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A systematic review and meta-analysis of the effects of gut microbiota-altering interventions on Depression

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	altering interventions on depression. Methods: A systematic review was conducted. MEDLINE, Embase, PsycINFO, the Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and the Cochrane Controlled Register of Trials were searched from inception to July 3, 2019. Search terms for interventions were combined with terms for the gastrointestinal tract and mental health. Inclusion criteria were: adult population, interventions administered with intent of altering the microbiome, placebo comparator, a depression outcome reported with a validated scale, and randomized controlled trial study design. Random effects models were specified for meta-analysis a priori, using the standardized mean difference as the measure of effect. Results: Fifty studies formed the final dataset. Probiotics offered significant benefit in those with and without depression (Hedges' g: 0.97; 95% CI: 0.17 to 1.78; Hedges' g: 0.23; 95% CI: 0.10 to 0.35, respectively). One outlier was unique in the administration of Clostridium and the requirement that participants take antidepressants at enrollment. No evidence of significant effect was found for prebiotics in participants with depression, or for synbiotics in participants without depression. Interpretation: Although findings are encouraging, interpretation of efficacy estimates for depression outcomes is challenging. Further high-quality studies are required to understand relationships between timing of anti-depressant and probiotic interventions.

PRISMA reporting checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 2
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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Title: A systematic review and meta-analysis of the effects of gut microbiota-altering interventions on Depression

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Abstract

Word Count: 231

Introduction: Despite their popularity, the effectiveness of gut microbiota-altering interventions on depressive symptoms is unknown. Our objective is to summarize evidence of the effect of gut microbiota-altering interventions on depression.

Methods: A systematic review was conducted. MEDLINE, Embase, PsycINFO, the Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and the Cochrane Controlled Register of Trials were searched from inception to July 3, 2019. Search terms for interventions were combined with terms for the gastrointestinal tract and mental health. Inclusion criteria were: adult population, interventions administered with intent of altering the microbiome, placebo comparator, a depression outcome reported with a validated scale, and randomized controlled trial study design. Random effects models were specified for meta-analysis *a priori*, using the standardized mean difference as the measure of effect.

Results: Fifty studies formed the final dataset. Probiotics offered significant benefit in those with and without depression (Hedges' *g*: 0.97; 95% CI: 0.17 to 1.78; Hedges' *g*: 0.23; 95% CI: 0.10 to 0.35, respectively). One outlier was unique in the administration of *Clostridium* and the requirement that participants take antidepressants at enrollment. No evidence of significant effect was found for prebiotics in participants with depression, or for synbiotics in participants without depression.

Interpretation: Although findings are encouraging, interpretation of efficacy estimates for depression outcomes is challenging. Further high-quality studies are required to understand relationships between timing of anti-depressant and probiotic interventions.

Protocol Registration: PROSPERO ID 143178

Introduction

Mounting evidence supports the concept of a microbiota-gut-brain axis and suggests this axis is perturbed in neuropsychiatric disorders. The central nervous system modulates gastrointestinal and mucosal immune functions shaping composition of the gut microbiota(1-4). Reciprocally, gut microbes can affect neural and cognitive functions via release of neurotransmitters, metabolites, and immunogenic molecules(1-3). The gut microbiota can modulate gut epithelial and blood-brain barrier permeability(3, 5), regulating host exposure to its products; alterations which have been documented in patients with major depressive disorder(6-9). In addition, major depressive disorder patients have shown significant shifts in both relative abundance of taxa and the neuroactive metabolic potential of the gut microbiota compared to healthy controls(10-15).

Because of this compelling preclinical data, manipulation of the microbiota-gut-brain axis is a potential treatment modality for major depressive disorder. Promising work has shown that certain probiotics(16-18) and prebiotics(19-21) attenuate depressive behavior in animal models, but translatability to psychiatric and “healthy” human populations is less clear. Multiple systematic reviews have been conducted to assess the effect of microbiota interventions on depression and depressive symptoms, but they include diverse populations, different study designs, disparate interventions, and, not surprisingly, report conflicting findings. For example, Wallace and Milev(2017)(22) identified five studies reporting effects of probiotics on depression outcomes, but did not include quantitative synthesis. Nokolova et al.(2019)(23) report effects of probiotics in patients with depression but used a search strategy that targeted Web of Science and PubMed databases only, capturing three studies for qualitative synthesis. Given the substantial hype around microbiome-based therapies for depression, a comprehensive and rigorous systematic review is required to inform clinical practice. Our objective is to summarize the effects of gut microbiota-altering interventions on depression.

Methods

Search

A systematic review and meta-analysis was conducted, guided by PRISMA reporting standards.(24) The protocol was registered with PROSPERO (ID: 143178). MEDLINE, Embase, PsycINFO, the Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and the Cochrane Controlled Register of Trials were searched from inception to July 3, 2019. Search terms for were combined with terms for the gastrointestinal tract and depression, such as “digestive”, and “depression.” MeSH headings, text words, and key words were searched (Appendix 1). The search strategy was developed by a research librarian and underwent Peer Review of Electronic Search Strategies review(25). Search results were filtered to exclude studies published in a language other than English or French, animal models, and commentaries, editorials, letters, and case reports. Reference lists of identified systematic reviews were hand-searched.

Study Selection

Titles and abstracts were screened independently in duplicate. Any citation included by either reviewer proceeded to full-text review, which was also conducted independently in duplicate. Disagreement between reviewers was discussed until consensus was reached. Inclusion criteria was: adults aged 18 and over; interventions administered with the intent of altering the microbiome such as probiotics, prebiotics, synbiotics, para-probiotics, or fecal transplants; depression outcome reported using a validated scale; use of placebo comparator; and randomized controlled trial study design. Interventions involving change of diet only were excluded. Any study population was considered for inclusion. To be considered a validated outcome, a publication describing validity of each tool in any population was

required (Appendix 2). Outcomes evaluated with single item Likert scales or visual analogue scales were excluded.

Data Extraction and Quality Assessment

The following data were extracted in duplicate using standardized forms: author, year, study design, population inclusion and exclusion criteria, follow-up, sample size, intervention(s), dose, additional supplements, and depression outcome. A hierarchy developed by an expert psychiatrist *a priori* was used when the same mental health outcome was measured with more than one validated tool in individual studies: observer-rated tools prioritized above self-rated tools; commonly used tools over less commonly used tools; and tools measuring specific symptoms over those measuring mixed symptoms. Study quality was assessed with the Cochrane Risk of Bias 2.0 tool(26).

Statistical Analysis

Random effects models with methods described by DerSimonian and Laird (1986)(27) were specified for meta-analysis *a priori*, to account for heterogeneity such as microorganisms used and treatment duration. Effect size was summarized with the standardized mean difference, which expresses difference in effects between treatments in units of standard deviations. Following the Cochrane Collaboration's recommendations for best practice, Hedges' *g* was used to correct for bias often encountered in studies of small sample size(28). Meta-analysis and forest plot generation was conducted with the "metafor"(29) package for R statistical software(30), and figures generated with the "ggplot2"(31) package. Patient populations with a diagnosis of depression at baseline were considered separately from patient populations where the presence of depression at baseline was not specified. Funnel plots were visually inspected for publication bias, and supplemented with trim and fill analysis.(32) Because this analysis uses only previously published data, ethics approval is not required.

Results

23,640 unique records were identified. After abstract review, 195 full-texts were assessed for eligibility – including 17 records identified through hand-searching. Of the full-texts, 142 were excluded for the following reasons: not adult population (n=7), intervention/comparator not of interest (n=20), outcome not of interest (n=58), study design not of interest (n=37), abstract only/conference proceeding (n=10), duplicate of included study (n=9), and not available in English/French (n=1) (**Error! Reference source not found.**). Reasons for full text exclusion are in Appendix 3. The final dataset included 50 studies with 4,313 patients.

Included study characteristics

Characteristics of included studies can be found in Appendix 4. Interventions included probiotics, prebiotics, synbiotics, and para-probiotics. The most common intervention type was probiotics (n=39 studies), followed by prebiotics (n=5 studies), para-probiotics (n=4 studies), and synbiotics (n=3 studies). One study by Kazemi et al.(2019)(33) included both probiotics and prebiotics as distinct interventions – with each intervention included separately in meta-analysis. Sixteen distinct tools were used to evaluate depression outcomes. The most used tools were the Beck Depression Inventory (n=16) and the Hospital Anxiety and Depression Scale-Depression score (n=16).

Although 39 studies presented sufficient information for meta-analysis, only 37 were included in meta-analysis. The two studies not included did not have comparable studies to pool effect sizes with. Of the studies included, the intervention was a probiotic in 31 studies (7 in depressed populations/24 in non-depressed populations), prebiotic in 2 studies (both in depressed populations), synbiotic in 2 studies (both in non-depressed populations), and para-probiotic in 3 studies (all in non-depressed populations). One study examined each of prebiotics in a non-depressed population and synbiotics in a depressed

population that did not have other studies to pool effect estimates with. These two studies presented sufficient information for meta-analysis, and are therefore included in **Error! Reference source not found.**. The remaining 11 studies failed to present necessary information for inclusion in meta-analysis, such as sample size, effect size, or measure of spread. Of these 11 studies, the intervention was a probiotic in 8 studies, prebiotic in 2 studies, and para-probiotic in 1 study (Appendix 5). In all studies that did not include sufficient information for meta-analysis, no evidence of significant effect due to intervention was reported.

Probiotic Interventions

Among studies with probiotic interventions, defined as consumption of live microorganisms, the most common genera of bacteria administered were *Lactobacillus* (n=33) and *Bifidobacterium* (n=23). Other genera administered were *Bacillus*, *Clostridium*, *Lactococcus*, and *Streptococcus*. Twelve studies administered probiotics from more than one genus. Among the seven studies with depressed participants, probiotic interventions offered statistically significant improvement in depression symptoms (Hedges' *g*: 0.97; 95% CI: 0.17 to 1.78) (**Error! Reference source not found.**).

One study, a visual outlier in **Error! Reference source not found.**, was unique in the administration of *Clostridium*(34). This study by Miyaoka et al.(2018)(34) was also unique in the requirement that participants with treatment resistant depression be on a stable dose of selective-serotonin reuptake inhibitor or serotonin-noradrenalin reuptake inhibitor for at least one month prior to enrolment. Exclusion of the visual outlier resulted in an effect size of 0.36 (95% CI: 0.06 to 0.66, tau-squared = 0.07, I^2 = 51.0%).

Twenty-four studies enrolled participants without depression. In these studies, probiotics also offered statistically significant benefits (Hedges *g*: 0.23; 95% CI: 0.10 to 0.35).

Prebiotic Interventions

Five studies examining the effect of prebiotic interventions, or compounds in food that induce growth/activity of gut microbiota, were identified.(35-39) Interventions were galactooligosaccharide, short chain fructooligosaccharide, inulin, and oligofructose with inulin. Two studies with prebiotic interventions enrolled participants with depression. Here, no evidence of significant effect was estimated (Hedges' *g*: 0.42; 95% CI: -0.15 to 0.99) (**Error! Reference source not found.**). One study deemed "high" risk of bias, with prebiotic intervention and participants without depression, found significant benefits of intervention measured with the Hospital Anxiety and Depression Scale-Depression score (standardized mean difference (SMD): 0.82, 95% confidence interval (CI): 0.29 to 1.35).

Synbiotic Interventions

Three studies examining effects of synbiotics, or combinations of prebiotics and probiotics, were identified(40-42). Interventions in these studies were: *L. casaei, L. acidofilus, L. rhamnosus, B. breve, B. longum, S. thermophiles*, and fructooligosaccharide; *L. rhamnosus* CGMCC1.3724 and oligofructose with inulin; and *B. bifidum* W23, *B. lactis* W51, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19, *Lactococcus lactis* W58, and resistant maize starch. In meta-analysis among two populations without depression, synbiotic interventions offered significant improvements (Hedges' *g*: 0.57; 95% CI: 0.21 to 0.93). The third study, conducted in participants with depression, did not find a significant effect (SMD: 0.63; 95% CI: -0.002 to 1.27).

Para-probiotics

Four RCTs examining the effect of para-probiotics, or sterilized bacteria, were identified; all conducted in Japan(43-46). Interventions in these studies were: fermented ginseng and sterilized *L. paracasei* A221, heat killed *L. gasseri* CP 2305, heat killed *L. gasseri* 2809 with and without alpha-lactalbumin, and heat killed *L. pentosus* b240. In the three studies included in meta-analysis, para-probiotic interventions were significantly less beneficial than placebo (Hedges' *g*: -0.45; 95% CI: -0.72 to -0.17) (**Error! Reference source not found.**). Because all three studies included in meta-analysis used the same outcome measurement, this result specifically applies to total mood disturbance represented by the profile of mood states overall score. This finding is influenced by a single study with high risk of bias(46).

Risk of Bias

Although many studies were deemed low risk of bias in multiple domains, only two trials were deemed low risk of bias overall; both of which were included in meta-analysis (Appendix 6)(40, 47). Most studies were low risk of bias due to measurement, but the study by Miyaoka et al.(2018)(34) was deemed high risk of bias in this domain due to lack of blinding. Of the five studies with prebiotic interventions, three studies were deemed high risk of bias overall(37-39), and two studies were deemed to have some concerns for overall risk of bias(33, 36). Among studies examining synbiotics, overall risk of bias was heterogeneous. Of the four RCTs examining para-probiotic interventions, three were deemed high risk of bias overall (**Error! Reference source not found.**)(43, 44, 46).

Assessment of Publication Bias

All three funnel plots in **Error! Reference source not found.** show a lack of studies finding benefits of interventions with small standard error; which suggests the presence of publication bias. In trim and fill analysis excluding the study by Miyaoka et al.(2018)(34), one missing study is estimated on the left side

of the funnel plot, with overall effect estimate of 0.28 (95% CI: -0.03 to 0.59; I^2 = 56.4%, tau-squared = 0.09) in patients with depression (**Error! Reference source not found.**). Among studies with probiotic intervention and no depression, there appear to be no outliers or evidence of publication bias. For prebiotic, synbiotic, and para-probiotic interventions, there was insufficient evidence to generate meaningful funnel plots.

Interpretation

This meta-analysis suggests statistically significant benefit associated with probiotic interventions in studies enrolling participants with depression. There was no evidence of benefit for prebiotic interventions among study samples with depression; or for synbiotic interventions. Significant benefits were found for probiotic and prebiotic interventions in study samples without depression. Compared to para-probiotics, placebo showed significant benefits measured with the profile of mood states in non-depressed study samples. No trials examining the effects of fecal microbiota transplant on depression were included.

Interpretation of probiotic intervention efficacy estimates for depression outcomes is challenging. Many papers did not explicitly include participants with pre-existing depression. For synbiotic interventions, it is unclear whether the lack of significant effect reflects a true lack of effect or the current evidence is underpowered to estimate an effect size of similar magnitude to that of probiotic interventions. Few studies examining effects of prebiotic interventions in participants with depression may also contribute to a lack of power. For para-probiotic interventions, these findings suggest that further research examining effects on depression is not warranted.

The effect of the probiotic intervention reported by Miyaoka et al.(2018)(34) was an outlier. This was the only study administering *Clostridium*. Inclusion of this study casts doubt on validity of the estimate of effect size of probiotic interventions in participants with depression. When excluded, estimated effect

sizes between depressed and non-depressed groups were of similar magnitude with confidence intervals that overlap almost entirely. *Bifidobacterium*- and *Lactobacillus*-containing probiotics are produced commercially, and widely available. The effect size estimated excluding the study by Miyaoka et al.(2018)(34) may better reflect effect sizes achievable with commercially available products.

The study by Miyaoka et al.(2018)(34) also included antidepressant treatment as criteria for trial enrollment, so probiotics played an adjunctive therapy role. Because it was not explicitly stated, we do not know if microbiome therapies were primary or add-on in the other studies. Differences in relative timing of antidepressant administration and probiotic interventions likely contribute to differences in efficacy and heterogeneity in meta-analysis. Effect sizes in participants with (excluding Miyaoka et al.(2018)(34)) and without depression of nearly identical magnitude suggests that mechanisms of these interventions do not differ by baseline depression status. Further high-quality studies are required to understand connections between timing of anti-depressant administration, timing of probiotic interventions, and different probiotic formulations.

Limitations

The primary limitation of this work is likely the high-level evidence synthesis. The standardized mean difference assumes that the same outcome is measured in each study. Many of the tools used to evaluate depression assess slightly different facets of the same phenomenon with significant overlap. A strength of this review is that the tools used to measure outcomes were not part of inclusion criteria; therefore, all validated tools measuring depression were captured. When the same outcome is measured with multiple tools, variation in outcome selection for meta-analysis may produce different results.

Conclusion

Our objective was to examine effects of gut microbiota-altering interventions on depression outcomes. Although findings are encouraging, interpretation is challenging. Many identified papers did not explicitly include participant populations experiencing clinical symptoms of depression. There is not yet strong enough evidence to favor inclusion of these interventions in treatment guidelines for Depression, but the signals are compelling. The evidence does not seem to yet support the enthusiasm with which these compounds are encouraged. The hype needs to be buoyed by stronger study design and reporting.

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References

1. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019;99(4):1877-2013.
2. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci. 2017;20(2):145-55.
3. Powell N, Walker MM, Talley NJ. The mucosal immune system: master regulator of bidirectional gut-brain communications. Nat Rev Gastroenterol Hepatol. 2017;14(3):143-59.
4. De Palma G, Blennerhassett P, Lu J, Deng Y, Park AJ, Green W, et al. Microbiota and host determinants of behavioural phenotype in maternally separated mice. Nat Commun. 2015;6:7735.
5. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6(263):263ra158.
6. Najjar S, Pearlman DM, Devinsky O, Najjar A, Zagzag D. Neurovascular unit dysfunction with blood-brain barrier hyperpermeability contributes to major depressive disorder: a review of clinical and experimental evidence. J Neuroinflammation. 2013;10:142.
7. Najjar S, Pearlman DM, Hirsch S, Friedman K, Strange J, Reidy J, et al. Brain biopsy findings link major depressive disorder to neuroinflammation, oxidative stress, and neurovascular dysfunction: a case report. Biol Psychiatry. 2014;75(12):e23-6.
8. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro Endocrinol Lett. 2008;29(1):117-24.
9. Maes M, Kubera M, Leunis JC, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J Affect Disord. 2012;141(1):55-62.
10. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain, behavior, and immunity. 2015;48:186-94.
11. Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linlokken A, Wilson R, et al. Correlation between the human fecal microbiota and depression. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2014;26(8):1155-62.
12. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019;4(4):623-32.
13. Lin P, Ding B, Feng C, Yin S, Zhang T, Qi X, et al. Prevotella and Klebsiella proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder. J Affect Disord. 2017;207:300-4.
14. Madan A, Thompson D, Fowler JC, Ajami NJ, Salas R, Frueh BC, et al. The gut microbiota is associated with psychiatric symptom severity and treatment outcome among individuals with serious mental illness. J Affect Disord. 2020;264:98-106.
15. Stevens BR, Roesch L, Thiago P, Russell JT, Pepine CJ, Holbert RC, et al. Depression phenotype identified by using single nucleotide exact amplicon sequence variants of the human gut microbiome. Mol Psychiatry. 2020.
16. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A. 2011;108(38):16050-5.
17. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. Neuroscience. 2010;170(4):1179-88.
18. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals. Trends Neurosci. 2016;39(11):763-81.

19. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice. Biol Psychiatry. 2017;82(7):472-87.
20. Tarr AJ, Galley JD, Fisher SE, Chichlowski M, Berg BM, Bailey MT. The prebiotics 3'Sialyllactose and 6'Sialyllactose diminish stressor-induced anxiety-like behavior and colonic microbiota alterations: Evidence for effects on the gut-brain axis. Brain Behav Immun. 2015;50:166-77.
21. Donoso F, Egerton S, Bastiaanssen TFS, Fitzgerald P, Gite S, Fouhy F, et al. Polyphenols selectively reverse early-life stress-induced behavioural, neurochemical and microbiota changes in the rat. Psychoneuroendocrinology. 2020;116:104673.
22. Wallace CJK, Milev R. The effects of probiotics on depressive symptoms in humans: a systematic review. Annals of General Psychiatry. 2017;16(14):1-10.
23. Nikolova V, Zaidi SY, Young AH, Cleare AJ, Stone JM. Gut feeling: randomized controlled trials of probiotics for the treatment of clinical depression: Systematic review and meta-analysis. Therapeutic Advances in Psychopharmacology. 2019;9:1-7.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyse: The PRISMA Statement. Annals of Internal Medicine. 2009;151(4):264-9.
25. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guidline Explanation and Elaboration (PRESS E&E): Canadian Agency for Drugs and Technologies in Health; 2016 [Available from: https://www.cadth.ca/sites/default/files/pdf/CP0015_PRESS_Update_Report_2016.pdf.
26. Higgins JPT, Savović J, Page MJ, Sterne JACobotdgfR. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0): Cochrane; 2016 [Available from: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/archive-rob-2-0-2016.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7(3):177-88.
28. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions 2011 [Available from: https://handbook-5-1.cochrane.org/chapter_9/9_2_3_2_the_standardized_mean_difference.htm.
29. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010;36(3):1-48.
30. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
31. Wickham H. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York; 2016.
32. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration; 2011 [Available from: https://handbook-5-1.cochrane.org/chapter_10/10_4_4_2_trim_and_fill.htm.
33. Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. Clinical Nutrition. 2019;38(2):522-8.
34. Miyaoka T, Kanayama M, Wake R, Hashioka S, Hayashida M, Nagahama M, et al. Clostridium butyricum MIYAIRI 588 as Adjunctive Therapy for Treatment-Resistant Major Depressive Disorder: A Prospective Open-Label Trial. Clinical Neuropharmacology. 2018;41(5):151-5.
35. Kazemi A, Noorbala AA, Azam K, Djafarian K. Effect of prebiotic and probiotic supplementation on circulating pro-inflammatory cytokines and urinary cortisol levels in patients with major depressive disorder: A double-blind, placebo-controlled randomized clinical trial. Journal of Functional Foods. 2019;52:596-602.

36. Azpiroz F, Dubray C, Bernalier-Donadille A, Cardot JM, Accarino A, Serra J, et al. Effects of scFOS on the composition of fecal microbiota and anxiety in patients with irritable bowel syndrome: a randomized, double blind, placebo controlled study. Neurogastroenterol Motil. 2017;29(2):e12911.
37. Silk DBA, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. Alimentary Pharmacology & Therapeutics. 2009;29(5):508-18.
38. Smith AP. The concept of well-being: relevance to nutrition research. Br J Nutr. 2005;93(S1):S1-S5.
39. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. Nutritional Neuroscience. 2019:1-15.
40. Ghorbani Z, Nazari S, Etesam F, Nourimajd S, Ahmadpanah M, Razeghi Jahromi S. The Effect of Synbiotic as an Adjuvant Therapy to Fluoxetine in Moderate Depression: A Randomized Multicenter Trial. Arch Neurosci. 2018;5(2).
41. Sanchez M, Darimont C, Panahi S, Drapeau V, Marette A, Taylor V, et al. Effects of a Diet-Based Weight-Reducing Program with Probiotic Supplementation on Satiety Efficiency, Eating Behaviour Traits, and Psychosocial Behaviours in Obese Individuals. Nutrients. 2017;9(3):284.
42. Smith-Ryan AE, Mock MG, Trexler ET, Hirsch KR, Blue MNM. Influence of a multistrain probiotic on body composition and mood in female occupational shift workers. Appl Physiol Nutr Metab. 2019;44(7):765-73.
43. Kitaoka K, Uchida K, Okamoto N, Chikahisa S, Miyazaki T, Takeda E, et al. Fermented Ginseng Improves the First-Night Effect in Humans. 2009;32(3):10.
44. Nishida K, Sawada D, Kawai T, Kuwano Y, Fujiwara S, Rokutan K. Para-psychobiotic *Lactobacillus gasseri* CP 2305 ameliorates stress-related symptoms and sleep quality. Journal of Applied Microbiology. 2017;123(6):1561-70.
45. Sashihara T, Nagata M, Mori T, Ikegami S, Gotoh M, Okubo K, et al. Effects of *Lactobacillus gasseri* OLL2809 and α-lactalbumin on university-student athletes: a randomized, double-blind, placebo-controlled clinical trial. Appl Physiol Nutr Metab. 2013;38(12):1228-35.
46. Shinkai S, Toba M, Saito T, Sato I, Tsubouchi M, Taira K, et al. Immunoprotective effects of oral intake of heat-killed *Lactobacillus pentosus* strain b240 in elderly adults: a randomised, double-blind, placebo-controlled trial. Br J Nutr. 2013;109(10):1856-65.
47. Gomi A, Yamaji K, Watanabe O, Yoshioka M, Miyazaki K, Iwama Y, et al. Bifidobacterium bifidum YIT 10347 fermented milk exerts beneficial effects on gastrointestinal discomfort and symptoms in healthy adults: A double-blind, randomized, placebo-controlled study. Journal of Dairy Science. 2018;101(6):4830-41.

Figures and Tables

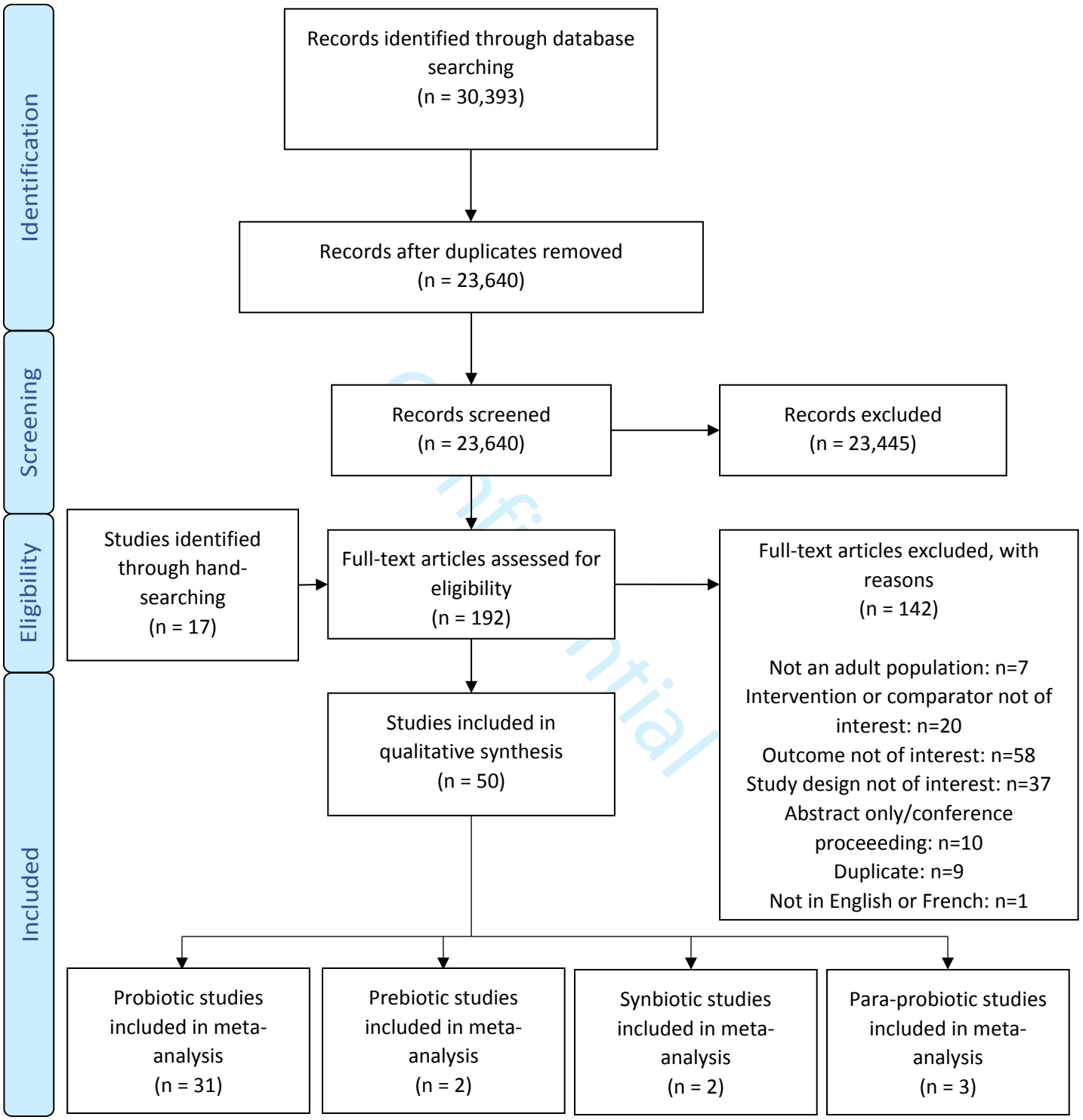

Figure 1. PRISMA flow diagram.

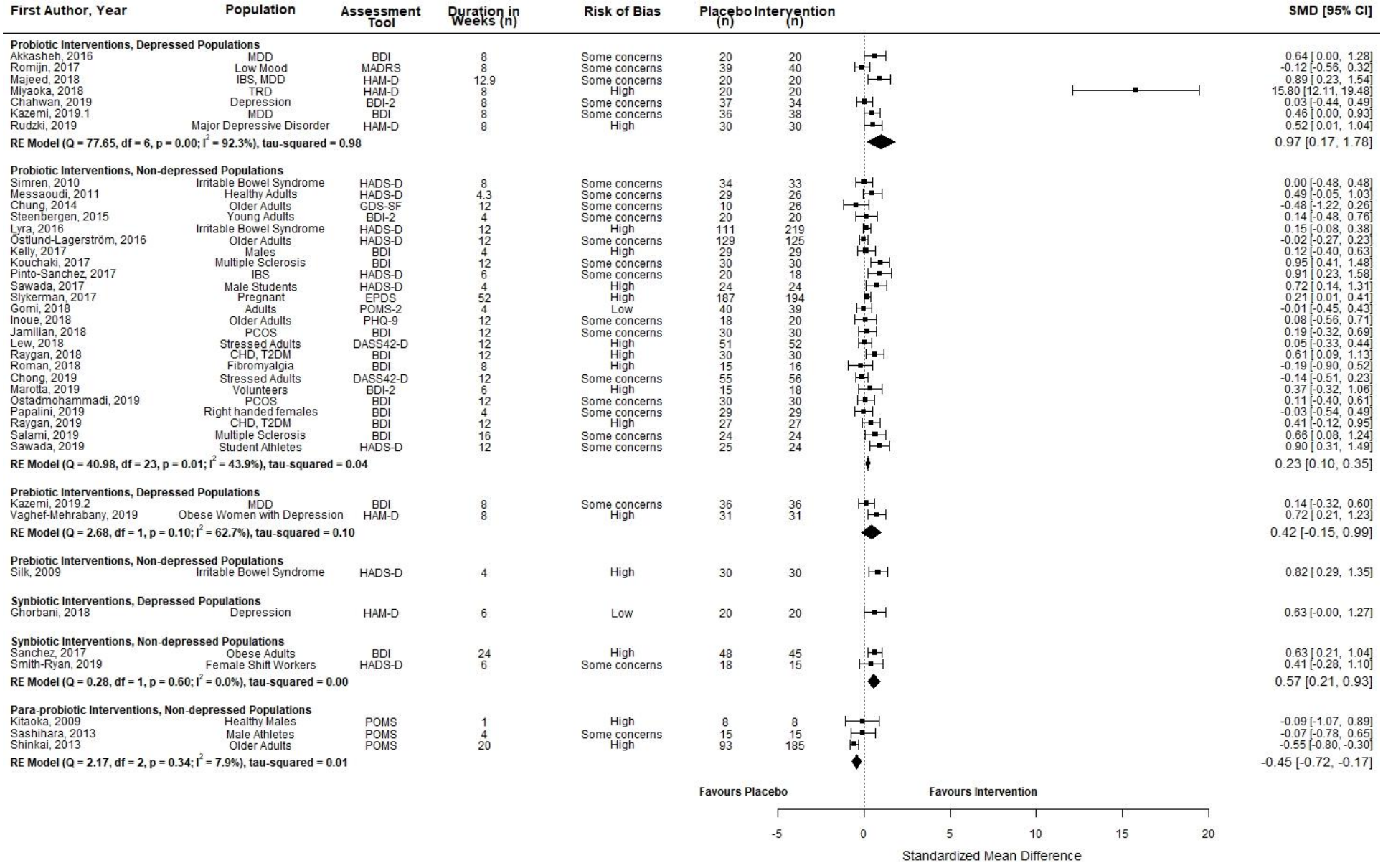

Figure 2. Forest plot.

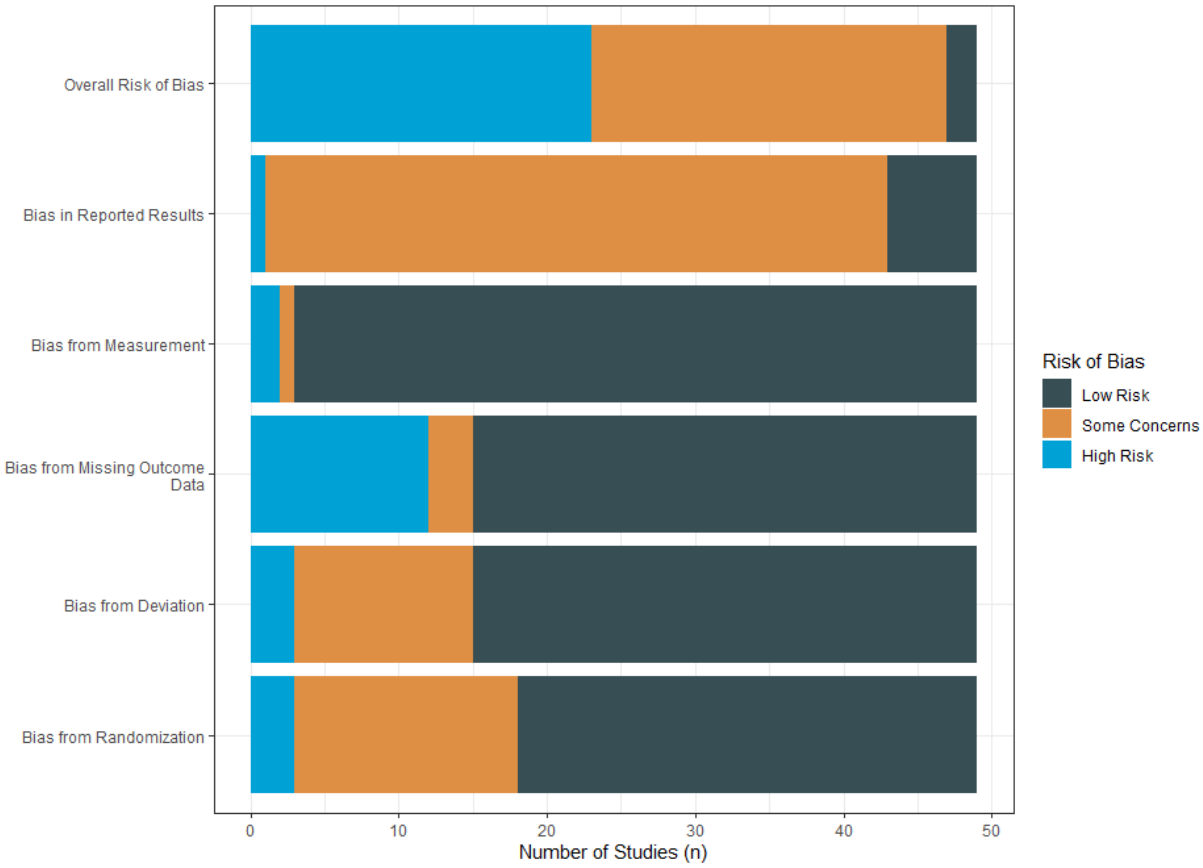

Figure 3. Risk of bias for included studies, assessed with Cochrane Risk of Bias 2.0 tool.

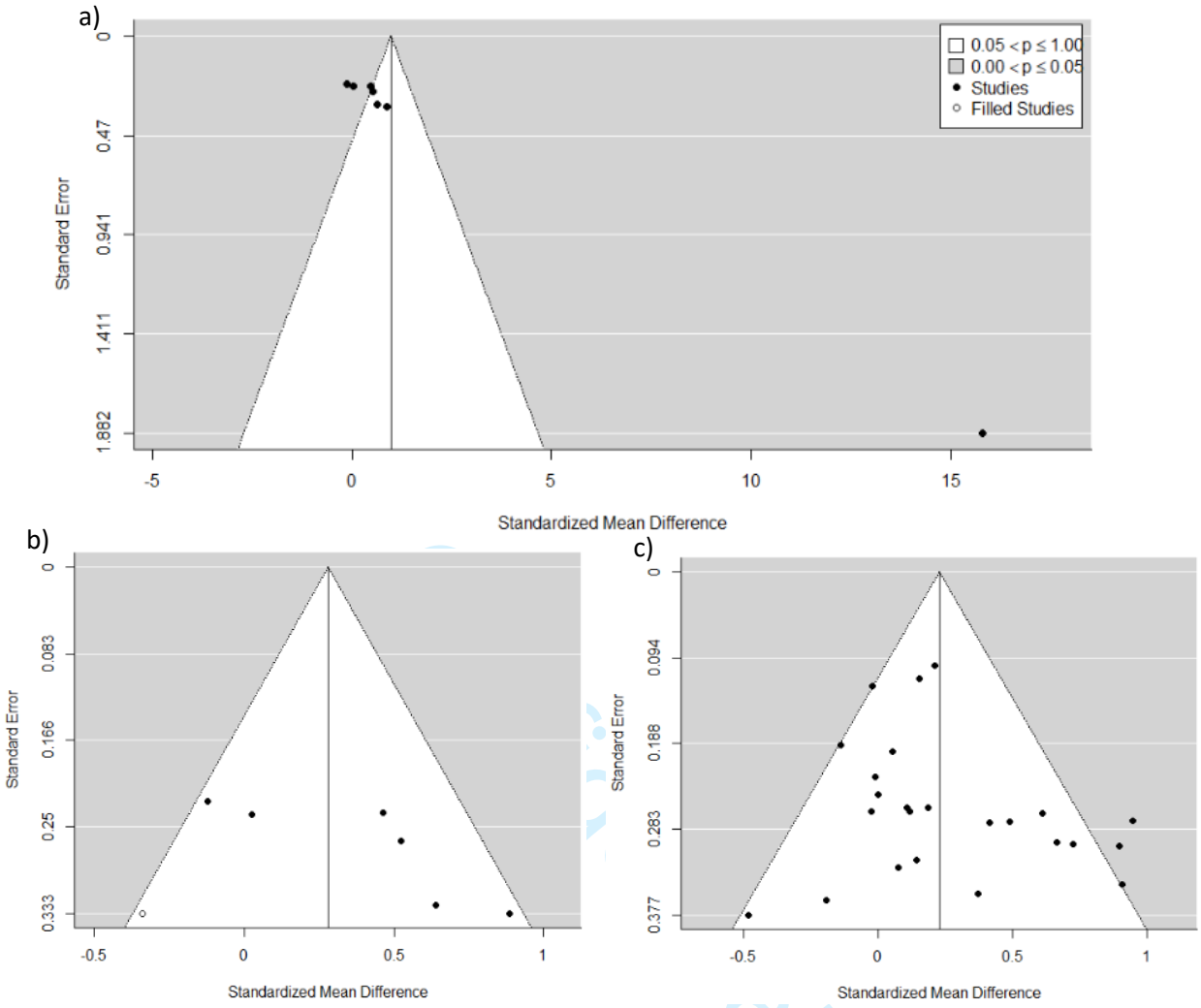

Figure 4. Funnel plots for assessment of publication bias in studies with a) probiotic interventions in depressed populations; b) probiotic interventions in depressed populations, excluding study by Miyaoka et al. (2018); and c) probiotic interventions in non-depressed populations.

Supplemental Appendices

Appendix 1: Search strategies

Appendix 2: Validated mental health outcomes in identified literature

Appendix 3: Excluded studies

Appendix 4: Included study characteristics

Appendix 5: Studies presenting insufficient information for inclusion in meta-analysis

Appendix 6: Risk of bias

Appendix 1: Search strategies

Medline

1. exp actinobacteria/
2. exp bacillus/
3. exp bacteroidetes/
4. exp bifidobacterium/
5. exp enterococcus/
6. fermentation/
7. exp firmicutes/
8. exp lactobacillaceae/
9. lactobacillus/
10. exp lactococcus/
11. exp leuconostoc/
12. exp microbiota/
13. probiotics/ or prebiotics/ or synbiotics/
14. exp saccharomyces cerevisiae proteins/
15. exp saccharomyces cerevisiae/
16. exp streptococcus/
17. (acidophilus or alistipes or allobaculum or bacillus or bacteroides or betabacteri* or bifidobacteri* or blautia or boulardii or clostriales or deferribacteres or desulfovibrio or enterococcus or ferment* or lachnospiraceae or lactobacill* or lactobacteri* or lactococcus or leuconostoc or leukonostoc or microbial or microbiome* or microbiota* or milk or mycobiome or oscillospira or periphyton or postbiotic* or prebiotic* or probiotic* or psychobiotic* or saccharomyces or streptococcus or synbiotic* or yeast* or yoghurt or yogourt or yogurt).tw,kf.
18. (((feces or faeces or fecal or faecal or stool or stools or bacteria or flora) adj2 (transplant* or enema or infusion or instillation or reconstitution or implantation)) or FMT).tw,kf.
19. ((alimentary or bowel or colon or digestive or enteric or faecal or faeces or fecal or gastro* or gut or intestinal or intestine* or intestinal or protobiotic or stomach) adj3 (flora or bacteria or bacterium or microbe or microbes or microflora or microorganism)).tw,kf.
20. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kf.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp anxiety disorders/ or anxiety/
23. exp autism spectrum disorder/
24. exp "bipolar and related disorders"/
25. exp cognition disorders/
26. exp dementia/
27. depression/
28. exp "Feeding and Eating Disorders"/
29. exp mood disorders/
30. exp Psychotic Disorders/
31. exp schizophrenia/
32. mental disorders/
33. exp neurocognitive disorders/
34. rett syndrome/
35. exp Stress Disorders, Traumatic/ or exp Stress, Psychological/
36. (agoraphobia or alzheimer* or anorexia or anxiety or asperger* or autism or autistic or binge eating disorder or bulimia or combat disorder* or dementia or depress* or eating disorder* or (Kanner* adj

syndrome) or manic or mania or mental retardation or obsessive compulsive or OCD or overinclusion or panic or paranoi* or personality disorder* or pervasive developmental disorder* or phobia* or phobic or PTSD or post-traumatic or posttraumatic or PPD or schizoaffective disorder or schizophrenia).tw,kf.
37. ((affective or cognitive or cognition or mental or mood or neurocognitive or psychiatric or psychic or psychological or mental or cognitive or cognition) adj2 (disorder* or disease* or dysfunction or disturbance* or illness or abnormality or problem* or incompeten* or defect* or deficit or disability or impairment or insufficiency or symptom*)).tw,kf.
38. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kf.
39. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kf.
40. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 21 and 40
42. animals/ not human/
43. 41 not 42
44. limit 43 to (english or french)
45. limit 44 to (comment or editorial or letter or news)
46. 44 not 45
47. limit 46 to case reports
48. 46 not 47

PsycINFO

1. (acidophilus or alistipes or allobaculum or bacillus or bacteroides or betabacteri* or bifidobacteri* or blautia or boulardii or clostriales or deferribacteres or desulfovibrio or enterococcus or ferment* or lachnospiraceae or lactobacill* or lactobacteri* or lactococcus or leuconostoc or leukonostoc or microbial or microbiome* or microbiota* or milk or mycobiome or oscillospira or periphyton or postbiotic* or prebiotic* or probiotic* or psychobiotic* or saccharomyces or streptococcus or synbiotic* or yeast* or yoghurt or yogourt or yogurt).tw.
2. (((feces or faeces or fecal or faecal or stool or stools or bacteria or flora) adj2 (transplant* or enema or infusion or instillation or reconstitution or implantation)) or FMT).tw.
3. ((alimentary or bowel or colon or digestive or enteric or faecal or faeces or fecal or gastro* or gut or intestinal or intestine* or intestinal or protobiotic or stomach) adj3 (flora or bacteria or bacterium or microbe or microbes or microflora or microorganism)).tw.
4. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw.
5. 1 or 2 or 3 or 4
6. exp Anxiety Disorders/ or exp Anxiety/
7. exp Autism Spectrum Disorders/
8. exp Bipolar Disorder/
9. exp cognitive impairment/
10. exp major depression/
11. exp eating disorders/
12. exp Affective Disorders/
13. exp Schizophrenia/ or exp Psychosis/
14. Mental Disorders/
15. exp Posttraumatic Stress Disorder/
16. exp Psychological Stress/
17. (agoraphobia or alzheimer* or anorexia or anxiety or asperger* or autism or autistic or binge eating disorder or bulimia or combat disorder* or dementia or depress* or eating disorder* or (Kanner* adj syndrome) or manic or mania or mental retardation or obsessive compulsive or OCD or overinclusion or

panic or paranoi* or personality disorder* or pervasive developmental disorder* or phobia* or phobic or PTSD or post-traumatic or posttraumatic or PPD or schizoaffective disorder or schizophrenia).tw.
18. ((affective or cognitive or cognition or mental or mood or neurocognitive or psychiatric or psychic or psychological or mental or cognitive or cognition) adj2 (disorder* or disease* or dysfunction or disturbance* or illness or abnormality or problem* or incompeten* or defect* or deficit or disability or impairment or insufficiency or symptom*)).tw.
19. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw.
20. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw.
21. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 5 and 21
23. limit 22 to animal
24. limit 22 to (animal and human)
25. 23 not 24
26. 22 not 25
27. limit 26 to (english or french)
28. limit 27 to (abstract collection or "column/opinion" or "comment/reply" or editorial or interview or letter or review-book or review-media or review-software & other)
29. 27 not 28
30. limit 29 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract")
31. 29 not 30

EMBASE
1. exp actinobacteria/
2. exp Bacillus/
3. exp Bacteroidetes/
4. exp Bifidobacterium/
5. exp Enterococcus/
6. exp Firmicutes/
7. exp Lactobacillaceae/
8. exp Lactobacillus/
9. exp Lactococcus/
10. exp Leuconostoc/
11. exp microflora/
12. probiotic agent/
13. prebiotic agent/
14. synbiotic agent/
15. exp "microbial products not classified elsewhere"/
16. Saccharomyces cerevisiae protein/
17. Saccharomyces cerevisiae/
18. exp Streptococcus/
19. (acidophilus or alistipes or allobaculum or bacillus or bacteroides or betabacteri* or bifidobacteri* or blautia or boulardii or clostriales or deferribacteres or desulfovibrio or enterococcus or ferment* or lachnospiraceae or lactobacill* or lactobacteri* or lactococcus or leuconostoc or leukonostoc or microbial or microbiome* or microbiota* or milk or mycobiome or oscillospira or periphyton or postbiotic* or prebiotic* or probiotic* or psychobiotic* or saccharomyces or streptococcus or synbiotic* or yeast* or yoghurt or yogourt or yogurt).tw,kw.

20. (((feces or faeces or fecal or faecal or stool or stools or bacteria or flora) adj2 (transplant* or enema or infusion or instillation or reconstitution or implantation)) or FMT).tw,kw.
21. ((alimentary or bowel or colon or digestive or enteric or faecal or faeces or fecal or gastro* or gut or intestinal or intestine* or intestinal or protobiotic or stomach) adj3 (flora or bacteria or bacterium or microbe or microbes or microflora or microorganism)).tw,kw.
22. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kw.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. exp anxiety disorder/ or exp autism/
25. exp anxiety/
26. exp bipolar disorder/
27. exp cognitive defect/
28. exp dementia/
29. exp depression/
30. exp eating disorder/
31. exp mood disorder/
32. exp psychosis/
33. exp schizophrenia/
34. mental disease/
35. exp "disorders of higher cerebral function"/
36. posttraumatic stress disorder/
37. mental stress/
38. (agoraphobia or alzheimer* or anorexia or anxiety or asperger* or autism or autistic or binge eating disorder or bulimia or combat disorder* or dementia or depress* or eating disorder* or (Kanner* adj syndrome) or manic or mania or mental retardation or obsessive compulsive or OCD or overinclusion or panic or paranoi* or personality disorder* or pervasive developmental disorder* or phobia* or phobic or PTSD or post-traumatic or posttraumatic or PPD or schizoaffective disorder or schizophrenia).tw,kw.
39. ((affective or cognitive or cognition or mental or mood or neurocognitive or psychiatric or psychic or psychological or mental or cognitive or cognition) adj2 (disorder* or disease* or dysfunction or disturbance* or illness or abnormality or problem* or incompeten* or defect* or deficit or disability or impairment or insufficiency or symptom*)).tw,kw.
40. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kw.
41. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kw.
42. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. 23 and 42
44. limit 43 to animal studies
45. limit 43 to (human and animal studies)
46. 44 not 45
47. 43 not 46
48. limit 47 to (english or french)
49. limit 48 to (conference abstract or editorial or letter)
50. 48 not 49
51. exp case study/
52. 50 not 51

DARE

1. (acidophilus or alistipes or allobaculum or bacillus or bacteroides or betabacteri* or bifidobacteri* or blautia or boulardii or clostriales or deferribacteres or desulfovibrio or enterococcus or ferment* or lachnospiraceae or lactobacill* or lactobacteri* or lactococcus or leuconostoc or leukonostoc or microbial or microbiome* or microbiota* or milk or mycobiome or oscillospira or periphyton or postbiotic* or prebiotic* or probiotic* or psychobiotic* or saccharomyces or streptococcus or synbiotic* or yeast* or yoghurt or yogourt or yogurt).tw,kf.
2. (((feces or faeces or fecal or faecal or stool or stools or bacteria or flora) adj2 (transplant* or enema or infusion or instillation or reconstitution or implantation)) or FMT).tw,kf.
3. ((alimentary or bowel or colon or digestive or enteric or faecal or faeces or fecal or gastro* or gut or intestinal or intestine* or intestinal or protobiotic or stomach) adj3 (flora or bacteria or bacterium or microbe or microbes or microflora or microorganism)).tw,kf.
4. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kf.
5. (agoraphobia or alzheimer* or anorexia or anxiety or asperger* or autism or autistic or binge eating disorder or bulimia or combat disorder* or dementia or depress* or eating disorder* or (Kanner* adj syndrome) or manic or mania or mental retardation or obsessive compulsive or OCD or overinclusion or panic or paranoi* or personality disorder* or pervasive developmental disorder* or phobia* or phobic or PTSD or post-traumatic or posttraumatic or PPD or schizoaffective disorder or schizophrenia).tw,kf.
6. ((affective or cognitive or cognition or mental or mood or neurocognitive or psychiatric or psychic or psychological or mental or cognitive or cognition) adj2 (disorder* or disease* or dysfunction or disturbance* or illness or abnormality or problem* or incompeten* or defect* or deficit or disability or impairment or insufficiency or symptom*)).tw,kf.
7. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kf.
8. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kf.
9. 1 or 2 or 3 or 4
10. 5 or 6 or 7 or 8
11. 9 and 10

Cochrane Database of Systematic Reviews

1. (acidophilus or alistipes or allobaculum or bacillus or bacteroides or betabacteri* or bifidobacteri* or blautia or boulardii or clostriales or deferribacteres or desulfovibrio or enterococcus or ferment* or lachnospiraceae or lactobacill* or lactobacteri* or lactococcus or leuconostoc or leukonostoc or microbial or microbiome* or microbiota* or milk or mycobiome or oscillospira or periphyton or postbiotic* or prebiotic* or probiotic* or psychobiotic* or saccharomyces or streptococcus or synbiotic* or yeast* or yoghurt or yogourt or yogurt).tw,kf.
2. (((feces or faeces or fecal or faecal or stool or stools or bacteria or flora) adj2 (transplant* or enema or infusion or instillation or reconstitution or implantation)) or FMT).tw,kf.
3. ((alimentary or bowel or colon or digestive or enteric or faecal or faeces or fecal or gastro* or gut or intestinal or intestine* or intestinal or protobiotic or stomach) adj3 (flora or bacteria or bacterium or microbe or microbes or microflora or microorganism)).tw,kf.
4. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kf.
5. (agoraphobia or alzheimer* or anorexia or anxiety or asperger* or autism or autistic or binge eating disorder or bulimia or combat disorder* or dementia or depress* or eating disorder* or (Kanner* adj syndrome) or manic or mania or mental retardation or obsessive compulsive or OCD or overinclusion or

panic or paranoi* or personality disorder* or pervasive developmental disorder* or phobia* or phobic or PTSD or post-traumatic or posttraumatic or PPD or schizoaffective disorder or schizophrenia).tw,kf.
6. ((affective or cognitive or cognition or mental or mood or neurocognitive or psychiatric or psychic or psychological or mental or cognitive or cognition) adj2 (disorder* or disease* or dysfunction or disturbance* or illness or abnormality or problem* or incompeten* or defect* or deficit or disability or impairment or insufficiency or symptom*)).tw,kf.
7. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kf.
8. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kf.
9. 1 or 2 or 3 or 4
10. 5 or 6 or 7 or 8
11. 9 and 10
12. limit 11 to (withdrawn records and protocols)
13. 11 not 12

Cochrane Central Register of Controlled Trials
1. exp actinobacteria/
2. exp bacillus/
3. exp bacteroidetes/
4. exp bifidobacterium/
5. exp enterococcus/
6. fermentation/
7. exp firmicutes/
8. exp lactobacillaceae/
9. lactobacillus/
10. exp lactococcus/
11. exp leuconostoc/
12. exp microbiota/
13. probiotics/ or prebiotics/ or synbiotics/
14. exp saccharomyces cerevisiae proteins/
15. exp saccharomyces cerevisiae/
16. exp streptococcus/
17. (acidophilus or alistipes or allobaculum or bacillus or bacteroides or betabacteri* or bifidobacteri* or blautia or boulardii or clostriales or deferribacteres or desulfovibrio or enterococcus or ferment* or lachnospiraceae or lactobacill* or lactobacteri* or lactococcus or leuconostoc or leukonostoc or microbial or microbiome* or microbiota* or milk or mycobiome or oscillospira or periphyton or postbiotic* or prebiotic* or probiotic* or psychobiotic* or saccharomyces or streptococcus or synbiotic* or yeast* or yoghurt or yogourt or yogurt).tw,kf.
18. (((feces or faeces or fecal or faecal or stool or stools or bacteria or flora) adj2 (transplant* or enema or infusion or instillation or reconstitution or implantation)) or FMT).tw,kf.
19. ((alimentary or bowel or colon or digestive or enteric or faecal or faeces or fecal or gastro* or gut or intestinal or intestine* or intestinal or protobiotic or stomach) adj3 (flora or bacteria or bacterium or microbe or microbes or microflora or microorganism)).tw,kf.
20. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kf.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. exp anxiety disorders/ or anxiety/
23. exp autism spectrum disorder/
24. exp "bipolar and related disorders"/
25. exp cognition disorders/
26. exp dementia/
27. depression/
28. exp "Feeding and Eating Disorders"/
29. exp mood disorders/
30. exp Psychotic Disorders/
31. exp schizophrenia/
32. mental disorders/
33. exp neurocognitive disorders/
34. rett syndrome/
35. exp Stress Disorders, Traumatic/ or exp Stress, Psychological/
36. (agoraphobia or alzheimer* or anorexia or anxiety or asperger* or autism or autistic or binge eating disorder or bulimia or combat disorder* or dementia or depress* or eating disorder* or (Kanner* adj syndrome) or manic or mania or mental retardation or obsessive compulsive or OCD or overinclusion or panic or paranoi* or personality disorder* or pervasive developmental disorder* or phobia* or phobic or PTSD or post-traumatic or posttraumatic or PPD or schizoaffective disorder or schizophrenia).tw,kf.
37. ((affective or cognitive or cognition or mental or mood or neurocognitive or psychiatric or psychic or psychological or mental or cognitive or cognition) adj2 (disorder* or disease* or dysfunction or disturbance* or illness or abnormality or problem* or incompeten* or defect* or deficit or disability or impairment or insufficiency or symptom*)).tw,kf.
38. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kf.
39. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kf.
40. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 21 and 40
42. animals/ not human/
43. 41 not 42
44. limit 43 to (english or french)

Appendix 2: Validated mental health outcomes in identified literature

Scale	Abbreviation	Validating Publication Citation
Beck Depression Inventory	BDI	Schotte CKW, Maes M, Cluydts R, De Doncker D, Cosyns P. Construct validity of the Beck Depression Inventory in a depressive population. Journal of Affective Disorders. 1997;46(2):115-125.
Beck Depression Inventory-II	BDI-2	Steer RA, Ball R, Ranieri WF, Beck AT. Further Evidence for the Construct Validity of the Beck Depression Inventory-II with Psychiatric Outpatients. Psychological Reports. 1997;80(2):443-446.
Centre for Epidemiological Studies Depression Scale	CES-D	Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psychological Measurement. 1977;1(3):385-401.
Depression Anxiety Stress Scales – 21 Items, Depression Scale	DASS21-D	Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. British Journal of Clinical Psychology. 2005;44(2):227-239.
Depression Anxiety Stress Scales – 42 Items, Depression Scale	DASS42-D	Crawford JR, Henry JD. The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample. British Journal of Clinical Psychology. 2003;42(2):111-131.
Edinburgh Postnatal Depression Scale	EPDS	Adouard F, Glangeaud-Freudenthal NMC, Golse B. Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of women with high-risk pregnancies in France. Archives of Women's Mental Health. 2005;8:89-95.
Geriatric Depression Scale – Short Form	GDS-SF	Durmaz B, Soysal P, Ellidokuz H, Isik AT. Validity and reliability of geriatric depression scale-15 (short form) in Turkish older adults. Northern Clinics of Istanbul. 2018;5(3):216-220.
Hospital Anxiety and Depression Scale – Depression Scale	HADS-D	Djukanovic I, Carlsson J, Årestedt K. Is the Hospital Anxiety and Depression Scale (HADS) a valid measure in a general population 65-80 years old? A psychometric evaluation study. Health and Quality of Life Outcomes. 2017;15(193):10.
Hamilton Depression Rating Scale	HAM-D	Dozois DJA. The Psychometric Characteristics of the Hamilton Depression Inventory. Journal of Personality Assessment. 2003;80(1):31-40.
Leiden Index of Depression Sensitivity - Revised	LEIDS-R	Figueroa CA, Mocking RJT, Mahmoud GA, et al. The measurement of cognitive reactivity to sad mood in patients remitted from major depressive disorder. British Journal of Clinical Psychology. 2018;57:313-327.
Montgomery- Åsberg Depression Scale	MADRS	Davidson J, Turnbull CD, Strickland R, Miller R, Graves K. The Montgomery-Åsberg Depression Scale: reliability and

		validity. Acta Psychiatrica Scandinavica. 1986;73:544-548.
Patient Health Questionnaire - 9	PHQ-9	Martin A, Rief W, Klaiberg A, Braehler E. Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population. General Hospital Psychiatry. 2006;28:71-77.
Profile of Mood States	POMS	Gibson SJ. The Measurement of Mood States in Older Adults. Journal of Gerontology: Psychological Sciences. 1997;52B(4):167-174.
Profile of Mood States – 2nd Edition	POMS2	Lin S, Hsiao Y-Y, Wang M. Test Review: The Profile of Mood States 2nd Edition. Journal of Psychoeducational Assessment. 2014;32(3):273-277.
Quick Inventory of Depressive Symptomatology	QIDS	Ma X-R, Hou C-L, Zang Y, et al. Could the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) be used in depressed schizophrenia patients? Journal of Affective Disorders. 2015;172:191-194.
Zung Self-Rating Depression Scale	Zung SDS	Jegede RO. Psychometric Properties of the Self-Rating Depression Scale (SDS). The Journal of Psychology. 1976;93:27-30.

Appendix 3: Excluded studies

Author Name	Reason for Exclusion
Abbas et al. (2014)[1]	Outcome not of interest
Agahi et al. (2018)[2]	Outcome not of interest
Agosta et al. (2011)[3]	Outcome not of interest
Akbari et al. (2016)[4]	Outcome not of interest
Alipour et al. (2014)[5]	Duplicate of included study
Allaert et al. (2016)[6]	Outcome not of interest
Allen et al. (2016)[7]	Outcome not of interest
Arnold et al. (2018)[8]	Conference proceeding
Aydin et al. (2019)[9]	Study design not of interest
Azpiroz et al. (2017)[10]	Duplicate of included study
Bambling et al. (2017)[11]	Study design not of interest
Bannaga et al. (2017)[12]	Conference proceeding
Barthow et al. (2016)[13]	Study design not of interest
Begtrup et al. (2013)[14]	Outcome not of interest
Benjamin et al. (2011)[15]	Outcome not of interest
Blondel et al. (2018)[16]	Study design not of interest
Buie et al. (2015)[17]	Study design not of interest
Carlsson et al. (2009)[18]	Outcome not of interest
Caso et al. (2016)[19]	Intervention not of interest
Ceccarelli et al. (2017)[20]	Outcome not of interest
Ceccarelli et al. (2017)[21]	Study design not of interest
Cepeda et al. (2017)[22]	Study design not of interest
Clapp et al. (2017)[23]	Study design not of interest
Clark et al. (2016)[24]	Study design not of interest
Colica et al. (2017)[25]	Outcome not of interest
Culpepper et al. (2016)[26]	Outcome not of interest
Dapoigny et al. (2012)[27]	Outcome not of interest
Darbaky et al. (2017)[28]	Not an adult population
De Lorenzo et al. (2017)[29]	Outcome not of interest
Dickerson et al. (2014)[30]	Duplicate of included study
Dinan et al. (2011)[31]	Study design not of interest
Dinan et al. (2018)[32]	Study design not of interest
Diop et al. (2008)[33]	Outcome not of interest
Dubberke et al. (2016)[34]	Outcome not of interest
Dubinkina et al. (2017)[35]	Study design not of interest
Dughera et al. (2007)[36]	Outcome not of interest
Farhangi et al. (2018)[37]	Outcome not of interest
Feher et al. (2014)[38]	Study design not of interest
Gerasimov et al. (2018)[39]	Not an adult population

Gertenrich et al. (1970)[40]	Outcome not of interest
Ghaderi et al. (2019)[41]	Duplicate of included study
Grimaldi et al. (2018)[42]	Not an adult population
Guglielmetti et al. (2011)[43]	Outcome not of interest
Guyonnet et al. (2007)[44]	Outcome not of interest
Han et al. (2017)[45]	Comparator not of interest
Hilimire et al. (2015)[46]	Intervention not of interest
Hwang et al. (2019)[47]	Outcome not of interest
Itzhaki et al. (2016)[48]	Study design not of interest
Jacka et al. (2019)[49]	Study design not of interest
Jaatinen et al. (2014)[50]	Intervention not of interest
Jiang et al. (2018)[51]	Study design not of interest
Jiang et al. (2018)[52]	Outcome not of interest
Jicha et al. (2015)[53]	Conference proceeding
Julianelle et al. (1923)[54]	Outcome not of interest
Jung-Park et al. (2019)[55]	Outcome not of interest
Kao et al. (2017)[56]	Outcome not of interest
Karadaq et al. (2012)[57]	Conference proceeding
Kato-Kataoka et al. (2016)[58]	Outcome not of interest
Kazemi et al. (2019)[59]	Duplicate of included study
Kim et al. (2002)[60]	Outcome not of interest
Kim et al. (2018)[61]	Study design not of interest
Kim et al. (2019)[62]	Outcome not of interest
Kleiman et al. (2015)[63]	Intervention not of interest
Kleiman et al. (2017)[64]	Intervention not of interest
Kleiman et al. (2017)[65]	Not an adult population
Kobayashi et al. (2019)[66]	Study design not of interest
Kreijkamp-Kaspers et al. (2004)[67]	Intervention not of interest
Kretzschmar (2017)[68]	Study design not of interest
Krug et al. (2019)[69]	Conference proceeding
Kurokawa et al. (2018)[70]	Study design not of interest
Langkamp-Henken et al. (2015)[71]	Outcome not of interest
Lecerf (2018)[72]	Study design not of interest
Lee et al. (2014)[73]	Intervention not of interest
Legette et al. (2019)[74]	Conference proceeding
Liu et al. (2016)[75]	Outcome not of interest
Lorenzo-Zuniga et al. (2014)[76]	Outcome not of interest
Ma et al. (2019)[77]	Study design not of interest
Marcos et al. (2004)[78]	Outcome not of interest
Mazzawi et al. (2018)[79]	Study design not of interest
Messaoudi et al. (2011)[80]	Duplicate of included study

Mi et al. (2015)[81]	Not an adult population
Miyaoka et al. (2018)[82]	Duplicate of included study
Mohammadi et al. (2016)[83]	Intervention not of interest
Moller et al. (2017)[84]	Duplicate of included study
Morita et al. (2016)[85]	Outcome not of interest
Morita et al. (2017)[86]	Comparator not of interest
Mucci et al. (2006)[87]	Outcome not of interest
Nagamine et al. (2018)[88]	Outcome not of interest
Nagamine et al. (2018)[89]	Outcome not of interest
Nakakita et al. (2016)[90]	Outcome not of interest
Nishida et al. (2017)[91]	Outcome not of interest
Nishihara et al. (2014)[92]	Outcome not of interest
Noorwali et al. (2017)[93]	Conference proceeding
Nova et al. (2006)[94]	Not an adult population
Okubo et al. (2019)[95]	Study design not of interest
Ostlund-Lagerstrom et al. (2016)[96]	Duplicate of included study
Paulsen et al. (2017)[97]	Intervention not of interest
Perez-Cornago et al. (2016)[98]	Intervention not of interest
Peter et al. (2018)[99]	Intervention not of interest
Prantera et al. (2002)[100]	Outcome not of interest
Quigley et al. (2009)[101]	Study design not of interest
Rao et al. (2018)[102]	Study design not of interest
Reale et al. (2012)[103]	Outcome not of interest
Reininghaus et al. (2018)[104]	Study design not of interest
Roman et al. (2017)[105]	Study design not of interest
Rong et al. (2019)[106]	Intervention not of interest
Sanborn et al. (2018)[107]	Study design not of interest
Schmidt et al. (2015)[108]	Outcome not of interest
Severance et al. (2016)[109]	Intervention not of interest
Severance et al. (2017) [110]	Outcome not of interest
Shafaghi et al. (2016)[111]	Outcome not of interest
Siddiqui et al. (2013)[112]	Study design not of interest
Singh et al. (2016)[113]	Study design not of interest
Smith et al. (2015)[114]	Outcome not of interest
Soldi et al. (2019)[115]	Outcome not of interest
Stevenson et al. (2014)[116]	Outcome not of interest
Stokes et al. (2015)[117]	Conference proceeding
Takada et al. (2017)[118]	Study design not of interest
Takada et al. (2016)[119]	Study design not of interest
Talbott et al. (2018)[120]	Conference proceeding
Tamtaji et al. (2018) [121]	Outcome not of interest

Tazzyman et al. (2015)[122]	Outcome not of interest
Tomasik et al. (2015)[123]	Outcome not of interest
Tran et al. (2019)[124]	Outcome not of interest
Uemura et al. (2019)[125]	Intervention not of interest
Urita et al. (2015)[126]	Not an adult population
Vaghef-Mehrabany et al. (2014)[127]	Outcome not of interest
Vaghef-Mehrabany et al. (2016)[128]	Outcome not of interest
Valles-Colomer et al. (2019)[129]	Intervention not of interest
Vulevic et al. (2018)[130]	Outcome not of interest
Wallace et al. (2018)[131]	Conference proceeding
Wang et al. (2018)[132]	Outcome not of interest
Wang et al. (2019)[133]	Intervention not of interest
Westfall et al. (2018)[134]	Study design not of interest
Wilson et al. (2018)[135]	Intervention not of interest
Xia et al. (2018)[136]	Outcome not of interest
Yang et al. (2016)[137]	Outcome not of interest
Yi et al. (2016)[138]	Study design not of interest
Yuan et al. (2015)[139]	Intervention not of interest
Yuan et al. (2018)[140]	Study design not of interest
Zamudio-Tiburcio et al. (2017)[141]	Not English or French
Zhang et al. (2013)[142]	Study design not of interest

1. Abbas Z, Yakoob J, Jafri W, et al. Cytokine and clinical response to Saccharomyces boulardii therapy in diarrhea-dominant irritable bowel syndrome: a randomized trial. *European Journal of Gastroenterology & Hepatology.* 2014;26(6):630-639.
2. Agahi A, Hamidi GA, Daneshvar R, et al. Does Severity of Alzheimer's Disease Contribute to Its Responsiveness to Modifying Gut Microbiota? A Double Blind Clinical Trial. *Front Neurol.* 2018;9:662.
3. Agosta C, Atlante M, Benvenuti C. Randomized controlled study on clinical efficacy of isoflavones plus lactobacilli, associated or not with a natural anxiolytic agent in menopause. *Minerva Ginecologica.*63(1):9.
4. Akbari E, Asemi Z, Daneshvar Kakhaki R, et al. Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front Aging Neurosci.* 2016;8.
5. Alipour B, Homayouni-Rad A, Vaghef-Mehrabany E, et al. Effects of *Lactobacillus casei* supplementation on disease activity and inflammatory cytokines in rheumatoid arthritis patients: a randomized double-blind clinical trial. *International Journal of Rheumatic Diseases.* 2014;17:519-527.
6. Allaert FA, Courau S, Forestier A. Effect of magnesium, probiotic, and vitamin food supplementation in healthy subjects with psychological stress and evaluation of a persistent effect after discontinuing intake. *Panminerva Medica.* 2016;58(4):8.
7. Allen AP, Hutch W, Borre YE, et al. Bifidobacterium longum 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers. *Transl Psychiatry.* 2016;6(11):e939-e939.

8. Arnold LE. Placebo-Controlled Pilot Data for Three Complementary/Alternative Treatments in Autism. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2018;57(10):S117.
9. Aydin MA, Agirbas EP, Aydin S. Can disruption of microbiota composition be the chemical basis of Parkinson's disease and schizophrenia? *Bioscience of Microbiota, Food and Health.* 2019;38(1):1-2.
10. Azpiroz F, Dubray C, Bernalier-Donadille A, et al. Effects of scFOS on the composition of fecal microbiota and anxiety in patients with irritable bowel syndrome: a randomized, double blind, placebo controlled study. *Neurogastroenterol Motil.* 2017;29(2):e12911.
11. Bambling M, Edwards SC, Hall S, Vitetta L. A combination of probiotics and magnesium orotate attenuate depression in a small SSRI resistant cohort: an intestinal anti-inflammatory response is suggested. *Inflammopharmacol.* 2017;25(2):271-274.
12. Bannaga A, Widlak MM, Tehami N, et al. Probiotics' Effects on Perception of Health and Bowel Frequency: A Double Blind Randomized Placebo Controlled Clinical Trial. *Gastroenterology.* 2017;152(5):S819.
13. Barthow C, Wickens K, Stanley T, et al. The Probiotics in Pregnancy Study (PiP Study): rationale and design of a double-blind randomised controlled trial to improve maternal health during pregnancy and prevent infant eczema and allergy. *BMC Pregnancy and Childbirth.* 2016;16(1):133.
14. Begtrup LM, de Muckadell OBS, Kjeldsen J, Christensen Rd, Jarbøl DE. Long-term treatment with probiotics in primary care patients with irritable bowel syndrome – a randomised, double-blind, placebo controlled trial. *Scandinavian Journal of Gastroenterology.* 2013;48(10):1127-1135.
15. Benjamin JL, Hedin CRH, Koutsoumpas A, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. *Gut.* 2011;60(7):923-929.
16. Blondel N. Des probiotiques pour eviter une rehospitalisation pour decompensation maniaque chez les patients bipolaires? *Revue medicale Suisse.* 2018.
17. Buie T. Potential Etiologic Factors of Microbiome Disruption in Autism. *Clinical Therapeutics.* 2015;37(5):976-983.
18. Carlsson M, Gustafson Y, Haglin L, Eriksson S. The Feasibility of Serving Liquid Yoghurt Supplemented with Probiotic Bacteria, *Lactobacills rhamnosus* LB 21, and *Lactococcus lactis* L1A - A Pilot Study Among Old People with Dementia in a Residential Care Facility. *The Journal of Nutrition.* 2009;13(9):7.
19. Caso JR, Balanza-Martinez V, Palaomo T, Garcia-Bueno B. The microbiota and gut-brain axis: contributions to the immunopathogenesis of schizophrenia. *Current Pharmaceutical Design.* 2016;22:6122-6133.
20. Ceccarelli G, Brenchley J, Cavallari E, et al. Impact of High-Dose Multi-Strain Probiotic Supplementation on Neurocognitive Performance and Central Nervous System Immune Activation of HIV-1 Infected Individuals. *Nutrients.* 2017;9(11):1269.
21. Ceccarelli G, Fratino M, Selvaggi C, et al. A pilot study on the effects of probiotic supplementation on neuropsychological performance and microRNA-29a-c levels in antiretroviral-treated HIV-1-infected patients. *Brain and Behavior.* 2017;7(8):e00756.
22. Cepeda MS, Katz EG, Blacketer C. Microbiome-Gut-Brain Axis: Probiotics and Their Association With Depression. *The Journal of Neuropsychiatry and Clinical Neurosciences.* 2017;29(1):39-44.
23. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: the gut-brain axis. *Clinics and Practice.* 2017;7(4).
24. Clark A, Mach N. Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes. *Journal of the International Society of Sports Nutrition.* 2016;13(1):43.

25. Colica C, Avolio E, Bollero P, et al. Evidences of a New Psychobiotic Formulation on Body Composition and Anxiety. *Mediators of Inflammation.* 2017;2017:1-10.
26. Culpepper T, Christman MC, Nieves C, et al. *Bifidobacterium bifidum* R0071 decreases stress-associated diarrhoea-related symptoms and self-reported stress: a secondary analysis of a randomised trial. *Beneficial Microbes.* 2016;7(3):327-336.
27. Dapoigny M. Efficacy and safety profile of LCR35 complete freeze-dried culture in irritable bowel syndrome: A randomized, double-blind study. *WJG.* 2012;18(17):2067.
28. Darbaky Y, Evrard B, Patrier S, et al. Oral probiotic treatment of *Lactobacillus rhamnosus* Lcr35 ® prevents visceral hypersensitivity to a colonic inflammation and an acute psychological stress. *Journal of Applied Microbiology.* 2017;122(1):188-200.
29. De Lorenzo A, Costacurta M, Merra G, et al. Can psychobiotics intake modulate psychological profile and body composition of women affected by normal weight obese syndrome and obesity? A double blind randomized clinical trial. *J Transl Med.* 2017;15(1):135.
30. Dickerson FB, Stallings C, Origoni A, et al. Effect of Probiotic Supplementation on Schizophrenia Symptoms and Association With Gastrointestinal Functioning: A Randomized, Placebo-Controlled Trial.12.
31. Dinan TG, Quigley EM. Probiotics in the Treatment of Depression: Science or Science Fiction? *Australian & New Zealand Journal of Psychiatry.* 2011;45(12):1023-1025.
32. Dinan TG, Cryan JF. Schizophrenia and the microbiome: Time to focus on the impact of antipsychotic treatment on the gut microbiota. *The World Journal of Biological Psychiatry.* 2018;19(8):568-570.
33. Diop L, Guillou S, Durand H. Probiotic food supplement reduces stress-induced gastrointestinal symptoms in volunteers: a double-blind, placebo-controlled, randomized trial. *Nutrition Research.* 2008;28(1):1-5.
34. Orenstein R, Dubberke E, Hardi R, et al. Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent *Clostridium difficile* Infection: Results of the PUNCH CD Study. *Clinical Infectious Diseases.* 2016;62(5):596-602.
35. Dubinkina VB, Tyakht AV, Odintsova VY, et al. Links of gut microbiota composition with alcohol dependence syndrome and alcoholic liver disease. *Microbiome.* 2017;5(1):141.
36. Dughera L, Elia C, Navino M, Cisarò F. Effects of symbiotic preparations on constipated irritable bowel syndrome symptoms.6.
37. Farhangi MA, Javid AZ, Sarmadi B, Karimi P, Dehghan P. A randomized controlled trial on the efficacy of resistant dextrin, as functional food, in women with type 2 diabetes: Targeting the hypothalamic–pituitary–adrenal axis and immune system. *Clinical Nutrition.* 2018;37(4):1216-1223.
38. Feher J, Pinter E, Kovács I, et al. Irritable Eye Syndrome: Neuroimmune Mechanisms and Benefits of Selected Nutrients. *The Ocular Surface.* 2014;12(2):134-145.
39. Gerasimov S, Gantzel J, Dementieva N, et al. Role of Lactobacillus rhamnosus (FloraActive™) 19070-2 and Lactobacillus reuteri (FloraActive™) 12246 in Infant Colic: A Randomized Dietary Study. *Nutrients.* 2018;10(12):1975.
40. Gertenrich RL, Hart RW. Treatment of oral ulcerations with Bacid (Lactobacillus acidophilus). *Oral Surgery, Oral Medicine, Oral Pathology.* 1970;30(2):196-200.
41. Ghaderi A, Banafshe HR, Mirhosseini N, et al. Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients. *BMC Psychiatry.* 2019;19(1):77.
42. Grimaldi R, Gibson GR, Vulevic J, et al. A prebiotic intervention study in children with autism spectrum disorders (ASDs). *Microbiome.* 2018;6(1):133.
43. Guglielmetti S, Mora D, Gschwender M, Popp K. Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life --

a double-blind, placebo-controlled study: Randomised clinical trial: B. bifidum MIMBb75 in IBS. *Alimentary Pharmacology & Therapeutics.* 2011;33(10):1123-1132.

44. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial: PROBIOTICS AND IRRITABLE BOWEL SYNDROME IN ADULTS. *Alimentary Pharmacology & Therapeutics.* 2007;26(3):475-486.
45. Han K, Wang J, Seo J-G, Kim H. Efficacy of double-coated probiotics for irritable bowel syndrome: a randomized double-blind controlled trial. *Journal of Gastroenterology.* 2017;52(4):432-443.
46. Hilimire MR, DeVylder JE, Forestell CA. Fermented foods, neuroticism, and social anxiety: An interaction model. *Psychiatry Research.* 2015;228(2):203-208.
47. Hwang Y-H, Park S, Paik J-W, et al. Efficacy and Safety of Lactobacillus Plantarum C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients.* 2019;11(2):305.
48. Itzhaki RF, Lathe R, Balin BJ, et al. Microbes and Alzheimer's Disease. *Journal of Alzheimer's Disease.* 2016;51(4):979-984.
49. Jacka FN. Targeting the gut to achieve improved outcomes in mood disorders. *Bipolar Disorders.* 2019;21(1):88-89.
50. Jaatinen N, Korpela R, Poussa T, et al. Effects of daily intake of yoghurt enriched with bioactive components on chronic stress responses: a double-blinded randomized controlled trial. *International Journal of Food Sciences and Nutrition.* 2014;65(4):507-514.
51. Jiang Hy, Xu Ll, Zhang X, Zhang Z, Ruan B. The Microbiome in Bipolar Depression: A Longitudinal Study of One Pair of Monozygotic Twins. *Bipolar Disorders.* 2018:bdi.12736.
52. Jiang L, Zhu W. Probiotics improved the effectiveness and safety of the quadruple Helicobacter pylori eradication therapy. *Biomedical Research.* 2018;29(10).
53. Jicha GA, Abner EL, Kryscio RJ, et al. A phase i, randomized, double-blind, placebo-controlled, multiple ascending dose study of AT-001 yeast selenium for the prevention of Alzheimer's disease. *Alzheimer's & Dementia.* 2015;11(7):P471.
54. Julianelle LA. Implantation of *Bacillus acidophilus* in Persons with Psychoses. *Archives of Neurology And Psychiatry.* 1923;9(6):769.
55. Jung Park H, Shim HS, Lee GR, et al. A randomized, double-blind, placebo-controlled study on the memory-enhancing effect of lactobacillus fermented Saccharina japonica extract. *European Journal of Integrative Medicine.* 2019;28:39-46.
56. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *JAMA.* 2017;318(20):1985.
57. Karadag N, Dilli D, Dursun A, et al. Treament of infantile colic with lactobacillus reuteri and the relationship with postpartum depression: a randomized controlled trial study. *Archives of Diseases in Childhood.* 2012;97.
58. Kato-Kataoka A, Nishida K, Takada M, et al. Fermented milk containing *Lactobacillus casei* strain Shirota prevents the onset of physical symptoms in medical students under academic examination stress. *Beneficial Microbes.* 2016;7(2):153-156.
59. Kazemi A, Noorbala AA, Azam K, Djafarian K. Effect of prebiotic and probiotic supplementation on circulating pro-inflammatory cytokines and urinary cortisol levels in patients with major depressive disorder: A double-blind, placebo-controlled randomized clinical trial. *Journal of Functional Foods.* 2019;52:596-602.

60. Kim LS. Immunological Activity of Larch Arabinogalactan and Echinacea: A Preliminary, Randomized, Double-blind, Placebo-controlled Trial. *Alternative Medicine Review.* 2002;7(2):12.
61. Kim H-K, Kim S-H, Jang C-S, et al. The combined effects of yogurt and exercise in healthy adults: Implications for biomarkers of depression and cardiovascular diseases. *Food Science & Nutrition.* 2018;6(7):1968-1974.
62. Kim C-S, Shin D-M. Probiotic food consumption is associated with lower severity and prevalence of depression: A nationwide cross-sectional study. *Nutrition.* 2019;63-64:169-174.
63. Kleiman SC, Watson HJ, Bulik-Sullivan EC, et al. The Intestinal Microbiota in Acute Anorexia Nervosa and During Renourishment: Relationship to Depression, Anxiety, and Eating Disorder Psychopathology. *Psychosomatic Medicine.* 2015;77(9):969-981.
64. Kleiman SC, Glenny EM, Bulik-Sullivan EC, et al. Daily Changes in Composition and Diversity of the Intestinal Microbiota in Patients with Anorexia Nervosa: A Series of Three Cases: Gut Microbes in AN. *European Eating Disorders Review.* 2017;25(5):423-427.
65. Kleiman SC, Bulik-Sullivan EC, Glenny EM, et al. The Gut-Brain Axis in Healthy Females: Lack of Significant Association between Microbial Composition and Diversity with Psychiatric Measures. *PLOS ONE.* 2017;12(1):e0170208.
66. Kobayashi Y, Kinoshita T, Matsumoto A, Yoshino K, Saito I, Xiao J. Bifidobacterium Breve A1 Supplementation Improved Cognitive Decline in Older Adults with Mild Cognitive Impairment: An Open-Label Single-Arm Study. *The Journal of Prevention of Alzheimer's Disease* 2019;6:70-75.
67. Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al. Effect of Soy Protein Containing Isoflavones on Cognitive Function, Bone Mineral Density, and Plasma Lipids in Postmenopausal Women: A Randomized Controlled Trial. *JAMA.* 2004;292(1).
68. Kretzschmar A. Microbiome and depression. New findings, new therapies? . *Psychopharmakotherapie.* 2017;24:130-131.
69. Krug A, Cannavale C, Khan N, Holscher H. The Effect of Prebiotic Consumption on the Gastrointestinal Microbiota of Healthy Adults: A Randomized, Controlled, Crossover Trial (P20-015-19). *Current Developments in Nutrition.* 2019;3(Supplement_1):nzz040.P020-015-019.
70. Kurokawa S, Kishimoto T, Mizuno S, et al. The effect of fecal microbiota transplantation on psychiatric symptoms among patients with irritable bowel syndrome, functional diarrhea and functional constipation: An open-label observational study. *Journal of Affective Disorders.* 2018;235:506-512.
71. Langkamp-Henken B, Rowe CC, Ford AL, et al. *Bifidobacterium bifidum* R0071 results in a greater proportion of healthy days and a lower percentage of academically stressed students reporting a day of cold/flu: a randomised, double-blind, placebo-controlled study. *British Journal of Nutrition.* 2015;113(3):426-434.
72. Lecerf JM. Psychobiotics: Human Studies. *Phytotherapie.* 2018;16(6):336-341.
73. Lee KJ, Ji GE. The effect of fermented red ginseng on depression is mediated by lipids. *Nutritional Neuroscience.* 2014;17(1):7-15.
74. Legette L, Ikonte C, Mitmesser S. Sampling Trial Showed S-equol Supplementation Helped Relieve Menopausal Symptoms (P06-111-19). *Current Developments in Nutrition.* 2019;3(Supplement_1):nzz031.P006-111-019.
75. Liu Y, Zhang L, Wang X, et al. Similar Fecal Microbiota Signatures in Patients With Diarrhea-Predominant Irritable Bowel Syndrome and Patients With Depression. *Clinical Gastroenterology and Hepatology.* 2016;14(11):1602-1611.e1605.
76. Lorenzo-Zúñiga V. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *WJG.* 2014;20(26):8709.

77. Ma ZF, Yusof N, Hamid N, et al. *Bifidobacterium infantis* M-63 improves mental health in victims with irritable bowel syndrome developed after a major flood disaster. *Beneficial Microbes.* 2019;10(2):111-120.
78. Marcos A, Wärnberg J, Nova E, et al. The effect of milk fermented by yogurt cultures plus Lactobacillus casei DN-114001 on the immune response of subjects under academic examination stress. *Eur J Nutr.* 2004;43(6):381-389.
79. Mazzawi T, Lied GA, Sangnes DA, et al. The kinetics of gut microbial community composition in patients with irritable bowel syndrome following fecal microbiota transplantation. *PLOS ONE.* 2018;13(11):e0194904.
80. Messaoudi M, Lalonde R, Violle N, et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *Br J Nutr.* 2011;105(5):755-764.
81. Mi G-L, Zhao L, Qiao D-D, Kang W-Q, Tang M-Q, Xu J-K. Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. *Antonie van Leeuwenhoek.* 2015;107(6):1547-1553.
82. Miyaoka T, Kanayama M, Wake R, et al. Clostridium butyricum MIYAIRI 588 as Adjunctive Therapy for Treatment-Resistant Major Depressive Disorder: A Prospective Open-Label Trial. *Clinical Neuropharmacology.* 2018;41(5):151-155.
83. Mohammadi AA, Jazayeri S, Khosravi-Darani K, et al. The effects of probiotics on mental health and hypothalamic–pituitary–adrenal axis: A randomized, double-blind, placebo-controlled trial in petrochemical workers. *Nutritional Neuroscience.* 2016;19(9):387-395.
84. Möller CM, Olsa EJA, Ginty AT, et al. Influence of Acute Multispecies and Multistrain Probiotic Supplementation on Cardiovascular Function and Reactivity to Psychological Stress in Young Adults: A Double-Blind, Randomized, Placebo-Controlled Trial. *Psychosomatic Medicine.* 2017;79(8):914-919.
85. Morita F, Yokokawa H, Matsuda N, et al. Comparitive efficacy of goreisan and probiotics in Japanese adults with acute infectious gastroenteritis: Randomized controlled trial. *Traditional & Kampo Medicine.* 2016;4(2).
86. Morita F, Yokokawa H, Matsuda N, et al. Comparative efficacy of goreisan and probiotics in Japanese adults with acute infectious gastroenteritis: Randomized controlled trial: Efficacy for gastroenteritis. *Traditional & Kampo Medicine.* 2017;4(2):89-93.
87. Mucci M, Carraro C, Mancino P, et al. Soy isoflavones, lactobacilli, magnolia bark extract, vitamin D3 and calcium. Controlled clinical study in menopause. *MINERVA GINECOLOGICA.* 2006;58.
88. Nagamine T, Ido Y, Nakamura M, Okamura T. 4^{G}-β-D-galactosylsucrose as a prebiotics may improve underweight in inpatients with schizophrenia. *Bioscience of Microbiota, Food and Health.* 2018;37(2):45-47.
89. Nagamine T, Ido Y, Okamura T, Nakamura M. The Effect of 4G-β-D-Galactosylsucrose on Antipsychotic Related Constipation.4.
90. Nakakita Y, Tsuchimoto, N., Takata, Y., Nakmura, T. Effect of dietary heat-killed Lactobacillus brevis SBC8803 (SBL88TM) on sleep: a non-randomised, double blind, placebo-controlled, and crossover pilot study. *Beneficial Microbes.* 2016;7:501-509.
91. Nishida K, Sawada D, Kuwano Y, et al. Daily administration of paraprobiotic *Lactobacillus gasseri* CP2305 ameliorates chronic stress-associated symptoms in Japanese medical students. *Journal of Functional Foods.* 2017;36:112-121.
92. Nishihira J, Kagami-Katsuyama H, Tanaka A, Nishimura M, Kobayashi T, Kawasaki Y. Elevation of natural killer cell activity and alleviation of mental stress by the consumption of yogurt containing Lactobacillus gasseri SBT2055 and Bifidobacterium longum SBT2928 in a double-blind, placebo-controlled clinical trial. *Journal of Functional Foods.* 2014;11:261-268.

93. Noorwali EA, Beaumont JD, Corfe BM, Owen L. The effects of probiotic supplementation on emotional memory and pain response. *Proceedings of the Nutrition Society.* 2017;76(OCE1):E6.
94. Nova E, Toro O, Varela P, López-Vidriero I, Morandé G, Marcos A. Effects of a nutritional intervention with yogurt on lymphocyte subsets and cytokine production capacity in anorexia nervosa patients. *Eur J Nutr.* 2006;45(4):225-233.
95. Okubo R, Koga M, Katsumata N, et al. Effect of bifidobacterium breve A-1 on anxiety and depressive symptoms in schizophrenia: A proof-of-concept study. *Journal of Affective Disorders.* 2019;245:377-385.
96. Östlund-Lagerström L, Kihlgren A, Repsilber D, Björkstén B, Brummer RJ, Schoultz I. Probiotic administration among free-living older adults: a double blinded, randomized, placebo-controlled clinical trial. *Nutr J.* 2015;15(1):80.
97. Paulsen JA, Ptacek TS, Carter SJ, et al. Gut microbiota composition associated with alterations in cardiorespiratory fitness and psychosocial outcomes among breast cancer survivors. *Supportive Care in Cancer.* 2017;25(5):1563-1570.
98. Perez-Cornago A, Sanchez-Villegas A, Bes-Rastrollo M, et al. Intake of High-Fat Yogurt, but Not of Low-Fat Yogurt or Prebiotics, Is Related to Lower Risk of Depression in Women of the SUN Cohort Study. *The Journal of Nutrition.* 2016;146(9):1731-1739.
99. Peter J, Fournier C, Durdevic M, et al. A Microbial Signature of Psychological Distress in Irritable Bowel Syndrome:. *Psychosomatic Medicine.* 2018;80(8):698-709.
100. Prantera C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. *Gut.* 2002;51(3):405-409.
101. Quigley EM. Prebiotics for irritable bowel syndrome. *Expert Review of Gastroenterology & Hepatology.* 2009;3(5):487-492.
102. Rao SSC, Rehman A, Yu S, de Andino NM. Brain fogginess, gas and bloating: a link between SIBO, probiotics and metabolic acidosis:. *Clinical and Translational Gastroenterology.* 2018;9(6):e162.
103. Reale M, Boscolo P, Bellante V, et al. Daily intake of Lactobacillus casei Shirota increases natural killer cell activity in smokers. *British Journal of Nutrition.* 2012;108(2):308-314.
104. Reininghaus Eva Z, Wetzlmair L-C, Fellendorf Frederike T, et al. The Impact of Probiotic Supplements on Cognitive Parameters in Euthymic Individuals with Bipolar Disorder: A Pilot Study. *Neuropsychobiology.* 2018:1-8.
105. Roman P, Estévez AF, Sánchez-Labraca N, Cañadas F, Miras A, Cardona D. Probiotics for Fibromyalgia: Study design for a pilot double-blind, randomized controlled trial. *Nutrición Hospitalaria.* 2017.
106. Rong H, Xie X-h, Zhao J, et al. Similarly in depression, nuances of gut microbiota: Evidences from a shotgun metagenomics sequencing study on major depressive disorder versus bipolar disorder with current major depressive episode patients. *Journal of Psychiatric Research.* 2019;113:90-99.
107. Sanborn V, Azcarate-Peril MA, Updegraff J, Manderino LM, Gunstad J. A randomized clinical trial examining the impact of LGG probiotic supplementation on psychological status in middle-aged and older adults. *Contemporary Clinical Trials Communications.* 2018;12:192-197.
108. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PWJ. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology.* 2015;232(10):1793-1801.
109. Severance EG, Gressitt KL, Stallings CR, et al. Candida albicans exposures, sex specificity and cognitive deficits in schizophrenia and bipolar disorder. *npj Schizophrenia.* 2016;2(1):16018.
110. Severance EG, Gressitt KL, Stallings CR, et al. Probiotic normalization of Candida albicans in schizophrenia: A randomized, placebo-controlled, longitudinal pilot study. *Brain, Behavior, and Immunity.* 2017;62:41-45.

111. Shafaghi A, Pourkazemi A, Khosravani M, et al. The Effect of Probiotic Plus Prebiotic Supplementation on the Tolerance and Efficacy of Helicobacter Pylori Eradication Quadruple Therapy: a Randomized Prospective Double Blind Controlled Trial. *Middle East Journal of Digestive Diseases.* 2016;8(3):179-188.
112. Siddiqui RA, Harvey KA. Dietary interventions with *n* -3 fatty acids or probiotics targeting post-myocardial infarction depression. *British Journal of Nutrition.* 2013;109(1):1-3.
113. Singh S, Jing E, Stollman N. Self-Limited Sepsis Syndrome Following Fecal Microbiota Therapy for Refractory C. difficile Infection. *Digestive Diseases and Sciences.* 2016;61(9):2488-2491.
114. Smith A, Sutherland D, Hewlett P. An Investigation of the Acute Effects of Oligofructose-Enriched Inulin on Subjective Wellbeing, Mood and Cognitive Performance. *Nutrients.* 2015;7(11):8887-8896.
115. Soldi S, Tagliacarne SC, Valsecchi C, et al. Effect of a multistrain probiotic (Lactoflorene® Plus) on inflammatory parameters and microbiota composition in subjects with stress-related symptoms. *Neurobiology of Stress.* 2019;10:100138.
116. Stevenson C, Blaauw R, Fredericks E, Visser J, Roux S. Randomized clinical trial: Effect of Lactobacillus plantarum 299 v on symptoms of irritable bowel syndrome. *Nutrition.* 2014;30(10):1151-1157.
117. Stokes CS, Schneider JG, Wilmes P, Lammert F. P1349 : Randomised placebo-controlled trial assessing whether probiotic supplements ameliorate depressive symptoms in patients with chronic hepatitis C virus infection. *Journal of Hepatology.* 2015;62:S863.
118. Takada M, Nishida K, Gondo Y, et al. Beneficial effects of *Lactobacillus casei* strain Shirota on academic stress-induced sleep disturbance in healthy adults: a double-blind, randomised, placebo-controlled trial. *Beneficial Microbes.* 2017;8(2):153-162.
119. Takada M, Nishida K, Kataoka-Kato A, et al. Probiotic *Lactobacillus casei* strain Shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models. *Neurogastroenterol Motil.* 2016;28(7):1027-1036.
120. Talbott S, Stephens B, Talbott J, Oddou M. E ect of Coordinated Probiotic/Prebiotic/Phytobiotic Supplementation on Microbiome Balance and Psychological Mood State in Healthy Stressed Adults.2.
121. Tamtaji OR, Heidari-soureshjani R, Mirhosseini N, et al. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: A randomized, double-blind, controlled trial. *Clinical Nutrition.* 2019;38(6):2569-2575.
122. Tazzyman S, Richards N, Trueman AR, et al. Vitamin D associates with improved quality of life in participants with irritable bowel syndrome: outcomes from a pilot trial. *BMJ Open Gastroenterology.* 2015;2(1):e000052.
123. Tomasik J, Yolken RH, Bahn S, Dickerson FB. Immunomodulatory Effects of Probiotic Supplementation in Schizophrenia Patients: A Randomized, Placebo-Controlled Trial. *Biomarker Insights.* 2015;10:BMI.S22007.
124. Tran N, Zhebrak M, Yacoub C, Pelletier J, Hawley D. The gut-brain relationship: Investigating the effect of multispecies probiotics on anxiety in a randomized placebo-cntrolled trial of healthy young adults. *Journal of Affective Disorders.* 2019;252:271-277.
125. Uemura M, Hayashi F, Ishioka K, et al. Obesity and mental health improvement following nutritional education focusing on gut microbiota composition in Japanese women: a randomised controlled trial. *Eur J Nutr.* 2019;58(8):3291-3302.
126. Urita Y, Goto M, Watanabe T, et al. Continuous consumption of fermented milk containing *Bifidobacterium bifidum* YIT 10347 improves gastrointestinal and psychological symptoms in patients with functional gastrointestinal disorders. *Bioscience of Microbiota, Food and Health.* 2015;34(2):37-44.

127. Vaghef-Mehrabany E, Alipour B, Homayouni-Rad A, Sharif S-K, Asghari-Jafarabadi M, Zavvari S. Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. *Nutrition.* 2014;30(4):430-435.
128. Vaghef-Mehrabany E, Homayouni-Rad A, Alipour B, Sharif S-K, Vaghef-Mehrabany L, Alipour-Ajiry S. Effects of Probiotic Supplementation on Oxidative Stress Indices in Women with Rheumatoid Arthritis: A Randomized Double-Blind Clinical Trial. *Journal of the American College of Nutrition.* 2016;35(4):291-299.
129. Valles-Colomer M, Falony G, Darzi Y, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. *Nature Microbiology.* 2019;4(4):623-632.
130. Vulevic J, Tzortzis G, Juric A, Gibson GR. Effect of a prebiotic galactooligosaccharide mixture (B-GOS®) on gastrointestinal symptoms in adults selected from a general population who suffer with bloating, abdominal pain, or flatulence. *Neurogastroenterol Motil.* 2018;30(11):e13440.
131. Wallace C, Foster J, Milex R. The efficacy, safety, and tolerability of probiotics on symptoms of depression: results from a pilot study. *Annual Nutritional Metabolism.* 2018;1.
132. Wang H, Braun C, Enck P. Effects of Rifaximin on Central Responses to Social Stress—a Pilot Experiment. *Neurotherapeutics.* 2018;15(3):807-818.
133. Wang H, Braun C, Murphy EF, Enck P. Bifidobacterium longum 1714™ Strain Modulates Brain Activity of Healthy Volunteers During Social Stress:. *The American Journal of Gastroenterology.* 2019;114(7):1152-1162.
134. Westfall E, Brandenburg D. Probiotics for Symptoms of Depression and Anxiety.1.
135. Wilson PB. Perceived life stress and anxiety correlate with chronic gastrointestinal symptoms in runners. *Journal of Sports Sciences.* 2018;36(15):1713-1719.
136. Xia X, Chen J, Xia J, et al. Role of probiotics in the treatment of minimal hepatic encephalopathy in patients with HBV-induced liver cirrhosis. *Journal of International Medical Research.* 2018;46(9):3596-3604.
137. Yang H, Zhao X, Tang S, et al. Probiotics reduce psychological stress in patients before laryngeal cancer surgery: Probiotics relieve psychological stress. *Asia-Pacific Journal of Clinical Oncology.* 2016;12(1):e92-e96.
138. Yi SH, Jernigan JA, McDonald LC. Prevalence of probiotic use among inpatients: A descriptive study of 145 U.S. hospitals. *American Journal of Infection Control.* 2016;44(5):548-553.
139. Yuan T-F, Ferreira Rocha N, Paes F, Arias-Carrión O, Machado S, de Sá Filho A. Neural Mechanisms of Exercise: Effects on Gut Miccrobiota and Depression. *CNS & Neurological Disorders - Drug Targets.* 2015;14(10):1312-1314.
140. Yuan X, Zhang P, Wang Y, et al. Changes in metabolism and microbiota after 24-week risperidone treatment in drug naïve, normal weight patients with first episode schizophrenia. *Schizophrenia Research.* 2018;201:299-306.
141. Zamudio-Tiburcio Á, Bermúdez-Ruiz H, Lezama-Guzmán HR, Guevara-Ortigoza MdP, Islas-Solares E, Sosa-López FA. Rompiendo paradigmas. Trasplante de microbiota intestinal: reporte preliminar. *Cirugía y Cirujanos.* 2017;85:6-12.
142. Zhang L, Liu Y, Wang Z, et al. Clinical charteristic and fecal microbiota responses to probiotic or antidepressant in patients with diarrhea-predominant irritable bowel syndrome with depression comorbidity: a pilot study. *Chinese Medical Journal.* 2013;132(3).

Appendix 4: Included study characteristics

Characteristics of studies included in meta-analysis:

Author, Year, Country	Research Methods	Participant Characteristics	Intervention	Relevant Outcomes	Findings
Akkasheh et al.[1] 2016 Iran	**Study design:** RCT **Dates of recruitment:** July 2014 - Sept 2014 **Inclusion Criteria:** Patients with a diagnosis of MDD based on DSM-IV criteria and with a score of 15 on the 17-item Hamilton Depression Rating Scale referred from Kargarneghad Hospital, Kashan University of Medical Sciences **Exclusion Criteria:** Age <20 years or >55 years; a history of coronary infarction, angina pectoris, pregnancy or lactation, or substance abuse; and taking dietary supplements or probiotic supplements during the previous 2 months.	**Intervention** n=20 (females: 17) Mean age (SD): 38.3 (12.1) **Control** n=20 (females: 17) Mean age ± SD: 36.2 ± 8.2	**Type:** *Lactobacillus acidophilus, L. casei,* and *Bifidobacterium bifidum* **Probiotic Dosage:** $2x10^9$ CFU/g for each; 1 capsule/day **Additional supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• After 8 week of intervention, patients who received probiotic supplements had significantly decreased Beck Depression Inventory total scores compared with the placebo

Chahwan et al.[2] Australia 2019	**Study Design:** RCT **Dates of Recruitment:** NR **Inclusion Criteria:** BDI score ≥ 12; age ≥ 18 years; could provide informed consent; were willing and able to travel to UTS Ultimo campus on a weekly basis to complete questionnaires on mental wellbeing; could provide a stool sample at the start and end of the treatment period; and not consume probiotic-rich foods and drinks such as fermented cheeses during the trial. **Exclusion Criteria:** Diagnosed with HIV/AIDS, cancer, or undergoing chemotherapy; Crohn's disease, ulcerative colitis, lactose-intolerance, or gluten-intolerance; currently experiencing severe depressive symptoms (BDI >57 or a score of 2 or 3 on Q9 of the BDI investigating suicidal ideation); actively suicidal or	**Intervention** n=34 (females: 21) Mean age (SD): 36.65 (11.75) **Control** n=37 (females: 28) Mean age (SD): 35.49 (12.34)	**Type:** *Bifidobacterium bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus lactis* W19, and *Lactococcus lactis* W58 **Probiotic Dosage:** 1 x 10^{10} CFU/day **Additional Supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional Supplement:** None	• BDI-2 • DASS21-D • LEIDS-R	• There was no significant main effect of group on BDI-2, LEIDS-R, or DASS21-D

	actively self-harming; diagnosed with bipolar disorder or a personality disorder, a psychotic disorder or otherwise experiencing psychosis; engaging in high-risk alcohol consumption (20 standard drinks per week for males, 12 standard drinks per week for females); currently receiving psychological or pharmacological treatment for mental health issues (including antidepressants); currently or having taken antibiotics or probiotic supplements within two weeks of trial; pregnant or planning to become pregnant within the time course of the trial; or currently participating in another research trial				
Chong et al.[3] 2019 Malaysia	**Study design:** RCT **Dates of Recruitment:** NR **Inclusion Criteria:** Men or women, aged 18-60 years old, willing to commit throughout the experiment,	**Intervention** n=56 (females: NR) Age: 31.1 ± 7.8 (type of value not specified) **Control**	**Type:** *Lactobacillus plantarum* DR7 **Probiotic Dosage:** 1 x 10^9 CFU / day **Additional supplement:** None	• DASS42-D	• No significant difference due to treatment group was identified.

	and a score of moderate stress level on Cohen's Perceived Stress Scale (PSS-10) **Exclusion Criteria:** Type 1 diabetes, long term medication due to certain severe illness, HIV/AIDS, and glucose-6-phosphate dehydrogenase deficient, and subjects who, in opinion of the investigator, were not likely to complete the trail for whatever reasons	n=55 (females: NR) Age: 32.1 ± 11.0 (type of value not specified)	**Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		
Chung et al.[4] 2014 South Korea	**Study design:** RCT **Dates of Recruitment:** NR **Inclusion Criteria:** Aged 60-75 years, experienced using computers and an education above middle school; scored ≥24 on the mini-mental status examination-Korean; were within ±30% of ideal body weight (BMI ≥ 16 and ≤ 35); and understood the objectives of the study and agreed to abide by the required rules during the	**Intervention (500mg)** n=10 (females: 6) Mean Age (SD): 64.50 (2.17) **Intervention (1000mg)** n=7 (females: 5) Mean Age (SD): 64.43 (4.47) **Intervention (2000mg)** n=9 (females: 4)	**Type:** *Lactobacillus helveticus IDCC3801* fermented skim milk powder **Probiotic Dosage:** 500mg, 1000mg, or 2000mg daily **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo	• GDS-SF	• No evidence of significant effect due to intervention

	study **Exclusion Criteria:** Diagnosed with a current axis I mental disorder or who had been treated for any axis I mental disorder within the past 5 years; scored ≥8 on the geriatric depression scale-short form; alcohol abuse or dependence within the past 3 months; gastrointestinal disease or had undergone gastrointestinal surgery, which might affect the absorption of study materials; significant neurological (epilepsy, mental retardation, or stroke) or medical illnesses (diabetes, hypertension, or cardiovascular diseases); took micronutrient supplements or herbal medicines during the 4 weeks preceding the start of the study; and had compliance less than 70% at each visit, i.e., weeks 2, 4, 8, and 12.	Mean Age (SD): 66.56 (4.98) **Control** n=10 (females: 6) Mean Age (SD): 64.50 (4.84)	**Additional supplement:** None		

Ghorbani et al.[5] 2018 Iran	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Adult (age 18 to 55 years) outpatients from university hospital psychiatry clinics, who fulfilled the diagnostic and statistical manual of mental disorders fifth edition for moderate depression, were required based on the structured clinical interview; and were treated with concurrent fluoxetine. **Exclusion Criteria:** The following DSM-V diagnoses were excluded: current or past history of schizophrenia and schizotypal personality disorder, bipolar disorder, and cognitive disorder in the past year. Participants were excluded whenever they showed a risk of suicide at any time during the study; of if they showed any clinically significant worsening in condition from baseline.	**Intervention** n=20 (females: 14) Mean age (SD): 35.50 (5.27) **Control** n=20 (females: 14) Mean age (SD): 34.45 (3.95)	**Type:** *Lactobacillus casaei, L. acidofilus, L. rhamnosus, Bifidobacterium breve, B. longum, Streptococcus thermophilus* **Synbiotic Dosage:** *Lactobacillus casaei* $3x10^8$ CFU/g, *L. acidofilus* $2x10^8$ CFU/g, *L. rhamnosus* $3x10^8$ CFU/g, *Bifidobacterium breve* $2x10^8$ CFU/g, *B. longum* 10^9 CFU/g, *Streptococcus thermophilus* $3x10^8$ CFU/g 100mg fructooligosaccharide **Synbiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None	• HAM-D	• Following the adjustment for gender, age, and BMI at baseline, there was a greater reduction in HAM-D score in probiotic treated patients (Mean±SD: - 19.25±1.71) compared to placebo taking group (Mean±SD: 17.75±2.05; P = 0.024).
Gomi et al.[6]	**Study design**: RCT	**Intervention**	**Type:** *Bifidobacterium*		

2018 Japan	**Dates of recruitment:** Oct 2016 –Mar 2017 **Inclusion Criteria**: healthy men and women aged from 20 to 64 years old, with an modified Frequency Scale for Symptoms of Gastroesophageal Reflux Disease score of ≥8, and who understood the details of the study and provided written informed consent **Exclusion Criteria**: H. pylori infection; (2) regular use of gastrointestinal drugs; (3) functional dyspepsia (Rome IV classification); (4) refusal to stop ingestion of probiotics, prebiotics, foods containing lactic acid bacteria or bifidobacteria, and other healthy foods that might affect gastrointestinal symptoms; (5) food allergy; (6) severe complications or diseases requiring urgent treatment; (7) a medical history of diseases or	n=39 (females: 20) Mean age (SD): 41.1 (10.1) **Control** n=40 (females: 21) Mean age (SD): 41.6 (9.9)	*bifidum* (YIT10347), *Streptococcus thermophiles* (YIT 2021) **Probiotic Dosage:** >3 × 10^7 CFU/mL of YIT10347 and >1 × 10^7 CFU/mL of *S. thermophilus* YIT 2021 per 100 ml/day **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None	• POMS-2	• No significant differences in mood change in intervention compared to control (intervention: -2.08 (6.93); control: -2.15 (5.48), p=0.683)

	operations affecting digestion, absorption, or defecation; (8) those deemed unsuitable for the study based on blood results of the screening test; (9) those who were pregnant or lactating or planning to become pregnant during the study; (10) those receiving treatment for or with a history of drug addiction or alcoholism; (11) those planning to participate or already participating in other clinical studies; and (12) those deemed unsuitable for the study by the investigator for other reasons				
Inoue et al.[7] 2018 Japan	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Subjects were recruited via announcements to second-year attendees of a weekly stretch training programme for the elderly at a public liberal aft school in the Hyogo prefecture, Japan. Those aged >65 years who	**Intervention** n= 20 (females:13) Mean age (SD): 69.9 (3.0) **Control** n= 18 (females:11) Mean age (SD): 70.9 (3.2)	**Type:** *Bifidobacterium longum* BB536, *B. infantis* M-63, *B. breve* M-16V, and *B. breve* B-3 **Probiotic Dosage:** 5 x 10^{10} CFU per sachet **Additional supplement:** None **Probiotic Duration:** 12 weeks	• PHQ-9	• No evidence of significant difference due to intervention

	had undergone stretch training for the previous 12 months were included. **Exclusion Criteria:** Those who received public heath nursing care, had any contraindications to resistance training, or had been diagnosed with dementia by a physician or were undergoing dementia treatment were excluded.		**Comparator:** Placebo **Additional supplement:** None		
Jamilian et al.[8] 2018 Iran	**Study design:** RCT **Dates of recruitment:** Dec 2017 – Mar 2018 **Inclusion Criteria:** Women with PCOS based on the Rotterdam criteria, aged 18 – 40 years old whom were referred to the Kosar Clinic in Arak, Iran, between December and March 2018. Written informed consent was obtained from all participants prior to the intervention. **Exclusion Criteria:** Pregnancy, Adrenal	**Intervention** n= 30 (females: 30) Mean age (SD): 26.0 (5.3) **Control:** n=30 (females:30) Mean age (SD): 25.6 (3.8)	**Type:** *Lactobacillus acidophilus, L. reuteri, L. fermentum, Bifidobacterium bifidum* **Probiotic Dosage:** 8 x 10^9 CFU/day **Additional supplement:** 200 µg selenium **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• Co-administration of probiotic and selenium for 12 weeks to women with PCOS resulted in a significant improvement in BDI compared with the placebo (p=0.003)

	hyperplasia, and rogen-secreting tumors, hyperprolactinemia, thyroid dysfunction, diabetes at enrollment.				
Kazemi et al.[9] 2018 Iran	**Study design:** RCT **Dates of recruitment:** Jul 2016 – Apr 2017 **Inclusion Criteria:** Patients with mild to moderate major depressed patients aged 18 – 50 years who took the anti-depressant drugs: sertraline, fluoxetine, citalopram or amitriptyline for 3 months or	**Intervention (Prebiotic)** n= 37 (females:) Mean age (SD): 37.35 (7.97)	**Probiotic Type:** *Lactobacillus helveticus* R0052, *Bifidobacterium longum* R0175 **Probiotic Dosage:** ≥10x10^9 CFU, frequency not specified **Additional supplement:** None	• BDI	• Probiotics improved BDI score compared to placebo while prebiotics had no significant effect

	more prior to beginning the trial. **Exclusion Criteria:** History of renal, hepatic, cardiovascular, or respiratory disease; pregnancy and lactation; regular intake of probiotics during last 2 months before recruitment for the study; intake of antioxidant or omega 3 supplements less than 6 weeks before the beginning of the study; alcohol intake; smoking cigarettes (more than 5 during last 6 months) or tobacco (pipe or hookah at least one time during last	**Intervention (Probiotic)** n=38 (females: 27) Mean age (SD): 36.15 (7.85)	**Prebiotic Type:** Galactooligosaccharide **Prebiotic Dosage:** 5g sachet, frequency not specified **Additional supplement:** None **Prebiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None		

	month); any addiction to opiates; history of heart attack or stroke; following a specific diet; participation in another study during last two months; any significant change in diet and life style; any change in drug regimen; inflammatory diseases which lasted for more than one week during the study; intake of antibiotics during the study. Participants were instructed not to consume any other probiotic supplements during the course of the trial.	**Control** n= 36 (females:24) Mean age (SD):36 (8.47)			
Kelly et al.[10] 2017 Ireland	**Study design:** RCT- Cross-over **Dates of recruitment:** NR **Inclusion Criteria:** Male 18-40 years old; healthy; able to speak English **Exclusion Criteria:** Having a significant acute or chronic illness, following	**Intervention/control** n=14 (females: 0) Mean age (SD): 25.64 (1.14) **Control/intervention** n=15 (females: 0) Mean age (SD): 23.6 (0.97)	**Type:** *Lactobacillus rhamnosus* (JB-1) **Probiotic Dosage:** 1×10^9 CFU each capsule 1/ day **Additional supplement:** None **Probiotic Duration:** 4 weeks	• BDI	• No evidence of significant effect due to intervention reported

	a diet or taking a medication that would interfere with the objectives of the study, pose a safety risk or confound the interpretation of the study results (e.g., probiotics, antibiotics, antipsychotics, anxiolytics, laxatives, enemas, anti-coagulants and over-the counter non-steroidal anti-inflammatorys (NSAIDS), antidepressants or any other psychotropic medication); people with evidence of immunodeficiency, bleeding disorder or coagulopathy, colour blindness, dyslexia or dyscalculia, or receiving any treatment involving experimental drugs		**Comparator:** Placebo: **Additional supplement:** None		
Kitaoka et al.[11] 2009 Japan	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Healthy male **Exclusion Criteria:** NR	**Intervention** n=8 (females: 0) Mean age (SD): 20.13 (1.13) **Control** n=8 (females: 0) Mean age (SD): 21.25 (2.19)	**Type:** Fermented Ginseng and sterilized *Lactobacillus paracasei A221* **Para-probiotic Dosage:** 1845mg fermented ginseng per day **Additional supplement:** No	• POMS	• No significant difference found in pre-post intervention in POMS

			Para-probiotic Duration: 1 weeks **Comparator:** Placebo **Additional supplement:** None		
Kouchaki et al.[12] 2017 Iran	**Study design:** RCT **Dates of recruitment:** Dec 2015 – Feb 2016 **Inclusion Criteria:** Aged between 18 – 55 with clinically definite multiple sclerosis diagnosed according to McDonald criteria and an expanded disability status scale score ≤4.5 referred to the Shahid Beheshti Hospital in Kashan (located in Esfahan province), Iran. Permission to obtain information from database of MS clinic to ensure following criteria were fulfilled: gender, age, at MS onset, RRMS, familial antecedents of MS and no probiotic and/or symbiotic supplementation before measurements.	**Intervention** n= 30 (females:25) Mean age (SD): 34.4 (9.2) **Control** n= 30 (females:25) Mean age (SD): 33.8 (8.9)	**Type:** *Lactobacillus acidophilus, L. casei, L. fermentum, Bifidobacterium bifidum* **Probiotic Dosage:** 4 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• Compared with the placebo, probiotic significantly improved BDI scores

	Exclusion Criteria: Women who were pregnant or lactating during the past six months, patients bearing nephrolithiasis for the past 5 years, menopaused women with irregular menstruation and unwillingness to utilize appropriate contraceptive tools.				
Lew et al.[13] 2018 Malaysia	**Study design:** RCT **Dates of recruitment:** Oct 2012 – Jan 2013 **Inclusion Criteria:** Aged 18 – 60 years old, body mass index within a healthy range, no severe illnesses, willing to commit throughout the experiment, and a score of moderate stress level on Cohen's Perceived Stress Scale. Written informed consent was obtained from all subjects prior to the start of the study. **Exclusion Criteria:** Type-I diabetes, long term medication due to certain	**Intervention** n= 52 (females:40) Mean age (SD): 31.03 (10.8) **Control** n= 51 (females:39) Mean age (SD): 32.1 (11.4)	**Type:** *Lactobacillus plantarum* P8 **Probiotic Dosage:** 2.0 x 10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• DASS42 – D	• The effects of treatment were insignificant across 12-weeks, and remained insignificantly different from each other at the evaluated time points of week 0,4,8, and 12

	severe illness, HIV/AIDS, and glucose-6-phospate dehydrogenase deficient, and subjects who, in opinion of the investigator, were not likely to complete the trial for whatever reasons.				
Lyra et al.[14] 2016 Finland	**Study design:** RCT **Dates of recruitment:** Oct 2012 - Nov 2014 **Inclusion Criteria:** adults (18-65 years) who were diagnosed with IBS according to Rome III criteria; sufficient general health and orientation for participation in the study, adequate Finnish language skills for being interviewed and completing questionnaires, high likelihood of compliance with and completion of the study, and a body mass index (BMI) between 19 and 35 **Exclusion Criteria:** suffering from severe IBS symptoms; participation in a	**Low Dose Intervention** n=129 (females: 94) Mean age (SEM): 47.1 (13.3) **High Dose Intervention** n=131 (females: 104) Mean age (SEM): 47.2 (12.5) **Control** n=131 (females: 94) Mean age (range): 49.4 (SEM: 12.9)	**Type:** *Lactobacillus acidophilus* NCFM (NCFM not defined) **Probiotic Dosage:** Low dose: 10^9 CFU/day High dose: 10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	HADS-D	• No evidence of significant difference attributable to probiotic

	clinical trial with an investigational product (IP) or drug within 3 months prior to the screening; participants who were likely to be noncompliant with the protocol or judged to be unsuitable for study participation by the investigator for any reason, were planning major changes in lifestyle (e.g., diet, dieting, exercise level, travel), had a history of drug or alcohol abuse, were pregnant or breastfeeding, were diagnosed with or suspected of having organic GI disease (e.g., colitis, Crohn's disease, celiac disease, bowel surgery, recurrent diverticulitis), or had severely impaired general health, including cancer and cancer therapy; lactose-intolerant volunteers not following a non-lactose diet; any previous allergic reaction to any substance in the study product; patients taking medications that could affect				

	the outcomes, including anticholinergic medications, antibiotics (including use during the 3 months prior to the start of the study), pain medications that contained opiates or morphine, weight loss medication, misoprostol, 5-HT3 receptor antagonists, antacids with magnesium or aluminum, diarrhea medication, medication that accelerates the emptying of the stomach, sulfasalazine, laxatives, cholestyramine, cytostatics, biological medications, oral steroids (3 months prior to and during the study), and probiotic products.				
Majeed et al.[15] 2018 India	**Study design:** RCT **Dates of recruitment:** Jun 2015 – Oct 2015 **Inclusion Criteria:** Male or female aged between 20 and 65 years; Fulfilling Rome III Diagnostic Criteria (30) for Functional IBS for the last 3 months with symptom onset at least 6 months prior to	**Intervention** n= 20 (females:17) Mean age (SD): 40.36 (10.28) **Control** n= 20 (females:17) Mean age (SD): 43.88 (9.85)	**Type:** *Bacillus coagulans* **Probiotic Dosage:** 2 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 90 Days **Comparator:** Placebo	• HAM-D • MADRS • CES-D	• Significant change (p=0.01) in favour of the probiotic was observed for the Hamilton Rating Scale for Depression, Montgomery- Åsberg Depression Scale, and Centre for Epidemiological Studies-Depression Scale.

	diagnosis: a. Discomfort or recurrent abdominal pain at least 3 days/month in the last 3 months associated with two or more of the following: improvement with defecation, stool frequency change and change in appearance of stool b. Bloating or visible distension at least 3 days/month in the last 3 months c. Watery or loose stools without pain occurring in at least 75% of stools Willingness to follow the protocol requirement as evidenced by written informed consent; Diagnosed patients with mild to moderate IBS in severity with possible sleep, pain and dementia-associated co-morbidities. Fulfilling Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (2000) Criteria for MDD; Willingness to complete subject diaries and study questionnaires; Agree not to use any		**Additional supplement:** None		

	medication (prescription and over the counter), including vitamins and minerals, during the course of this study; Agree not to use any yogurt during the course of this study; Subjects whose blood chemistries are within a normal range or not considered clinically significant if outside the normal range; Subject's assurance that they have not taken antibiotics or other supplements whose primary site of action is in the gastrointestinal tract for a period up to 1 month prior to the start of the study; Willing to come for regular follow-up visit. **Exclusion Criteria:** Any clinically significant medical history, medical finding or an ongoing medical condition exists which in the opinion of the investigator could jeopardise the safety of the subject, impact validity of the study results or interfere with the completion of study				

	according to the protocol; Significant abnormal findings as determined by baseline history, physical examination, vital signs, haematology, serum chemistry and urinalysis; History or presence of significant alcoholism or supplement/drug abuse in the past 1 year; Any medical or surgical conditions which might significantly interfere with the gastrointestinal tract, liver, kidneys and/or blood-forming organs; History of cardiovascular, renal, hepatic, asthma, glaucoma, pulmonary, neurologic, metabolic or psychiatric disease; Participation in a clinical study during the preceding 90 days; History of malignancy or other serious disease; Any contraindication to blood sampling; Smoking or consumption of tobacco products; Blood or blood products donated in past 30 days prior to study supplement administration;				

	Pregnant female subjects and lactating women; Prior surgical therapy for obesity; Patients using yogurt in their daily meal.				
Marotta et al.[16] 2019 Italy	**Study design:** RCT **Dates of recruitment:** Nov 2016 – Jun 2017 **Inclusion Criteria:** Between ages 18 – 35. **Exclusion Criteria:** Psychiatric or neurological disorders, celiac disease, lactose intolerance, or allergies or other ongoing illnesses (i.e. irritable bowel syndrome, diabetes, ulcerative colitis, etc.) or recent antibiotic treatment (i.e., <3months before the beginning of the study) and participants who smoked more than 10 cigarettes per day.	**Intervention** n= 18 (females:7) Mean age (SD): 21.61 (2.2) **Control** n= 15 (females:5) Mean age (SD): 21.67 (2.19)	**Type:** *Lactobacillus fermentum* LF16 (DSM26956), *L. rhamnosus* LR06 (DSM 21981), *L. plantarum* LP01 (LMG P-21021), *Bifidobacterium longum* BL04 (DSM23233) **Probiotic Dosage:** 4 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI-2 • LEIDS-R • POMS-2	• No significant between-group difference found for BDI-2 • Overall scores for POMS-2 and LEIDS-R not calculated or tested for significance
Messaoudi et al.[17] 2011 France	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** healthy	**Intervention** n= 26 (females:19) Mean age (SD): 42.4 (7.5)	**Type:** *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175	• HADS-D	• No significant difference observed in HADS-Depression score

	adults from general population; standard biological safety parameters and a score of ≤ 12 in the HADS-anxiety subscale (HADS-A) and in the HADS-depression subscale (HADS-D) and ≤ 20 in the HADS total score on initial examination **Exclusion Criteria:** suffering from neurological, psychiatric, renal, hepatic, cardiovascular and respiratory diseases, or food allergy; taking psychotropic drugs during the previous month; stimulating nutritional supplements (vitamin C), ginger, guarana, ginseng, dehydroepiandrosterone, melatonin, antioxidants, anxiolytics, antidepressants, selenium, narcotics, replacement hormones, more than 5 cups of coffee or tea/day; 0·2 litres of cola, 30–40 g of chocolate, three glasses of wine, or two fermented dairy products; smoking more	**Control** n= 29 (females:22) Mean age (SD):43.2 (8.5)	**Probiotic Dosage:** 3 x 10^9 CFU per stick; 1 stick/day **Additional supplement:** None **Probiotic Duration:** 30 Days **Comparator:** Placebo **Additional supplement:** None		

	than twenty cigarettes; Pregnant women and subjects who had participated in another clinical study over the past 2 months				
Miyaoka et al.[18] 2018 Japan	**Study design:** RCT **Dates of Recruitment:** NR **Inclusion Criteria:** Patients experiencing symptoms of TRD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, were enrolled in this study. Diagnosis of TRD was based on chart reviews and defined as an inadequate or nonresponse to 2 or more 8-week trials with 2 different classes of antidepressants. All patients were taking selective-serotonin reuptake inhibitor or serotonin-noradrenalin reuptake inhibitor medications, including fluvoxamine, paroxetine, escitalopram, sertraline, duloxetine, and milnacipram.	**Intervention** n=20 (females: 12) Mean age (SD): 44.2 (15.6) **Control** n=20 (females: 12) Mean age (SD): 41.9 (14.2)	**Type:** *Clostridium butyricum* MIYAIRI 588 **Probiotic Dosage:** 20 mg orally twice daily for the first week and 20 mg orally three times daily from weeks 2 to 8 **Additional supplement:** SSRI or SNRI **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• HAM-D • BDI	• In combination with antidepressants, the probiotic studied offered significant benefit

	Exclusion Criteria: Patients were excluded if they met the criteria for an Axis I diagnosis of delirium, dementia, or other cognitive disorder, bipolar disorder, schizophrenia or other psychotic disorder, or a clinically significant Axis II diagnosis of obsessive-compulsive, schizoid, schizotypal, paranoid, antisocial, or histrionic personality disorder. Patients were also excluded if they acknowledged substance abuse or dependence within the past 6 months, or if they were pregnant, were nursing, or posed a significant risk of suicide during the study period. Patients with chronic deteriorating illnesses such as diabetes, human immunodeficiency virus, gastrointestinal disease, and seizure disorders were also excluded.				
Ostadmohammadi	**Study design:** RCT	**Intervention** n= 30 (females: 30)	**Type:** *Lactobacillus acidophilus,*	• BDI	• Vitamin D and probiotic

et al. [19] 2019 Iran	**Dates of recruitment:** NR **Inclusion Criteria:** Women with polycystic ovary syndrome, diagnosed based on the Rotterdam criteria, with the body mass index (BMI) in the range of 17-34kg/m^2 and insulin resistance in the range of 1.4-4, aged 18 – 40 years old whom referred to the Naghavi Clinic in Kashan, Iran, between July and October 2018. Written informed consent was taken from participants prior to the initiation of the trial. **Exclusion Criteria:** Pregnancy, lactation, adrenal hyperplasia, androgen-secreting tumor, hyperprolactinemia, thyroid dysfunction, and diabetes, women with psychological or psychiatric comorbidities such as anxiety or depressive symptoms at the enrollment.	Mean age (SD): 24.4 (4.7) **Control** n= 30 (females: 30) Mean age (SD): 25.4 (5.1)	*Bifidobacterium bifidum, L. reuteri, L fermentum* **Probiotic Dosage:** 8 x 10^9 CFU/day **Additional supplement:** 50,000 IU Vitamin D **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		co-administration for 12 weeks significantly reduced BDI scores
Östlund-Lagerström et al.[20]	**Study design:** RCT **Dates of recruitment:**	**Intervention** n= 125 (females:71)	**Type:** *Lactobacillus reuteri* **Probiotic Dosage:**	• HADS-D	• No evidence of significant difference due

2016 United States	Jan 2013 – Mar 2013 **Inclusion Criteria:** free-living, older adults (≥ 65 years) representing the general population in Orebro, Sweden. Informed consent signed by the participant and mentally and physically fit to complete questionnaires during the study period. **Exclusion Criteria:** Any known gastrointestinal disease, with strictures, malignance's and ischemia, inflammatory bowel diseases, Participation in other clinical trials in the past three months	Mean age (SD): 72.6 (5.8) **Control** n= 124 (females:81) Mean age (SD): 72 (5.6)	1 x 10^8 CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		to probiotic
Papalini et al.[21] 2019 Netherlands	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Right handed, healthy female volunteers aged between 18 and 40 years old, using (oral or intra-uterine) hormonal contraceptives, with a	**Intervention** n= 29 (females:29) Mean age (SEM): 21 (0.4) **Control** n= 29 (females:29) Mean age (SEM): 22	**Type:** Ecologic® barrier consisted of the following bacterial strains: *Bifidobacterium bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and, *L. lactis* W58	• BDI • LEIDS-R	• No evidence of significant treatment effects

	healthy weight, i.e. a body mass index between 18 and 25. They were not in the "stop week" of oral contraceptives during test session to ensure similar hormone levels between both sessions across participants. **Exclusion Criteria:** personal history of psychiatric, neurological, gastrointestinal, endocrine disorders, and relevant medical history; regular medication use; pre- and pro supplementation; smoking; use of antibiotics within two months before the start of the study; lactose intolerance; on a vegan diet; those with a high alcohol intake (i.e. more than 10 glasses of any alcoholic drink per week); patients who changed their diet within three months of the first testing session; MRI compatibility	(0.5)	**Probiotic Dosage:** 5 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None		
Pinto-Sanchez et	**Study design:** RCT	**Intervention** n=18 (females: 12)	**Type:** *Bifidobacterium longum*	• HADS-D	• No evidence of

al.[22] 2017 Canada	**Dates of recruitment:** Mar 2011 – May 2014 **Inclusion Criteria:** Aged 21-65 with a diagnosis of irritable bowel syndrome with diarrhea or mixed=stool pattern (Rome III criteria) and mild to moderate anxiety and/or depression scores based on the Hospital Anxiety and Depression (HAD) scale (HAD-A or HAD-D score 8 – 14) **Exclusion Criteria:** History of organic diseases, immune deficiency, major abdominal surgery, psychiatric condition other than anxiety or depression, use of immunosuppressants, glucocorticosteroids, opioids, antidepressants or anxiolytics in regular doses, alcohol or illicit drug consumption, consumption of antibiotics 3 months prior to the run-in period and the trial, probiotics in any form were forbidden during the 1 month run in period and	Median age (IQR): 46.5 (30-58) **Control** n= 20 (females: 12) Median age (IQR): 40.0 (26-57)	**Probiotic Dosage:** 1 x 10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None		significant difference due to intervention reported.

	trial.				
Raygan et al.[23] 2018 Iran	**Study design:** RCT **Dates of recruitment:** Aug 2017 - Nov 2017 **Inclusion Criteria:** 45-85 years old, diagnosed with type 2 diabetes and coronary heart disease with 2 and 3-vessel CHD **Exclusion Criteria:** Consuming vitamin D, probiotic and/or symbiotic within the last 3 months, and patients with thyroid disorders	**Intervention** n=30 (females: 14) Mean age (SD): 71.5 (10.9) **Control** n=30 (females: 16) Mean age (SD): 67.3 (11.0)	**Type:** *Lactobacillus acidophilus, Bifidobacterium bifidum, L. reuteri, and L. fermentum* **Probiotic Dosage:** 8×10^9 CFU/g (each organism 2 x 10^9 CFU/ day) **Additional supplement:** 50,000 IU vitamin D3 every 2 weeks **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• Significant improvement in BDI score in intervention compared to control: (intervention: -2.8 ± 3.8, control: -0.9 ± 2.1, p = 0.01)
Raygan et al.[24] 2019 Iran	**Study design:** RCT **Dates of recruitment:** Dec 2017 – Mar 2018 **Inclusion Criteria:** Patients aged 45-85 years old diagnosed with both type 2 diabetes and chronic heart disease as diagnosed by the	**Intervention** n= 27 (females:16) Mean age (SD): 64.8 ± 8.3 **Control** n=27 (females: 17) Mean age (SD): 62.4	**Type:** *Lactobacillus acidophilus, L. reuteri, L. fermentum and Bifidobacterium bifidum* **Probiotic Dosage:** 8×10^9 CFU/g (each organism 2 x 10^9 CFU/ day) **Additional supplement:** 200 µg/day Selenium	• BDI	• Probiotic and selenium co-supplementation significantly improved BDI score in intervention compared to control

	American Diabetes Association and American Heart Association criteria. **Exclusion Criteria:** Participants reported selenium, probiotic and/or symbiotic consumption within the last 3 months, patients with thyroid disorders, severe renal insufficiency and hepatic failure, and those experiencing an acute myocardial infarction and cardiac surgery within the past 3 months were excluded.	(13.1)	**Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		
Roman et al.[25] 2018 Spain	**Study design:** RCT **Dates of recruitment:** Dec 2015 - Feb 2016 **Inclusion Criteria:** Diagnosed with Fibromyalgia at least 1 year prior to study **Exclusion Criteria:** taking antibiotics and nutritional supplements, allergies, currently participating in	**Intervention** n=16 (females: 15) Mean age (SD): 55 (2.09) **Control** n=15 (females: 13) Mean age (SD): 50.3 (2.03)	**Type:** *Lactobacillus Rhamnosus GG®, L. casei, L. acidophilus*, and *Bifidobacterium bifidus* **Probiotic Dosage:** 6 million revivification of germs per capsule (4 / day) **Additional supplement:** None **Probiotic Duration:** 8	• BDI	• No evidence of significant difference due to intervention

	other studies, pregnant or breastfeeding, severe intestinal disease, psychiatric disorder other than depression and/ or anxiety		weeks **Comparator:** Placebo **Additional supplement:** None		
Romijn et al.[26] 2017 New Zealand	**Study design:** RCT **Dates of recruitment:** May 2013 – May 2014 **Inclusion Criteria:** either ⩾11 on the Quick Inventory of Depressive Symptomatology (QIDS) or ⩾14 on the depression subscale of the Depression, Anxiety and Stress Scale (DASS-42); aged 16+ at the time of screening; free of any psychiatric medication for at least 4 weeks prior to the trial **Exclusion Criteria:** any neurological disorder; renal, hepatic, cardiovascular or respiratory disease; any serious medical condition with major medical interventions anticipated during the trial; pregnancy or breastfeeding; use of any	**Intervention** n=40 (female: 32) Mean age (SD): 35.8 (14) **Control** n=39 (female: 30) Mean age (SD): 35.1 (14.5)	**Type:** *Lactobacillus helveticus* R0052 (strain I-1722) and *Bifidobacterium longum* R0175 (CNCM strain I-3470) **Probiotic Dosage:** ⩾3×10^9 CFU per 1.5 g sachet/day **Additional supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• MADRS • DASS42-D • QIDS	• No significant improvements in intervention compared to control

	supplement considered potentially antidepressant (e.g. St John's Wort, 5-HTP, SAMe); serious risk of suicide or violence; current or recent probiotic or antibiotic use				
Rudzki et al.[27] 2019 Poland	**Study design:** RCT **Dates of recruitment:** June 2014 – March 2016 **Inclusion Criteria:** SSRI monotherapy or drug-free at admission; DSM-IV MDD diagnosis **Exclusion Criteria:** inflammatory, oncological, and autoimmune disorders; diabetes; previous diagnosis of other psychiatric diseases other than depression; psychoactive substances abuse; organic brain dysfunctions; smoking; patients with changes in routine blood biochemical parameters; pregnancy, lactation, BMI<18.5 kg/m^2 and >30 kg/m^2, treatment with antipsychotic drugs, mood stabilizers, antibiotics,	**Intervention** n=30 (female: 23) Mean age (SD): 39.13 (9.96) **Control** n=30 (female: 20) Mean age (SD): 38.9 (12)	**Type:** *Lactobacillus Plantarum* (strain 299v) **Probiotic Dosage:** 10×10^9 CFU/capsule twice/day **Additional supplement:** SSRI **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• HAM-D	• No evidence of significant improvement due to intervention

	glucocorticosteroids				
Salami et al.[28] 2019 Iran	**Study design:** RCT **Dates of recruitment:** Sept 2017 – Jan 2018 **Inclusion Criteria:** 20 - 60 years old, course of disease relapsing-remitting Multiple Sclerosis (RRMS) **Exclusion Criteria:** Primary progressive MS (PPMS); secondary progressing MS; clinical relapse and glucocorticoid therapy during past month; pregnant or lactating; patients with bearing nephrolithiasis within prior five years; and consumption of probiotics or symbiotic during past three months.	**Intervention** n=24 (females: 18) Mean age (SD): 34.79 (1.06) **Control** n=24 (females: 18) Mean age (SD): 36.54 (1.44)	**Type:** *Bifidobacterium infantis, B. lactis, Lactobacillus reuteri, L. casei, L. plantarum* and *L. fermentum* **Probiotic Dosage:** $2x10^9$ CFU each capsule/ day **Additional supplement:** None **Probiotic Duration:** 16 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• Significant improvement in intervention group compared to control (p =0.026)
Sanchez et al.[29] 2017 Canada	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** men and women between 18 and 55 years of age; absence of pregnancy, breastfeeding, or menopause (determined by	**Intervention** n=62 (female: 38) Mean age (SD): 35 (10) **Control** n=63 (female: 39)	**Type:** *Lactobacillus rhamnosus* CGMCC1.3724 (LPR) **Synbiotic Dosage:** 1.62 10^8 CFU per capsule/twice a day **+** 300 mg of a mix of oligofructose and inulin (70/30; v/v)	• BDI	• Synbiotic offered a significant decrease in BDI score (p<0.05).

	the cessation of menstruation); stable body weight (body weight change <5 kg for three months before screening); BMI between 29 and 41 kg/m2, without associated co-morbidities **Exclusion Criteria:** NR	Mean age (SD): 37 (10)	**Synbiotic Duration:** 24 weeks **Comparator:** Placebo **Additional supplement:** None		
Sashihara et al.[30] 2013 Japan	**Study design:** RCT **Dates of recruitment:** Feb 2011 – Apr 2011 **Inclusion Criteria:** male Japanese; healthy; <30 years old; engaged in high-intensity training ≥5 days per week. **Exclusion Criteria:** allergic diseases such as cedar pollinosis, perennial allergic rhinitis, or atopic dermatitis.	**Group 1 Intervention** n=15 (female: 0) Mean age (SD): 19.8 (0.9) **Group 2 Intervention** n=15 (female: 0) Mean age (SD): 19.9 (0.9) **Control** n=14 (female: 0) Mean age (SD): 20.2 (1.1)	**Type:** Heat killed *Lactobacillus gasseri* (LG2809), α-lactalbumin (αLA) **Para-probiotic Dosage:** Group 1: LG2809 alone (1 × 10^{10} heat-killed cells)/tablet, 2 tablets 3 times/day Group 2: LG2809+αLA (1 × 10^{10} heat killed LG2809 cells + 900mg αLA))/tablet, 2 tablets 3 times/day **Additional supplement:** α-lactalbumin **Para-probiotic Duration:** 4 weeks	• POMS	• No evidence of significant effect due to intervention

			Comparator: Placebo **Additional supplement:** None		
Sawada et al. [31] 2017 Japan	**Study design:** RCT - Crossover **Dates of recruitment:** Sept to Dec; year NR **Inclusion Criteria:** male students; not habitual smokers; no mental or other diseases or allergies to milk or other foods; taking the cadaver dissection course **Exclusion Criteria:** had taken medication for 3 months prior to enrolment	**Intervention** n=24 (female: 0) Mean age (SD): NR **Control** n=24 (female: 0) Mean age (SD): NR	**Type:** *Lactobacillus gasseri CP2305* cultured in medium containing 10% skim milk and 0.25% yeast extract **Probiotic Dosage:** $1.0x10^{10}$ CFU/pouch (2.5g)/day **Additional supplement:** No **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None	• HADS-D • Zung-SDS	• No evidence of significant difference due to probiotic
Sawada et al.[32] 2019 Japan	**Study design:** RCT **Dates of recruitment:** Sept 2016 – Dec 2016 **Inclusion Criteria:** 18-22	**Intervention** n=24 (females: 0) Mean age (SD): 19.8 (1.4)	**Type:** *Lactobacillus gasseri* CP2305 (CP2305) mixed in sport drink containing sweetener, acidifier, flavorings, vitamin C, and minerals	• HADS-D	• Significant reduction in intervention group compared to control

	years of age, male, healthy university students members of the long-distance relay race team **Exclusion Criteria:** history of psychiatric or somatic diseases in the past and present; taking medication at least for three months prior to the enrollment and during the experimental period; allergic to milk and soybean	**Control** n=25 (females: 0) Mean age (SD): 20.1 (1.1)	(Na, Ca, K, Mg) **Probiotic Dosage:** 1 x 10^{10} CFU per each 200ml/ day **Additional supplement:** Vitamin C and minerals (Na, Ca, K, Mg) **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		
Shinkai et al.[33] 2012 Japan	**Study design:** RCT **Dates of recruitment:** Mar 2010 – Jul 2010 **Inclusion Criteria:** Adults 65 years or older **Exclusion Criteria:** Current smoker; vigorous exerciser (more than six metabolic equivalents); with non-standard values for blood pressure or pulse; with hepatitis, cancer, IBS, rheumatoid arthritis or other	**Intervention 1** n= 92 (females: 48) Mean age (SD): 71.0 (4.0) **Intervention 2** n= 93 (females: 45) Mean age (SD): 70.8 (=3.4) **Control** n= 93 (females:47) Mean age (SD): 70.9	**Type:** Heat killed *Lactobacillus pentosus* strain b240 **Para-probiotic Dosage:** **Intervention 1:** 2x10^{9} heat killed cells per each capsule/ day **Intervention 2:** 2x10^{10} heat killed cells per each capsule/ day **Additional supplement:** None	• POMS	• No evidence of significant effect due to intervention

	diseases affecting the digestive tract or immune system; with chronic obstructive lung diseases such as asthma and chronic bronchitis, allergic rhinitis with any medication and a past history of pneumonia; with periodontitis or haemorrhagic stomatitis; taking antibiotics; taking antiflatulents, antidiarrhoeals, steroids, immune-suppressive drugs or other drugs related to the activation or suppression of the digestive or immune systems; participants declared ineligible for participation by a medical doctor	(=3.8)	**Para-probiotic Duration:** 20 weeks **Comparator:** placebo **Additional supplement:** None		
Silk et al.[34] 2009 United Kingdom	**Study design:** Crossover RCT **Dates of recruitment:** Jan 2006 - Dec 2006 **Inclusion Criteria:** 18-80 years old, diagnosed with IBS; and not organic gastrointestinal disease, including inflammatory bowel disease	**Intervention 1:** n= 16 (females: NR) Mean age (range): NR **Control 1:** n= 16 (females: NR) Mean age (range): NR **Intervention 2:**	**Type:** Trans-galactooligosaccharide **Prebiotic Dosage:** 3.5 g or 7.0 g per each dry powder/ day **Additional supplement:** None **Prebiotic Duration:** 4	• HADS-D	• No evidence of significant effect due to intervention

	Exclusion Criteria: functional disorder of the upper gastrointestinal tract for which treatment had not been stable for the preceding three months; abnormal haematological and biochemical indices; abnormal findings on barium enema or colonoscopy within previous 5 years; ingestion of pre- or probiotics in the 2 weeks preceding the trial	n= 14 (females: NR) Mean age (range): NR **Control 2:** n= 14 (females: NR) Mean age (range): NR	weeks **Comparator:** Placebo **Additional supplement:** None		
Simren et al.[35] 2010 Sweden	**Study design:** RCT **Dates of recruitment:** Sept 2005 - Oct 2006 **Inclusion Criteria:** 18 - 70 years old, diagnosed with IBS; able to understand and willing to comply to the study procedures **Exclusion Criteria:** Participation in another clinical study one month prior to screening visit and through the study; abnormal results on the screening	**Intervention** n=37 (females: 26) Mean age (SD): 42 (15) **Control** n=37 (females: 26) Mean age (SD): 44 (16)	**Type:** Fermented milk with yoghurt bacteria (*Lactobacillus bulgaricus* and *Streptococcus thermophiles*) and 3 probiotics: *L. paracasei, ssp. paracasei* F19, *L. acidophilus* La5 and *Bifidobacterium lactis* Bb12 (Cultura; active) **Probiotic Dosage:** $5x10^7$ CFU/ ml each 400 ml/ day **Additional supplement:** None	• HADS-D	• No evidence of significant difference due to intervention

	laboratory test clinical relevant to study participation; other gastrointestinal disease(s) explaining the patient's symptoms as judged by the investigator; other severe disease(s) such as malignancy, severe heart disease, kidney disease or neurological disease; symptoms indicating other severe disease(s) such as gastrointestinal bleeding, weight loss or fever; severe psychiatric disease; previous history of drug or alcohol abuse 6 months prior to screening; intolerance or allergy against milk products or gluten; use of other probiotic products 2 weeks prior to study and through the study; consumption of antibiotic one months prior to screening and through the study; consumption of cortisone, NSAID or other anti-inflammatory drugs on a regular basis two weeks prior to screening and throughout the study;		**Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** No		

	pregnant or lactating or planning to become pregnant during the study period				
Slykerman et al.[36] 2017 New Zealand	**Study design:** RCT **Dates of recruitment:** Dec 2012 – Nov 2014 **Inclusion Criteria:** Pregnant women 14-16 weeks gestation; English-speaking; planning to breastfeed; if either they or the unborn child's biological father had a history of asthma, hay fever or eczema requiring medication **Exclusion Criteria:** aged <16 years; planning to move outside the study centres during study duration; planning on taking probiotics; serious medical or health problems related to the pregnancy	**Intervention** n=193 (female: 193) Mean age (SD): 33.5 (4.24) **Control** n=187 (female: 187) Mean age (SD): 33.7 (4.44)	**Type:** *Lactobacillus rhamnosus* (HN001) **Probiotic Dosage:** HN001, 6×10^9 CFUs/day **Additional supplement:** None **Probiotic Duration:** 12 months **Comparator:** Placebo **Additional supplement:** None	• EPDS	• Mothers in the probiotic treatment group reported significantly lower depression scores than those in the placebo group (-1·2, 95% CI (-2·4, -0·1), p=0.035)
Smith-Ryan et al.[37] 2019 United States	**Study design:** RCT **Dates of recruitment:** Sep 2016 – Jan 2018	**Intervention** n=15 (female: 15) Mean age (SD): 30.5 (7.7)	**Type:** *Bifidobacterium bifidum* W23*, B. lactis* W51*, B. lactis* W52*, Lactobacillus acidophilus* W37*, L. brevis* W63*, L.*	• HADS-D	• No significant difference between intervention and control.

	Inclusion Criteria: premenopausal female volunteers between the ages of 21 and 55 years; employed as shift workers (i.e., nurses, certified nursing assistants, emergency medical services personnel), working for at least 6 months on a rotating day/night or night-shift schedule prior to study participation; healthy, with no history of cardiovascular disease or renal, hepatic, or musculoskeletal disorders **Exclusion Criteria:** not maintained a stable body mass (±3 kg); had been consuming a daily probiotic supplement in the 2 months prior to baseline testing	**Control** n=18 (female: 18) Mean age (SD): 30.2 (10.0)	*casei* W56, *L. salivarius* W24, and *Lactococcus lactis* (W19 and W58) Prebiotic: resistant maize starch (W117). **Synbiotic Dosage:** Probiotic mixture: 2.5 × 10^9 CFU/g, 4g packet/day Prebiotic mixture: 10g/ day **Additional supplement:** None **Synbiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None		
Steenbergen et al.[38] 2015 Netherlands	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** non-smoking young adults, with no reported cardiac, renal, or hepatic conditions, no	**Intervention** n=20 (female: 15) Mean age (SD): 20.2 (2.4) **Control** n=20 (female: 17)	**Type:** *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *and Lactococcus lactis* (W19 and W58)	• LEIDS-R • BDI-2	• Probiotic significantly improved LEIDS-R ($p<0.001$). • No evidence of significant improvement in BDI due to probiotic

	allergies or intolerance to lactose or gluten, no prescribed medication or drug use; consuming no more than 3–5 alcohol units per week; no psychiatric or neurological disorders; no personal or family history of depression or migraine **Exclusion Criteria:** NR	Mean age (SD): 19.7 (1.7)	**Probiotic Dosage:** $2.5x10^9$ CFUs/g, 2g/day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None		
Vaghef-Mehrabany et al.[39] 2019 Iran	**Study design:** RCT **Dates of recruitment:** Jun 2018- Sept 2018 **Inclusion Criteria:** female, 20-50 years old; diagnosed with MDD based on DSM-5 criteria ; antidepressant therapy for at least 6 months before the study; obese BMI: 30–40 kg/m^2; non-menopausal **Exclusion Criteria:** Pregnancy or lactation; co-morbidity with other major psychiatric or neurological diseases, or	**Intervention** n= 31 (females: 31) Mean age (SD): 37.45 (6.77) **Control** n=31 (females: 31) Mean age (SD): 40.0 (8.66)	**Type:** Inulin **Prebiotic Dosage:** 10 g/ day **Additional supplement:** None **Prebiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• HAM-D BDI-2	• No evidence of significant effect due to intervention

	thyroid dysfunctions; drug/ substance abuse or smoking; under weight-loss diets or weight loss drugs during the last year; using fiber, prebiotic or probiotic products or supplements or antibiotics during 2 months prior to the study				

Abbreviations: RCT – randomized controlled trial; MDD – major depressive disorder; DSM-IV/V – Diagnostic and Statistical Manual of Mental Disorders IV/V; CFU – colony forming units; BDI – Beck Depression Inventory; HIV/AIDS – human immunodeficiency virus/ acquired immunodeficiency syndrome; DASS21/42-D – Depression Anxiety and Stress Scales 21/42 items-Depression Scale; LEIDS-R – Leiden Index of Depression Sensitivity-Revised; GDS-SF – Geriatric Depression Scale-Short Form; NR – not reported; HAM-D – Hamilton Depression Rating Scale; POMS-2 – Profile of Mood States 2; PHQ-9/15 – Patient Health Questionnaire-9/15 items; MS – multiple sclerosis; IBS – irritable bowel syndrome; HADS-D – Hospital Anxiety and Depression Scale-Depression Score; MADRS - Montgomery–Åsberg Depression Rating Scale; CES-D – Centre for Epidemiological Studies-Depression Scale; TRD – treatment resistant depression; QIDS – Quick Inventory of Depressive Symptomatology; Zung-SDS – Zung Self-Rating Depression Scale; EPDS – Edinburgh Postnatal Depression Scale; SSRI - selective-serotonin reuptake inhibitor; SNRI - serotonin-noradrenalin reuptake inhibitor

Characteristics of studies presenting insufficient information for inclusion in meta-analysis:

Author, Year, Country	Research Methods	Participant Characteristics	Intervention	Relevant Outcomes	Findings	Reason for Exclusion from Meta-Analysis
Azpiroz et al.[40] 2017 France, Spain	**Study design:** RCT **Dates of Recruitment:** NR **Inclusion Criteria:** IBS patients (18-60 years age) fulfilling Rome III criteria **Exclusion Criteria:** Antibiotic use in the last two months, were currently under treatment for depression, presented known psychiatric pathology, had a history of organic intestinal disease, gastrointestinal surgery, family history of colon cancer, inflammatory bowel disease, thyroid dysfunction, Hirschsprung disease, diabetes, anorexia, scleroderma, pregnancy, known allergy, alcohol or tobacco abuse (more than 30g alcohol or 20 cigarettes per day) or were included in another clinical study	**Intervention** n=41 (females: 32) Mean age (SD): 41.0 (11.1) **Control** n=38 (females: 28) Mean age (SD): 42.4 (10.6)	**Type:** Short chain fructooligoscaccharides **Prebiotic Dosage:** 5g /day **Additional supplement:** None **Prebiotic Duration:** 28 days **Comparator:** Placebo **Additional supplement:** None	• HADS-D	• No evidence of significant difference due to intervention	• Insufficient detail reported

Benton et al.[41] 2007 NR	**Study Design:** RCT **Dates of Recruitment:** NR **Inclusion Criteria:** by self-report, in good health and did not consume yoghurt containing live bacteria **Exclusion Criteria:** Depression; dementia; schizophrenia; any neurological disorder; clinically significant problems of the heart, lungs, kidney, or liver; if malignancy had occurred, it had been in remission for at least 2 years; diabetes not controlled by diet or oral hypoglycaemic agents; hypothyroidism not stabilized by replacement therapy for more than 6 months; untreated or unstable hypertension for at least 3 months	**Intervention** n=NR (females: NR) Age: NR **Control** n=NR (females: NR) Age: NR **Intervention (probiotic + dietary treatment)** n=9 (females: NR) Median age (range): 51 (44 to 72) **Control (dietary treatment)** n=10 (females: NR) Median age (range): 36.5 (21 to 72)	**Type:** *Lactobacillus casei* Shirota **Probiotic Dosage:** $6.5x10^9$ live bacteria **Probiotic Duration:** 3 weeks **Comparator:** Placebo **Additional supplement:** Skimmed milk powder	• POMS	• No evidence of effect due to intervention reported.	• Insufficient detail reported
Cremon et al.[42] 2018 Italy	**Study design:** RCT – Cross over **Dates of recruitment:** NR **Inclusion Criteria:** 18- 65	**Intervention** n=20 (females: 11) Mean age (SD): 37.35 (11.25)	**Type:** *Lactobacillus paracasei* CNCM I-1572 (LCDG) **Probiotic Dosage:** 24 billion viable cells of the bacterial	• HADS-D	• No evidence of significant effect due to intervention reported	• Insufficient detail reported

	years old diagnosed with all IBS subtypes; negative colonoscopy or barium enema examination within the previous 2 years, and negative relevant additional screening or consultation whenever appropriate. **Exclusion Criteria:** pregnant, breast-feeding, or not using 11 reliable methods of contraception; intestinal organic diseases, such as celiac disease, diverticular disease, or inflammatory bowel diseases (IBDs; e.g., Crohn's disease, ulcerative 14 colitis, infectious colitis, ischemic colitis, or microscopic colitis); previous major abdominal surgery; untreated food intolerance, such as ascertained or suspected lactose intolerance; consumption of probiotics or topical and/or systemic antibiotic therapy during the month before study enrolment; frequent consumption of contact laxatives; presence of any	**Control** n=20 (females: 15) Mean age (SD): 44.55 (12.98)	strain LCDG each capsule 2/day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None			

	relevant organic, systemic, or metabolic disease as assessed by medical history, appropriate consultations, and laboratory tests; or abnormal laboratory values deemed clinically significant on the basis of predefined values					
Dickerson et al.[43] 2018 United States	**Study design:** RCT **Dates of Recruitment:** Nov 2012 - Dec 2016 **Inclusion Criteria: A**ge 18-65 years, inclusive; capacity to provide written informed consent; current admission to an inpatient or day hospital program for symptoms of a manic episode and with a primary diagnosis of bipolar I (single manic episode, most recent episode manic, or most recent episode mixed) or schizoaffective disorder, bipolar type (manic or mixed state) (DSM-IV-TR) confirmed with the Structured Clinical Interview for Diagnosis for DSM-IV Axis I disorders; proficient in English; and	**Intervention** n=33 (females: 24) Mean age (SD): 37.9 (11.7) **Control** n= 33 (females: 18) Mean age (SD): 33.3 (13.3)	**Type:** *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *Lactis* strain Bb12 **Probiotic Dosage:** >10^8 CFU daily **Additional supplement:** None **Probiotic Duration:** 24 weeks **Comparator:** Placebo **Additional supplement:** None	• MADRS	• No evidence of significant effect due to intervention reported	• Insufficient detail reported

	available for follow-up visits **Exclusion Criteria:** Substance or medically induced symptoms of mania at hospital admission; HIV infection or other immunodeficiency condition; serious medical condition affecting brain or cognitive functioning; diagnosis of mental retardation; diagnosis of substance abuse or dependence according to DSM-IV-TR criteria within the last 3 months; history of any intravenous drug use; participation in an investigational drug trial in the past 30 days; pregnant or planning to become pregnant during the study period; documented celiac disease.					
Makino et al.[44] 2018 Japan	**Study design:** RCT **Dates of recruitment:** Jun 2015 – Sep 2015 **Inclusion Criteria:** Males with summer heat fatigue, residents of Tokyo and its suburbs, aged	**Intervention** n= 25 (females:0) Mean age (SD): 40.1 (6.0) **Control** n= 24 (females:0)	**Type:** Yogurt fermented with *Lactobacillus bulgaricus* OLL1073R-1 and *Streptococcus thermophilus* OLS3059 **Probiotic Dosage:** Fermented yogurt with	• POMS	• No evidence of significant effect due to intervention	• Insufficient detail reported

	between 30 and 49 years, body mass index (BMI) between 18.5 and 29.9, non-smokers, day-shift desk workers, with stable dietary habits. **Exclusion Criteria:** presence of immunodeficiency, patients with malignancy, outpatients or patients requiring drug treatment, allergies to food or medicines, lactose intolerance, regular intake of alcohol at more than 60 g/day, more than 2 intakes per week of fermented milk or beverages containing lactic acid bacteria in the past 3 months, intake habits for antibiotics, laxatives, functional foods, or supplements containing oligosaccharides, dietary fibers, or lactic acid bacteria in the past 3 months, participants of other clinical studies in the past 1 month	Mean age (SD): 39.8 (6.2)	exopolysaccharide ≥ 2.9 mg in 100 mL yogurt / day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None			
Nishida et al.[45]	**Study design:** RCT	**Intervention** n= 16 (females: 5)	**Type:** Heat killed *Lactobacillus gasseri* strain	• Zung-SDS	• No evidence of	• Insufficient

2017 Japan	**Dates of recruitment:** Sept 2007 – Oct 2007 **Inclusion Criteria:** Second year undergraduate medical students at Tokushima University between 18 – 24 years of age **Exclusion Criteria:** Habitual smokers, medication taken for 3 months prior to enrolment, individuals with psychological or physical disorders or milk or other food allergies	Mean age (SEM): 20.75 (0.40) **Control** n= 16 (females: 6) Mean age (SEM): 21.31 (0.90)	CP2305 **Para-probiotic Dosage:** 1 x 10^{10} bacterial cells/day **Additional supplement:** None **Para-probiotic Duration:** 5 weeks **Comparator:** Placebo **Additional supplement:** None	• HADS-D	significant effect of intervention on HADS-D • Zung-SDS outcomes not reported	detail reported
Rao et al.[46] 2009 Canada	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Candidates for inclusion were screened from a pool of Chronic Fatigue Syndrome patients in a tertiary setting. Adult patients aged 18 – 65 in the formal diagnostic criteria for CFS and suitability to complete a two-month trial, provide written informed consent. **Exclusion Criteria:** patients with unstable physical illness,	**Intervention** n=19 (females: NR) Mean age (SD): NR **Control** n= 16 (females: NR) Mean age (SD): NR	**Type:** *Lactobacillus casei* strain Shirota **Probiotic Dosage:** 8 x 10^{9} CFU/day **Additional supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• No evidence of significant effect due to intervention	• Insufficient detail reported

	severe CFS such that they were largely bedridden, patients meeting criteria for psychiatric disorders other than depression and/or anxiety					
Smith et al.[47] 2005 United Kingdom	**Study design:** RCT- Crossover **Dates of recruitment:** Not reported **Inclusion Criteria:** Volunteers **Exclusion Criteria:** Not reported	**Intervention** n= 142 (females: 72) Mean age (range): 32 (19-64) **Control** n= 142 (females: 72) Mean age (range): 32 (19-64)	**Type:** Oligofructose-enriched Inulin **Prebiotic Dosage:** 5 g per each sachet of dry powder 2/ day **Prebiotic Duration:** 2 weeks **Comparator:** placebo **Additional supplement:** No	• HADS-D	• No evidence of significant effect due to intervention	• Prebiotic intervention
Tillisch et al.[48] 2013 United States	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** 18-55 years	**Intervention** n= 12 (females: 12) Mean age (SD): NR	**Type:** Fermented milk product with probiotic: *Bifidobacterium animalis* subsp *Lactis*, *Streptococcus thermophiles, Lactobacillus*	• HADS-D	• No evidence of significant effect due to intervention	• Insufficient detail reported

	of age; healthy women with no gastrointestinal or psychiatric symptoms; , body mass index 18 –30; have not taken antibiotics or probiotics in the month prior to the study and were willing to avoid use of probiotics for the duration of the study **Exclusion Criteria:** Lactose intolerance; chronic gastrointestinal symptoms; chronic or acute pain disorder; psychiatric disorder or other medical condition; subjects with *Bifidobacterium lactis* present in the stool at baseline, as well as subjects in the Control and No-Intervention groups, who had *B lactis* in the stool at study completion	**Control- nonfermented milk** n= 11 (females: 11) Mean age (SD): NR **Control- no intervention** n= 13 (females: 13) Mean age (SD): NR	*bulgaricus, and Lactococcus lactis* subsp *Lactis* **Probiotic Dosage:** 1.25x10^{10} CFUs *B lactis* CNCM I-2494/DN-173 010/ cup and 1.2 × 10^{9} CFU/cup of *S thermophilus* and *L bulgaricus.* 125-g pot consumed twice daily **Additional supplement:** None **Probiotic Duration:** 2 weeks **Comparator:** nonfermented milk/ no-intervention **Additional supplement:** None			
Whorwell et al.[49] 2006 United Kingdom	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Women 18-65 years old diagnosed with IBS and in whom organic diseases, including inflammatory	**Intervention 1- BIFIDO6** n=90 (females: 90) Mean age (SD): 40.8 (1.10) **Intervention 2- BIFIDO8**	**Type:** *Bifidobacterium infantis* 35624 (BIFIDO) **Probiotic Dosage:** *BIFIDO6* 1x10^{6} CFU/ ml each capsule 1/ day *BIFIDO8* 1x10^{8} CFU/ ml each capsule 1/ day *BIFIDO10* 1x10^{10} CFU/ ml	• HADS-D	• No evidence of significant effect due to intervention	• Insufficient detail reported

	bowel disease, and significant systemic diseases had been excluded **Exclusion Criteria:** Pregnant; over 55 years of age and had not had a sigmoidoscopy or colonoscopy performed in the previous 5 years, had used antipsychotic medications within the prior 3 months or systemic steroids within the prior month, had suffered major psychiatric disorder within the past 2 years; lactose intolerance or immunodeficiency; had undergone any abdominal surgery, with the exception of hernia repair or appendectomy	n=90 (females: 90) Mean age (SD): 42.7 (1.10) **Intervention 3- BIFIDO10** n=90 (females: 90) Mean age (SD): 41.8 (1.10) **Control** n=92 (females: 92) Mean age (SD): 42.4 (1.09)	each capsule 1/ day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None			
Wong et al.[50] 2015 Singapore	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** 20 - 76 years old, diagnosed with IBS **Exclusion Criteria:** Stool culture was positive for bacterial pathogens (Salmonella and Shigella);	**Intervention** n=20 (females: 8) Mean age (SD): 53.35 (4.15) **Control** n=22 (females: 11) Mean age (SD): 40.86 (3.51)	**Type:** *Bifidobacterium* (*B. longum, B. infantis and B. breve*); *Lactobacillus* (*L. acidophilus, L. casei, L. delbrueckii ssp. bulgaricus and L. plantarum*); and *Streptococcus salivarius* ssp. *thermophilus* **Probiotic Dosage:** 112.5 billion viable lyophilized	• HADS-D	• No evidence of significant effect due to intervention	• Insufficient detail reported

	parasites (Giardia) and ova/cysts on microscopy; positive faecal occult blood test; pregnant or breast-feeding; had organic gastrointestinal, anal, hepatic, or other systemic disorders; previous gastrointestinal surgery history except appendectomy; history of cerebral disease or surgery		bacteria each capsule 4/ day **Additional supplement:** None **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None			

Abbreviations: RCT – randomized controlled trial; NR – not reported; IBS – irritable bowel syndrome; HADS-D – Hospital Anxiety and Depression Scale-Depression Score; CFU – colony forming units; BID – Beck Depression Inventory; POMS – Profile of Mood States; HAM-D – Hamilton Depression Rating Scale; MADRS - Montgomery–Åsberg Depression Rating Scale; DSM-IV-TR – Diagnostic and Statistical Manual of Mental Disorders IV – Text Revision; QIDS – Quick Inventory of Depressive Symptomatology; GI – gastrointestinal; FMT – fecal microbiota transplant; Zung-SDS – Zung Self-Rating Depression Scale; MDD – major depressive disorder;

Appendix 5: Studies presenting insufficient information for inclusion in meta-analysis

Randomized controlled trials excluded from meta-analysis for failure to provide necessary information for meta-analysis. If design not indicated in left-most column, study is a parallel arm RCT.

Author, Year (design)	Intervention	Population	Assessment Tools	Duration in Weeks (n)	Overall Risk of Bias	Placebo (n)	Intervention (n)	Conclusion
Azpiroz, 2017[40]	Prebiotic	IBS	HADS-D	4	Some Concerns	38	41	No significant difference
Benton, 2007[41]	Probiotic	Good Health	POMS	3	High	NR	NR	No significant difference
Cremon, 2018[42] (crossover RCT)	Probiotic	IBS	HADS-D	4	Some Concerns	20	20	No significant difference
Dickerson, 2018[43]	Probiotic	Bipolar I; or Schizoaffective Disorder; or Bipolar Type Manic or Mixed	MADRS	24	Some Concerns	33	33	No significant difference
Makino, 2018[44]	Probiotic	Males, summer heat fatigue	POMS	12	High	24	25	No significant difference
Nishida, 2017[45]	Para-probiotic	Medical Students	Zung SDS, HADS-D	5	High	16	16	No significant difference in HADS-D; Zung SDS not reported
Rao, 2009[46]	Probiotic	Chronic Fatigue Syndrome	BDI	8	High	16	19	No significant difference
Smith, 2005[47] (crossover RCT)	Prebiotic	Volunteers	HADS-D	2	High	142	142	No significant difference
Tillisch, 2013[48]	Probiotic	Healthy Women	HADS-D	2	High	24	12	No significant difference
Whorwell, 2006[49]	Probiotic	IBS	HADS-D	4	High	270	92	No significant difference
Wong, 2015[50]	Probiotic	IBS	HADS-D	6	High	22	20	No significant difference

Appendix 6: Risk of bias

Cochrane Risk of Bias 2.0 Results for parallel arm and crossover randomized controlled trials

First Author (Year)	Bias from Randomiz-ation	Bias from Deviation	Bias from Missing Outcome Data	Bias from Measurement	Bias in Reported Results	Overall Risk of Bias
Probiotics						
Akkasheh et al.[1] (2016)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Benton et al.[41] (2007)	Some Concerns	Low Risk	High Risk	Low Risk	High Risk	High Risk
Chahwan et al.[2] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Chong et al.[3] (2019)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Chung et al.[4] (2014)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Cremon et al.[42] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Dickerson et al.[43] (2018)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Gomi et al.[6] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Inoue et al.[7] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Jamilian et al.[8] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Kazemi et al.[9] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Kelly et al.[10] (2017)	Some Concerns	High Risk	Low Risk	Low Risk	Some Concerns	High Risk
Kouchaki et al.[12] (2016)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Lew et al.[13] (2018)	Low Risk	Some Concerns	High Risk	Low Risk	Some Concerns	High Risk
Lyra et al.[14] (2016)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Majeed et al.[15] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Makino et al.[44] (2018)	Some Concerns	Low Risk	Some Concerns	Low Risk	Some Concerns	High Risk
Marotta et al.[16] (2019)	Low Risk	Some Concerns	Some Concerns	Low Risk	Some Concerns	High Risk

Messaoudi et al.[17] (2011)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Miyaoka et al.[18] (2018)	High Risk	Some Concerns	Low Risk	High Risk	Some Concerns	High Risk
Ostadmohammadi et al.[19] (2019)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Östlund-Lagerström et al.[20] (2016)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Papalini et al.[21] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Pinto-Sanchez et al.[22] (2017)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Rao et al.[46] (2009)	Some Concerns	High Risk	High Risk	Low Risk	Some Concerns	High Risk
Raygan et al.[24] (2018)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Raygan et al.[23] (2019)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Roman et al.[25] (2018)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Romjin et al.[26] (2017)	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
Rudzki et al.[27] (2019)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Salami et al.[28] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Sawada et al.[31] (2017)	Some Concerns	Low Risk	Some Concerns	Low Risk	Some Concerns	High Risk
Sawada et al.[32] (2019)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Simren et al.[35] (2010)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Slykerman et al.[36] (2017)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Steenbergen et al.[38] (2015)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Tillisch et al.[48] (2013)	Some Concerns	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk

Whorwell et al.[49] (2006)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	High Risk
Wong et al.[50] (2015)	High Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk
Prebiotics						
Azpiroz et al.[40] (2017)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Kazemi et al.[9] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Silk et al.[34] (2009)	Some Concerns	Some Concerns	Some Concern	Low Risk	Some Concerns	High Risk
Smith et al.[47] (2005)	High Risk	Some Concerns	High Risk	Some Concerns	Some Concerns	High Risk
Vaghef-Mehrabany et al.[39] (2019)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Synbiotics						
Ghorbani et al.[5] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sanchez et al.[29] (2017)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Smith-Ryan et al.[37] (2019)	Some Concerns	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Para-probiotics						
Kitaoka et al.[11] (2008)	Some Concerns	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk
Nishida et al.[45] (2017)	Some Concerns	High Risk	Low Risk	High Risk	High Risk	High Risk
Sashihara et al.[30] (2013)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Shinkai et al.[33] (2012)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	High Risk

References for Appendices Four, Five, and Six

1. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition.* 2016;32(3):315-320.
2. Chahwan B, Kwan S, Isik A, van Hemert S, Burke C, Roberts L. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. *Journal of Affective Disorders.* 2019;253:317-326.
3. Chong HX, Yusoff'l NAA. Lactobacil/us plantarum DR7 alleviates stress and anxiety in adults: a randomised , double-blind, placebo-controlled study. *Beneficial Microbes.*19.
4. Chung Y-C, Jin H-M, Cui Y, et al. Fermented milk of Lactobacillus helveticus IDCC3801 improves cognitive functioning during cognitive fatigue tests in healthy older adults. *Journal of Functional Foods.* 2014;10:465-474.
5. Ghorbani Z, Nazari S, Etesam F, Nourimajd S, Ahmadpanah M, Razeghi Jahromi S. The Effect of Synbiotic as an Adjuvant Therapy to Fluoxetine in Moderate Depression: A Randomized Multicenter Trial. *Arch Neurosci.* 2018;5(2).
6. Gomi A, Yamaji K, Watanabe O, et al. Bifidobacterium bifidum YIT 10347 fermented milk exerts beneficial effects on gastrointestinal discomfort and symptoms in healthy adults: A double-blind, randomized, placebo-controlled study. *Journal of Dairy Science.* 2018;101(6):4830-4841.
7. Inoue T, Kobayashi Y, Mori N, et al. Effect of combined bifidobacteria supplementation and resistance training on cognitive function, body composition and bowel habits of healthy elderly subjects. *Beneficial Microbes.* 2018;9(6):843-853.
8. Jamilian M, Mansury S, Bahmani F, Heidar Z, Amirani E, Asemi Z. The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. *J Ovarian Res.* 2018;11(1):80.
9. Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clinical Nutrition.* 2019;38(2):522-528.
10. Kelly JR, Allen AP, Temko A, et al. Lost in translation? The potential psychobiotic Lactobacillus rhamnosus (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. *Brain, Behavior, and Immunity.* 2017;61:50-59.
11. Kitaoka K, Uchida K, Okamoto N, et al. Fermented Ginseng Improves the First-Night Effect in Humans. 2009;32(3):10.
12. Kouchaki E, Tamtaji OR, Salami M, et al. Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition.* 2017;36(5):1245-1249.
13. Lew L-C, Hor Y-Y, Yusoff NAA, et al. Probiotic Lactobacillus plantarum P8 alleviated stress and anxiety while enhancing memory and cognition in stressed adults: A randomised, double-blind, placebo-controlled study. *Clinical Nutrition.* 2019;38(5):2053-2064.
14. Lyra A, Hillilä M, Huttunen T, et al. Irritable bowel syndrome symptom severity improves equally with probiotic and placebo. *WJG.* 2016;22(48):10631.
15. Majeed M, Nagabhushanam K, Arumugam S, Majeed S, Ali F. Bacillus coagulans MTCC 5856 for the management of major depression with irritable bowel syndrome: a randomised, double-blind, placebo controlled, multi-centre, pilot clinical study. *Food & Nutrition Research.* 2018;62(0).
16. Marotta A, Sarno E, Del Casale A, et al. Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality. *Front Psychiatry.* 2019;10:164.

17. Messaoudi M, Lalonde R, Violle N, et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. *Br J Nutr.* 2011;105(5):755-764.
18. Miyaoka T, Kanayama M, Wake R, et al. Clostridium butyricum MIYAIRI 588 as Adjunctive Therapy for Treatment-Resistant Major Depressive Disorder: A Prospective Open-Label Trial. *Clinical Neuropharmacology.* 2018;41(5):151-155.
19. Ostadmohammadi V, Jamilian M, Bahmani F, Asemi Z. Vitamin D and probiotic co-supplementation affects mental health, hormonal, inflammatory and oxidative stress parameters in women with polycystic ovary syndrome. *J Ovarian Res.* 2019;12.
20. Östlund-Lagerström L, Kihlgren A, Repsilber D, Björkstén B, Brummer RJ, Schoultz I. Probiotic administration among free-living older adults: a double blinded, randomized, placebo-controlled clinical trial. *Nutr J.* 2015;15(1):80.
21. Papalini S, Michels F, Kohn N, et al. Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. *Neurobiology of Stress.* 2019;10:100141.
22. Pinto-Sanchez MI, Hall GB, Ghajar K, et al. Probiotic Bifidobacterium longum NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome. *Gastroenterology.* 2017;153(2):448-459.e448.
23. Raygan F, Ostadmohammadi V, Asemi Z. The effects of probiotic and selenium co-supplementation on mental health parameters and metabolic profiles in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition.* 2019;38(4):1594-1598.
24. Raygan F, Ostadmohammadi V, Bahmani F, Asemi Z. The effects of vitamin D and probiotic co-supplementation on mental health parameters and metabolic status in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2018;84:50-55.
25. Roman P, Estévez AF, Miras A, et al. A Pilot Randomized Controlled Trial to Explore Cognitive and Emotional Effects of Probiotics in Fibromyalgia. *Sci Rep.* 2018;8(1):10965.
26. Romijn AR, Rucklidge JJ, Kuijer RG, Frampton C. A double-blind, randomized, placebo-controlled trial of Lactobacillus helveticus and Bifidobacterium longum for the symptoms of depression. *Aust N Z J Psychiatry.* 2017;51(8):810-821.
27. Rudzki L, Ostrowska L, Pawlak D, et al. Probiotic Lactobacillus Plantarum 299v decreases kynurenine concentration and improves cognitive functions in patients with major depression: A double-blind, randomized, placebo controlled study. *Psychoneuroendocrinology.* 2019;100:213-222.
28. Salami M, Kouchaki E, Asemi Z, Tamtaji OR. How probiotic bacteria influence the motor and mental behaviors as well as immunological and oxidative biomarkers in multiple sclerosis? A double blind clinical trial. *Journal of Functional Foods.* 2019;52:8-13.
29. Sanchez M, Darimont C, Panahi S, et al. Effects of a Diet-Based Weight-Reducing Program with Probiotic Supplementation on Satiety Efficiency, Eating Behaviour Traits, and Psychosocial Behaviours in Obese Individuals. *Nutrients.* 2017;9(3):284.
30. Sashihara T, Nagata M, Mori T, et al. Effects of *Lactobacillus gasseri* OLL2809 and α-lactalbumin on university-student athletes: a randomized, double-blind, placebo-controlled clinical trial. *Appl Physiol Nutr Metab.* 2013;38(12):1228-1235.
31. Sawada D, Kawai T, Nishida K, Kuwano Y, Fujiwara S, Rokutan K. Daily intake of Lactobacillus gasseri CP2305 improves mental, physical, and sleep quality among Japanese medical students enrolled in a cadaver dissection course. *Journal of Functional Foods.* 2017;31:188-197.

32. Sawada D, Kuwano Y, Tanaka H, et al. Daily intake of Lactobacillus gasseri CP2305 relieves fatigue and stress-related symptoms in male university Ekiden runners: A double-blind, randomized, and placebo-controlled clinical trial. *Journal of Functional Foods.* 2019;57:465-476.
33. Shinkai S, Toba M, Saito T, et al. Immunoprotective effects of oral intake of heat-killed *Lactobacillus pentosus* strain b240 in elderly adults: a randomised, double-blind, placebo-controlled trial. *Br J Nutr.* 2013;109(10):1856-1865.
34. Silk DBA, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics.* 2009;29(5):508-518.
35. Simrén M, Öhman L, Olsson J, et al. Clinical trial: the effect of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome (IBS) - a randomized, double-blind, controlled study. *Alimentary Pharmacology & Therapeutics.* 2009.
36. Slykerman RF, Hood F, Wickens K, et al. Effect of Lactobacillus rhamnosus HN001 in Pregnancy on Postpartum Symptoms of Depression and Anxiety: A Randomised Double-blind Placebo-controlled Trial. *EBioMedicine.* 2017;24:159-165.
37. Smith-Ryan AE, Mock MG, Trexler ET, Hirsch KR, Blue MNM. Influence of a multistrain probiotic on body composition and mood in female occupational shift workers. *Appl Physiol Nutr Metab.* 2019;44(7):765-773.
38. Steenbergen L, Sellaro R, van Hemert S, Bosch JA, Colzato LS. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. *Brain, Behavior, and Immunity.* 2015;48:258-264.
39. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. *Nutritional Neuroscience.* 2019:1-15.
40. Azpiroz F, Dubray C, Bernalier-Donadille A, et al. Effects of scFOS on the composition of fecal microbiota and anxiety in patients with irritable bowel syndrome: a randomized, double blind, placebo controlled study. *Neurogastroenterol Motil.* 2017;29(2):e12911.
41. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr.* 2007;61(3):355-361.
42. Cremon C, Guglielmetti S, Gargari G, et al. Effect of *Lactobacillus paracasei* CNCM I-1572 on symptoms, gut microbiota, short chain fatty acids, and immune activation in patients with irritable bowel syndrome: A pilot randomized clinical trial. *United European Gastroenterology Journal.* 2018;6(4):604-613.
43. Dickerson F, Adamos M, Katsafanas E, et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. *Bipolar Disord.* 2018;20(7):614-621.
44. Makino S, Hemmi J, Kano H, Kashiwagi M, Hojo K, Asami Y. Anti-Fatigue Effects of Yogurt Fermented with Lactobacillus delbrueckii subsp. bulgaricus OLL1073R-1 in Healthy People Suffering from Summer Heat Fatigue: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients.* 2018;10(7):798.
45. Nishida K, Sawada D, Kawai T, Kuwano Y, Fujiwara S, Rokutan K. Para-psychobiotic *Lactobacillus gasseri* CP 2305 ameliorates stress-related symptoms and sleep quality. *Journal of Applied Microbiology.* 2017;123(6):1561-1570.
46. Rao AV, Bested AC, Beaulne TM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog.* 2009;1(1):6.

47. Smith AP. The concept of well-being: relevance to nutrition research. *Br J Nutr.* 2005;93(S1):S1-S5.
48. Tillisch K, Labus J, Kilpatrick L, et al. Consumption of Fermented Milk Product With Probiotic Modulates Brain Activity. *Gastroenterology.* 2013;144(7):1394-1401.e1394.
49. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an Encapsulated Probiotic Bifidobacterium infantis 35624 in Women with Irritable Bowel Syndrome. *Am J Gastroenterol.* 2006;101(7):1581-1590.
50. Wong RK, Yang C, Song G-H, Wong J, Ho K-Y. Melatonin Regulation as a Possible Mechanism for Probiotic (VSL#3) in Irritable Bowel Syndrome: A Randomized Double-Blinded Placebo Study. *Dig Dis Sci.* 2015;60(1):186-194.