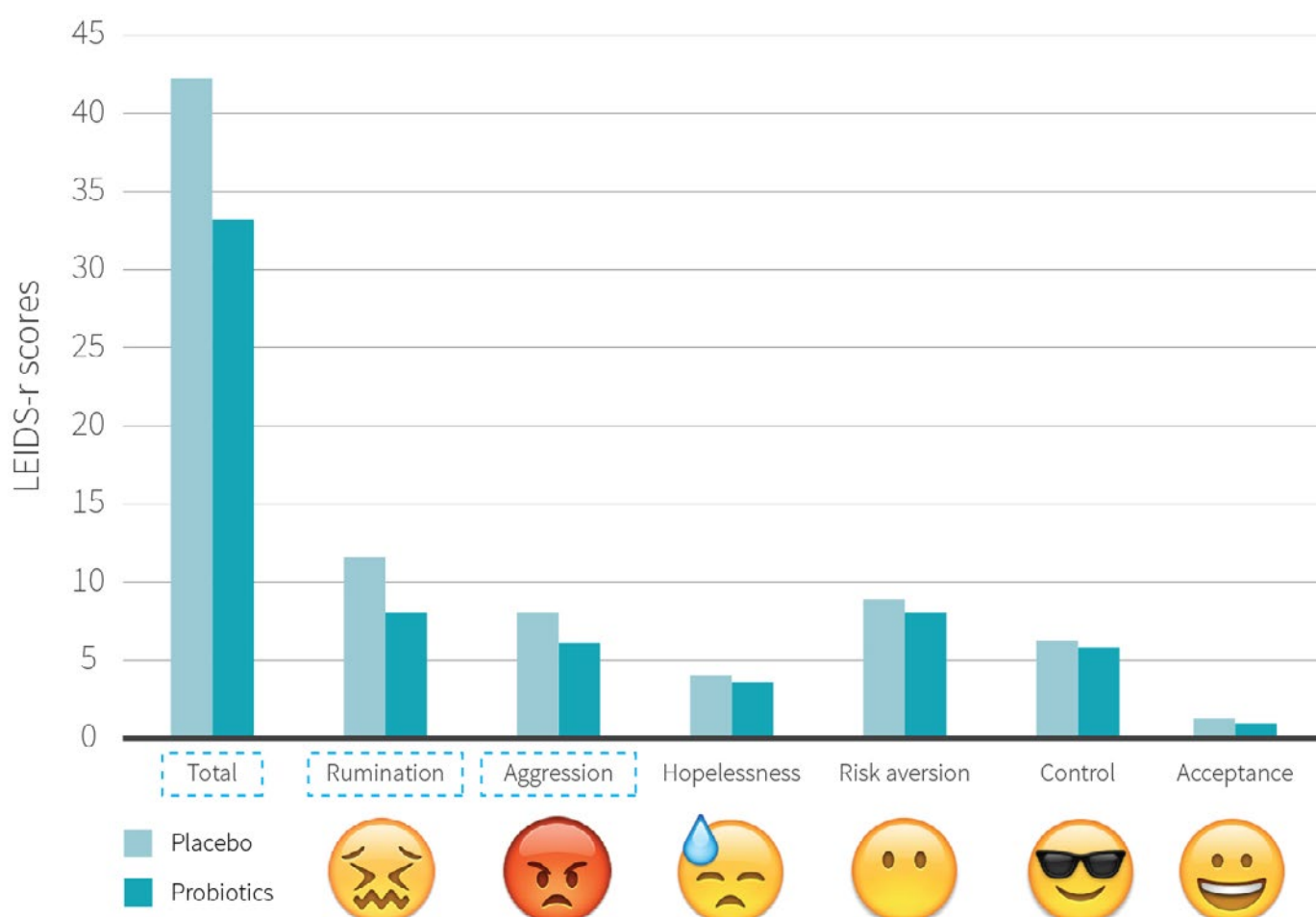
**Forty healthy college-age adults with no personal or family history of depression took either placebo or a probiotic mixture. Cognitive reactivity was measured with the LEIDS-r questionnaire before supplementation began and after four weeks of supplementation. Anxiety and depression were also measured using questionnaires.**

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## What were the findings?

The study findings are summarized in Figure 2. None of the participants (in either group) showed any signs

Figure 2: Study results



of depression (using the BDI-II) or anxiety (using BAI) at baseline or follow-up. Differences were seen on the LEIDS-r, however, which measures vulnerability to future depression. Participants who received the four-week probiotic supplement showed a significantly lower score for overall cognitive reactivity to sad mood, mainly accounted for by reduced rumination and aggressive thoughts. No differences were found between groups for hopelessness, control, risk aversion, or acceptance.

## What does the study really tell us?

*“The present results indicate, for the first time, that probiotics intervention can influence cognitive mechanisms that are known to determine vulnerability to mood disorders.”*

This study set out to determine the effects of a multi-species probiotic supplement on cognitive reactivity, an important marker in predicting future depression, in healthy young men and women without any personal or family history of mood disorders. Though none of the participants showed any signs of current anxiety or depression, a four-week probiotic intervention showed significantly reduced cognitive reactivity scores, suggesting a reduced vulnerability to future depression. Reductions in total cognitive reactivity score were largely due to decreases in the aggression and rumination subcategories. This is relevant because the [people who ruminate](#) about the causes of being in a sad mood may have a harder time recovering from depression.

These participants were healthy and had no diagnosable anxiety or depression at baseline, so improvements in these scores would not necessarily be expected. The lack of any existing mood disorders in the participants is important because it allows the researchers to test for any influence on *future* depression, which the [LEIDS-r](#) questionnaire has been [shown](#) to do. Of course, further long-term studies using the probiotic interven-

“ Participants who received the four-week probiotic supplement showed a significantly lower score for overall cognitive reactivity to sad mood, mainly accounted for by reduced rumination and aggressive thoughts.”

tion would be needed to confirm if these predictions become clinically relevant.

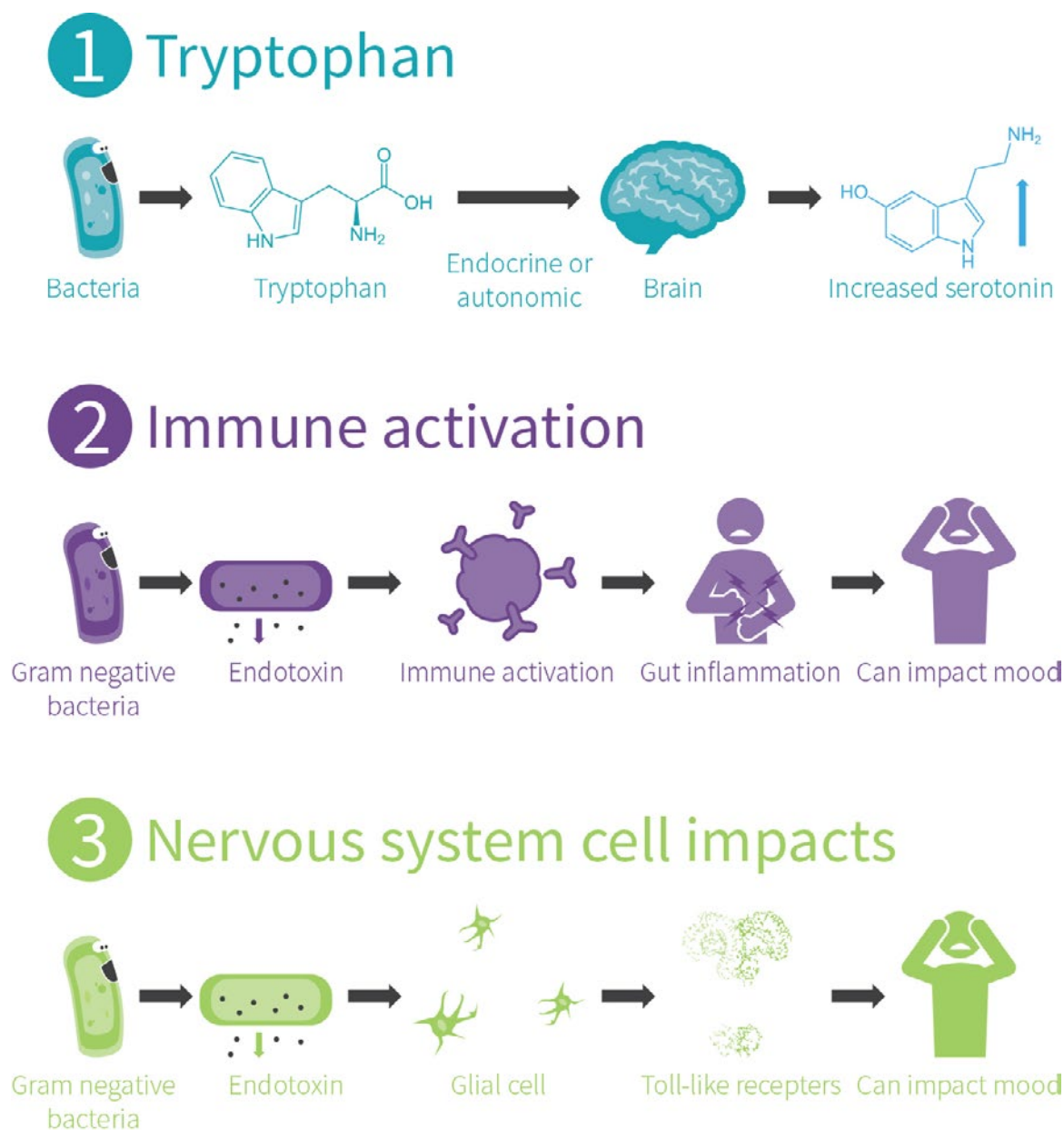
However, we can calculate a guesstimate of the odds reduction of developing depression based on the LEIDS-r score. The roughly nine-point reduction in the LEIDS-r score seen in this study due to probiotic supplementation translates to an odds ratio of 0.76, in terms of developing depression over a two-year period, based on [previous research](#).

While no mechanisms of action were studied, a number of hypotheses can be considered, which are shown in Figure 3. Cognitive reactivity scores can predict the depressive [response to serotonin](#) depletion, and gut bacteria may increase serotonin in the brain by [increasing plasma tryptophan](#) levels. Decreased intestinal permeability from the probiotic supplementation could

also play a role, as increased [gut permeability](#) can lead to symptoms of depression. A [review](#) of the effects of probiotic supplements on intestinal permeability found a positive effect in 48% of the controlled studies.

While compliance was not confirmed by stool analysis and dietary control did not include consideration for other probiotic-rich foods (i.e. yogurt), the biggest limitation in being able to draw wider conclusions from this study is the disproportionate female to male balance. Participants in this study were 80% female, which is opposite to the [male gender bias](#) often found in the scientific literature. This is relevant because men and women have [different gut microbiomes](#) due to differences in sex hormones, and we are also somewhat different both emotionally and cognitively. This is also a fairly small study in a young population, which makes generalization difficult. Although ethnicity wasn't

Figure 3: Three of the ways that microbiota can impact the brain





explicitly mentioned in this study, this study was conducted in the Netherlands, which may warrant caution when generalizing to broader populations. As we've seen in ERD #6 in "The gut microbiome's role in type I diabetes," nationality and ethnicity can correlate with microbiome differences.

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**This study suggests that a multispecies probiotic supplement reduces cognitive reactivity, which is associated with a lower risk of future depression. This is plausible, since there are several mechanisms by which the gut microbiome may affect vulnerability to depression, although these mechanisms were not examined in the study under review. The small sample size and limited diversity in age, gender, and ethnicity makes the results difficult to generalize.**

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## The big picture

A [number of human](#) and [animal studies](#) show reduced signs of depression and anxiety with probiotic supplementation, though improvements are often seen only with pre-existing anxiety or depression.

Taking a probiotic supplement made up of multiple strains of bacteria can have [increased effectiveness](#)

through an additive or synergistic effect of the individual strains, compared with mono-species supplements. However, some probiotics may work in an antagonistic manner, so combinations of strains should be studied both individually and in combination before creating a multispecies product. A previous [study](#) by one of the co-authors of this study reported improvements in intestinal barrier function by each probiotic strain used in this study separately, as well as in the combined product. Another [study](#) that included that same co-author found a decrease in migraines during the second and third month of taking the same supplement. However, no control group was used and no placebo was given.

As mentioned in last month's ERD article on HMB supplementation, the fact that a company sponsors the research does not automatically taint the results. However, it is worth noting that the aforementioned study about intestinal barrier function was done by the company's own internal research and development scientists. Both the study about migraines, as well as the study under review, featured the same employee from Winlove Probiotics as a co-author. Despite this, the authors of this paper state that "no competing interests exist."

## Conflicts of interest

Conflicts of interest occur when the people who design, conduct, or analyze research have a motive to find results that suit their needs. The most obvious source of a conflict of interest is monetary. Sometimes, such as in this paper and the vitamin K2 study reviewed in this issue of the ERD, possible conflicts may exist even though the authors claim there are none. But these authors aren't alone. [One study](#) suggests that nondisclosure of possible conflicts of interest is somewhat common.

However, having competing interests doesn't automatically negate the results of studies. For instance, [one review](#) of major cardiovascular trials found that conflicts of interest had no impact on the results.

Conflicts of interest must be evaluated carefully. Don't automatically assume that they don't exist just because they're not disclosed, but also don't assume that they necessarily influence the results if they do exist.

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Many studies to date have suggested that probiotics may have an effect on anxiety and depression, especially in animals, although human trials were mostly conducted on populations with pre-existing anxiety or depression. Multistrain probiotics could be more beneficial than individual strains in some, but not all, cases. Ideally, research should compare single versus multi-strain supplementation.

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## Frequently asked questions

*Would probiotic supplementation have the same effect in men and women?*

This study recruited both men and women, though it was predominantly (80%) made up of women and results were not listed separately by gender. Other trials using probiotic supplements have found both [similar](#) and [differing](#) effects among men and women. It is difficult to say how this product would compare between genders.

*Could the benefits of this supplement extend beyond depression and anxiety?*

Previous research using the same supplement has shown improvements in [gut barrier function](#) and a

reduction in [migraines](#). Additionally, a number of the species used in this product (but different strains) have shown [cholesterol lowering](#) effects, as well as contributing to [improved immune function](#).

## What I should know?

This study showed that healthy individuals consuming a multispecies probiotic for four weeks experienced a reduction in cognitive reactivity scores, which are a marker of vulnerability to future depression. In particular, these reductions were characterized by reduced aggressive and ruminative thoughts in response to sad mood.

This trial could provide a basis for larger trials in more diverse populations, possibly also testing the efficacy of multi-strain versus single species probiotics. ♦

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We'll certainly be covering more trials on the gut-brain axis in future issues of ERD. In the meantime, discuss the ones we've already reviewed over at the [ERD Facebook forum](#).

“ Previous research using the same supplement has shown improvements in gut barrier function and a reduction in migraines. ”

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