Supplementary Appendix

Appendix 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

Section 1: Protocol deviations:

Although different to the registered PROSPERO protocol, much of this manuscript adheres to the submitted protocol, including the focus on effects of these interventions, focus on mental health outcomes assessed using validated measures, placebo comparator, data extraction, risk of bias assessment, and strategy for data synthesis. Although differences introduced through protocol deviations increase susceptibility to type I error in meta-analysis, both the protocol registered with PROSPERO and the completed manuscript are exploratory in nature. Neither was intended to provide definitive and conclusive measures of effect size. Given the rapid expansion and breadth of this body of literature, an iterative approach was required to ensure quality and relevance of this systematic review.

To ensure that all relevant literature capturing the effects of all gut-microbiota targeting interventions, a broad literature search was developed. Following abstract review and consultation with domain experts, we identified that the interventions of interest were: probiotics, prebiotics, synbiotics, para-probiotics, and fecal microbiota transplant.

Due to the numerous results encountered, and the focus on effects of these interventions, results were limited to randomized controlled trials only to support causal inference of effect. Even with this additional inclusion criteria, the results were too numerous and diverse to fit into a single manuscript. Therefore, this manuscript explores depressive symptom outcomes. A second manuscript exploring symptoms of all other outcomes (anxiety, cognition, psychosis, and a composite outcome) is being developed.

We had originally intended to stratify analysis by population groups: medical (individuals with a diagnosed medical condition), clinical (individuals with a diagnosis of a mental health condition), and community (individuals without a diagnosed condition). Upon consultation with expert psychiatrists, our approach was refined to focus on populations with depression/depressive symptoms at baseline versus those without. This approach was thought to be more relevant, and less likely to obscure important differences in the primary outcome.

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Section 2: Search strategies

Medline (OVID)

Search start date: 1946

Original Search Date: July 3, 2019

Updated on March 5, 2021

***number of results are provided from searches up to March 4, 2021 in brackets following search terms**

1. exp actinobacteria/ (174059 results)
2. exp bacillus/ (68970 results)
3. exp bacteroidetes/ (25431 results)
4. exp bifidobacterium/ (6347 results)
5. exp enterococcus/ (20395 results)
6. fermentation/ (47510 results)
7. exp firmicutes/ (346925 results)
8. exp lactobacillaceae/ (31191 results)
9. lactobacillus/ (17014 results)
10. exp lactococcus/ (5318 results)
11. exp leuconostoc/ (1969 results)
12. exp microbiota/ (45516 results)
13. probiotics/ or prebiotics/ or synbiotics/ (21106 results)
14. exp saccharomyces cerevisiae proteins/ (49644 results)
15. exp saccharomyces cerevisiae/ (106249 results)
16. exp streptococcus/ (80581 results)
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. (826229 results)
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. (4403 results)
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. (32716 results)
20. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kf. (215419 results)
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 (1361245 results)
22. exp anxiety disorders/ or anxiety/ (159631 results)
23. exp autism spectrum disorder/ (32659 results)
24. exp "bipolar and related disorders"/ (41664 results)
25. exp cognition disorders/ (100031 results)
26. exp dementia/ (174826 results)
27. depression/ (127659 results)
28. exp "Feeding and Eating Disorders"/ (31923 results)
29. exp mood disorders/ (126063 results)
30. exp Psychotic Disorders/ (53627 results)

31. exp schizophrenia/ (107219 results)
32. mental disorders/ (167017 results)
33. exp neurocognitive disorders/ (268257 results)
34. rett syndrome/ (2671 results)
35. exp Stress Disorders, Traumatic/ or exp Stress, Psychological/ (172372 results)
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. (1105031 results)
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. (326142 results)
38. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kf. (32818 results)
39. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kf. (1797)
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 (1641606 results)
41. 21 and 40 (17234 results)
42. animals/ not human/ (4798670 results)
43. 41 not 42 (12930 results)
44. limit 43 to (english or french) (12012 results)
45. limit 44 to (comment or editorial or letter or news) (241 results)
46. 44 not 45 (11771 results)
47. limit 46 to case reports (950 results)
48. 46 not 47 (10821 results)

PsycINFO (OVID)
Search start date: 1806
Original Search Date: July 3, 2019
Updated on March 5, 2021

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 (OVID)
Search start date: 1974
Original Search Date: July 3, 2019
Updated on March 5, 2021

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

Database of Abstracts of Reviews of Effects (DARE) (OVID)
1st Quarter 2016
Updated on March 5, 2021

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 (OVID)
Search start date: 2005
Original Search Date: July 3, 2019
Updated on March 5, 2021

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,kw.
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,kw.
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,kw.
4. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kw.
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,kw.
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,kw.
7. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kw.
8. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kw.
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 Controlled Register of Trials (CENTRAL) (OVID)
March 2021
Original Search Date: July 3, 2019
Updated on March 5, 2021

1. exp actinobacteria/
2. exp bacillus/

3. exp bacteroidetes/
4. exp bifidobacterium/
5. exp enterococcus/
6. fermentation/
7. firmicute.mp
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,kw.
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,kw.
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,kw.
20. ("anti-bacterial agents" or ("anti-bacterial" adj3 "agents") or "antibiotics").tw,kw.
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 Disorder/
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. neurocognitive disorder.mp
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

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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.
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,kw.
38. ((bipolar adj (affective or disorder* or illness)) or (manic adj (disorder* or state*))).tw,kw.
39. ((DSM IV or DSM V) adj3 (psychiatric or mental)).tw,kw.
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 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

Section 3: 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.
Centre for Epidemiological Studies Depression Scale – Korean Version	Korean CES-D	Cho MJ, Kim KH. Use of the Center for Epidemiologic Studies Depression (CES-D) Scale in Korea. The Journal of Nervous & Mental Disease. 1998;186(5):304-310.
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.
Geriatric Depression Scale – Korean Version	GDS-K	Kim JY, Park JH, Lee JJ, Huh Y, Lee SB, Han SK, Choi SW, Lee DY, Kim KW, Woo JI. Standardization of the korean version of the geriatric depression scale: reliability, validity, and factor structure. Psychiatry investigation. 2008;5(4):232–238.
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.
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.

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Section 4: 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
Arteaga-Henríquez et al. (2020)[9]	Study design not of interest
Aydin et al. (2019)[10]	Study design not of interest
Azpiroz et al. (2017)[11]	Duplicate of included study
Bambling et al. (2017)[12]	Study design not of interest
Bannaga et al. (2017)[13]	Conference proceeding
Barthow et al. (2016)[14]	Study design not of interest
Barthow et al. (2019)[15]	Study design not of interest
Begtrup et al. (2013)[16]	Outcome not of interest
Benjamin et al. (2011)[17]	Outcome not of interest
Benton et al. (2007)[18]	Outcome not of interest
Blondel et al. (2018)[19]	Study design not of interest
Buie et al. (2015)[20]	Study design not of interest
Carlsson et al. (2009)[21]	Outcome not of interest
Caso et al. (2016) [22]	Study design not of interest
Ceccarelli et al. (2017)[23]	Outcome not of interest
Ceccarelli et al. (2017)[24]	Study design not of interest
Cepeda et al. (2017)[25]	Study design not of interest
Chahwan et al. (2019)[26]	Duplicate of included study
Clapp et al. (2017)[27]	Study design not of interest
Clark et al. (2016)[28]	Study design not of interest
Colica et al. (2017)[29]	Outcome not of interest
Culpepper et al. (2016)[30]	Outcome not of interest
Dalile et al. (2020)[31]	Intervention not of interest
Dapoigny et al. (2012)[32]	Outcome not of interest
Darbaky et al. (2017)[33]	Not an adult population
De Lorenzo et al. (2017)[34]	Outcome not of interest
Dickerson et al. (2014)[35]	Duplicate of included study
Dinan et al. (2011)[36]	Study design not of interest
Dinan et al. (2018)[37]	Study design not of interest
Diop et al. (2008)[38]	Outcome not of interest
Dubberke et al. (2016)[39]	Outcome not of interest

Dubinkina et al. (2017)[40]	Study design not of interest
Dughera et al. (2007)[41]	Outcome not of interest
Eskandarzadeh et al. (2021)[42]	Outcome not of interest
Farhangi et al. (2018)[43]	Outcome not of interest
Feher et al. (2014)[44]	Study design not of interest
Gerasimov et al. (2018)[45]	Not an adult population
Gertenrich et al. (1970)[46]	Outcome not of interest
Ghaderi et al. (2019)[47]	Duplicate of included study
Gomi et al. (2018)[48]	Outcome not of interest
Grimaldi et al. (2018)[49]	Not an adult population
Gualtierei et al. (2020)[50]	Outcome not of interest
Guglielmetti et al. (2011)[51]	Outcome not of interest
Gupta et al. (2021)[52]	Outcome not of interest
Guyonnet et al. (2007)[53]	Outcome not of interest
Han et al. (2017)[54]	Intervention not of interest
Hilimire et al. (2015)[55]	Study design not of interest
Huang et al. (2019)[56]	Comparator not of interest
Hwang et al. (2019)[57]	Outcome not of interest
Itzhaki et al. (2016)[58]	Study design not of interest
Jaatinen et al. (2014)[59]	Intervention not of interest
Jacka et al. (2019)[60]	Study design not of interest
Jamilian et al. (2021)[61]	Outcome not of interest
Jiang et al. (2018)[62]	Outcome not of interest
Jiang et al. (2019)[63]	Study design not of interest
Jicha et al. (2015)[64]	Conference proceeding
Johnsen et al. (2020)[65]	Outcome not of interest
Julianelle et al. (1923)[66]	Outcome not of interest
Kao et al. (2017)[67]	Outcome not of interest
Karadag et al. (2012)[68]	Conference proceeding
Karakula-Juchnowicz et al. (2019)[69]	Study design not of interest
Karbownik et al. (2020)[70]	Outcome not of interest
Kazemi et al. (2019)[71]	Duplicate of included study
Kazemi et al. (2020)[72]	Outcome not of interest
Kim et al. (2002)[73]	Outcome not of interest
Kim et al. (2018)[74]	Study design not of interest
Kim et al. (2019)[75]	Outcome not of interest
Kitaoka et al. (2009)[76]	Outcome not of interest
Kleiman et al. (2015)[77]	Study design not of interest
Kleiman et al. (2017)[78]	Study design not of interest
Kleiman et al. (2017)[79]	Not an adult population
Kobayashi et al. (2019)[80]	Study design not of interest

Appendix 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

Kreijkamp-Kaspers et al. (2004)[81]	Intervention not of interest
Kretzschmar (2017)[82]	Study design not of interest
Krug et al. (2019)[83]	Conference proceeding
Kurokawa et al. (2018)[84]	Study design not of interest
Langkamp-Henken et al. (2015)[85]	Outcome not of interest
Lecerf (2018) [86]	Study design not of interest
Lee et al. (2014)[87]	Intervention not of interest
Legette et al. (2019)[88]	Conference proceeding
Liu et al. (2016)[89]	Outcome not of interest
Lorenzo-Zuniga et al. (2014)[90]	Outcome not of interest
Ma et al. (2019)[91]	Study design not of interest
Makino et al. (2018)[92]	Outcome not of interest
Marcos et al. (2004)[93]	Outcome not of interest
Marotta et al. (2019)[94]	Duplicate of included study
Mazzawi et al. (2018)[95]	Study design not of interest
Messaoudi et al. (2011)[96]	Duplicate of included study
Mi et al. (2015)[97]	Not an adult population
Miyaoka et al. (2018)[98]	Duplicate of included study
Mohammadi et al. (2016)[99]	Intervention not of interest
Moller et al. (2017)[100]	Duplicate of included study
Morita et al. (2016)[101]	Outcome not of interest
Morita et al. (2017)[102]	Outcome not of interest
Mucci et al. (2006)[103]	Outcome not of interest
Nagamine et al. (2018)[104]	Outcome not of interest
Nagamine et al. (2018)[105]	Outcome not of interest
Nakakita et al. (2016)[106]	Outcome not of interest
Nishida et al. (2017)[107]	Outcome not of interest
Nishihara et al. (2014)[108]	Outcome not of interest
Noorwali et al. (2017)[109]	Conference proceeding
Nova et al. (2006)[110]	Not an adult population
Okubo et al. (2019)[111]	Study design not of interest
Ostlund-Lagerstrom et al. (2016)[112]	Duplicate of included study
Park et al. (2019)[113]	Outcome not of interest
Park et al. (2020)[114]	Comparator not of interest
Paulsen et al. (2017)[115]	Study design not of interest
Perez-Cornago et al. (2016)[116]	Study design not of interest
Peter et al. (2018)[117]	Study design not of interest
Prantera et al. (2002)[118]	Outcome not of interest
Quigley et al. (2009)[119]	Study design not of interest
Rao et al. (2018)[120]	Study design not of interest
Reale et al. (2012)[121]	Outcome not of interest

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Reininghaus et al. (2018)[122]	Study design not of interest
Reininghaus et al. (2020)[123]	Comparator not of interest
Ren et al. (2020)[124]	Intervention not of interest
Roman et al. (2017)[125]	Study design not of interest
Rong et al. (2019)[126]	Study design not of interest
Sanborn et al. (2018)[127]	Study design not of interest
Sanborn et al. (2020)[128]	Outcome not of interest
Sashihara et al. (2013)[129]	Outcome not of interest
Schmidt et al. (2015)[130]	Outcome not of interest
Severance et al. (2016)[131]	Study design not of interest
Severance et al. (2017)[132]	Outcome not of interest
Shafaghi et al. (2016)[133]	Outcome not of interest
Shinkai et al. (2013)[134]	Outcome not of interest
Siddiqui et al. (2013)[135]	Study design not of interest
Singh et al. (2016)[136]	Study design not of interest
Smith et al. (2015)[137]	Outcome not of interest
Soldi et al. (2019)[138]	Outcome not of interest
Stevenson et al. (2014)[139]	Outcome not of interest
Stokes et al. (2015)[140]	Conference proceeding
Takada et al. (2016)[141]	Study design not of interest
Takada et al. (2017)[142]	Study design not of interest
Talbott et al. (2018)[143]	Conference proceeding
Tamtaji et al. (2018)[144]	Outcome not of interest
Tazzyman et al. (2015)[145]	Outcome not of interest
Tomasik et al. (2015)[146]	Outcome not of interest
Tran et al. (2019)[147]	Outcome not of interest
Tran et al. (2019)[147]	Outcome not of interest
Uemura et al. (2019)[148]	Intervention not of interest
Urita et al. (2015)[149]	Not an adult population
Vaghef-Mehrabany et al. (2014)[150]	Outcome not of interest
Vaghef-Mehrabany et al. (2016)[151]	Outcome not of interest
Valles-Colomer et al. (2019)[152]	Study design not of interest
Venkataraman et al. (2021)[153]	Outcome not of interest
Vulevic et al. (2018)[154]	Outcome not of interest
Wallace et al. (2018)[155]	Conference proceeding
Wallace et al. (2021)[156]	Study design not of interest
Wang et al. (2018)[157]	Outcome not of interest
Wang et al. (2019)[158]	Outcome not of interest
Westfall et al. (2018)[159]	Study design not of interest
Wilson et al. (2018)[160]	Study design not of interest
Xia et al. (2018)[161]	Outcome not of interest

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Xiao et al. (2020)[162]	Outcome not of interest
Yang et al. (2016)[163]	Outcome not of interest
Yi et al. (2016)[164]	Study design not of interest
Yuan et al. (2015)[165]	Study design not of interest
Yuan et al. (2018)[166]	Study design not of interest
Zamudio-Tiburcio et al. (2017)[167]	Not English or French
Zhang et al. (2019)[168]	Study design not of interest

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Appendix 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

Section 5: 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
Browne et al.[2] 2021 Netherlands	**Study design:** RCT **Dates of recruitment:** March 2017 - Sept 2018	**Intervention** n=20 (females: 20) Mean age (SD): 29.65 (3.9) **Control**	**Type:** *Bifidobacterium bifidum* W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lactococcus*	• EPDS • LEIDS-R	• Depressive symptoms reduced in both the placebo and intervention groups after 8 weeks, however, differences were non-significant.

	Inclusion Criteria: Elevated levels of depressive symptoms (EPDS ≥ 10) and/or anxiety (STAI-S ≥ 40); start daily probiotic/placebo product intake between 26 and 30 weeks gestational age and continue until delivery **Exclusion Criteria:** (1) multiple pregnancy, (2) high suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview, (3) illegal drug use, (4) psychiatric history of psychoses or bipolar disorder, (5) inflammatory bowel disease, (6) other autoimmune disorders and/or treatment with immunosuppressive therapy, (7) known pre-existing diabetes mellitus, hyperemesis gravidarum, hypertensive disorder, liver and/or renal disease, (8) malignancy and/or treatment with radiation or chemotherapy, (9) history of major gastro-intestinal surgery, (10) allergy or hypersensitivity to any ingredients in the Ecologic Barrier/placebo product, (11) history of using Ecologic Barrier, (12) presently using food containing probiotics (probiotic intake needed to stop at least 2 weeks prior to the	n=20 (females: 20) Mean age (SD): 31.7 (4)	*lactis* W19 and *Lactococcus lactis* W58 **Probiotic Dosage:** $2.5x10^9$ CFU/g; 2g/day **Additional supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None		

	start of the probiotic/placebo product intake), (13) not speaking and/or writing Dutch.				
Chahwan et al.[3] 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 actively self-harming; diagnosed with bipolar disorder or a personality	**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 statistically significant main effect of intervention on BDI-2, LEIDS-R, or DASS21-D

	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.[4] 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, 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-	**Intervention:** n=56 (females: NR) Age: 31.1 ± 7.8 (type of value not specified) **Control:** n=55 (females: NR) Age: 32.1 ± 11.0 (type of value not specified)	**Type:** *Lactobacillus plantarum* DR7 **Probiotic Dosage:** 1 x 10^9 CFU / day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• DASS42-D	• No statistically significant effect due to treatment identified.

	phosphate dehydrogenase deficient, and subjects who, in opinion of the investigator, were not likely to complete the trail for whatever reasons				
Chung et al.[5] 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 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	**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) Mean Age (SD): 66.56 (4.98) **Control:** n=10 (females: 6) Mean Age (SD): 64.50 (4.84)	**Type:** *Lactobacillus helveticus IDCC3801* fermented skim milk powder **Probiotic Dosage:** 500mg, 1000mg, or 2000mg daily **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• GDS-SF	• No statistically significant effect due to treatment identified.

	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.				
Dawe et al.[6] 2020 New Zealand	**Study design:** RCT **Dates of recruitment:** April 2015 – June 2017 **Inclusion Criteria:** Women were eligible and approached to participate in the study if they had a singleton pregnancy, were between 12°−17 weeks and 6 day's gestation, had a BMI of ≥30.0 kg/m2, and were able to provide informed written consent. **Exclusion Criteria:** pre-existing diabetes or an HbA1c (average blood glucose) of ≥50 mmol/ mol at time of recruitment, had known fetal congenital	**Intervention** n= 88 (females: 88) Mean age (SD): 30.06 (5.51) **Control** n= 76 (females: 76) Mean age (SD):29.39 (5.39)	**Type:** *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* BB12 **Probiotic Dosage:** 6.5 x 10^9 CFU per day **Additional supplement:** None **Probiotic Duration:** 12 – 17 weeks gestation to 36 weeks gestation **Comparator:** Placebo **Additional supplement:** None	• EPDS	• No statistically significant effect due to treatment identified.

	abnormalities, were already taking probiotic capsules or supplements containing probiotics, had a multiple pregnancy, had received bariatric surgery, were taking medications or had a medical condition that altered glucose metabolism, and/or had severe hyperemesis. Additionally, participants were excluded if they declined to participate or were unable to provide informed written consent				
Ghorbani et al.[7] 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	**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	• 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).

	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.		**Additional supplement:** None		
Hadi et al.[8] 2019 Iran	**Study design:** RCT **Dates of recruitment:** Dec 2018 – Feb 2019 **Inclusion Criteria:** men or women between the ages of 20-50 with a body mass index (BMI) greater than 25 and less than 35 kg/m^2. **Exclusion Criteria:** History of cardiovascular, renal, hepatic, or pancreatic diseases, diabetes, hypertension, inflammatory or infectious disease, neurological or psychiatric disorders, thyroid dysfunctions, and malignancy, if they were following a weight-loss diet or prescribed any weight loss medications during the last year, smoked, were pregnant or lactating, were taking alcohol, herbal drugs,	**Intervention** n= 30 (females:11) Mean age (SD): 34.49 (6.02) **Control** n= 29 (females:9) Mean age (SD): 36.64 (7.26)	**Type:** *Lactobacillus acidophilus, L. casei* and *Bifidobacterium bifidum* **Synbiotic Dosage:** 2 x 10^9 CFU per 500 mg capsule, per day **Additional supplement:** 0.8 g inulin **Synbiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None	• DASS21-D	• After 8 weeks, synbiotics resulted in significant improvements in depression scores compared to the placebo group.

	antidepressant drugs, prebiotic or probiotic products, or any other supplements/drugs which could interfere with the study objectives.				
Haghighat et al.[9] 2019 Iran	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** clinically stable HD patients with the arteriovenous fistula, aged 30–65, and receiving thrice-weekly HD, attending dialysis centers for at least 3 months before starting the study. Dialysis duration was 3–4.5 h per session, three times per week, with a blood flow of 250 mL/min and a dialysate flow of 500 mL/min. **Exclusion Criteria:** previous kidney transplant or likely to receive a transplant; medically diagnosed severe infections; malignancy; smoking; chronic liver disease; use of a central catheter for hemodialysis access; inflammatory diseases which lasted for	**Intervention 1 (Probiotic)** n= 25 (females: NR) Mean age (SD): NR **Intervention 2 (Synbiotic)** n= 25 (females: NR) Mean age (SD): NR **Control** n=25 (females: NR) Mean age (SD): NR	**ProbioticType:** *Lactobacillus acidophilus* strain T16, *Bifidobacterium bifidum* strain BIA-6, *B. lactis* strain BIA-7, *B. longum* strain BIA-8 **Probiotic Dosage:** 2.7 x 10^7 CFU per sachet **Additional supplement:** None **Probiotic Duration:** 12 weeks **Synbiotic Type:** *Lactobacillus acidophilus* strain T16, *Bifidobacterium bifidum* strain BIA-6, *B. lactis* strain BIA-7, *B. longum* strain BIA-8*;* prebiotic 5 g fructo-oligosaccharides (FOS) (b) 5 g galacto-oligosaccharides (GOS) (c) 5 g of inulin **Additional supplement:** None **Synbiotic Duration:** 12 weeks	• HADS-D	• From baseline to 12 weeks, synbiotic supplementation resulted in a significant decrease in HADS-D score in a subgroup of patients with depressive symptom (HADS-DEP ≥ 8 at baseline) compared to the placebo and probiotic supplementation (p = .001, p = .002, respectively)

	more than one week during the study; amputated limbs; pregnancy and lactation; any change in drug regimen; using catabolic or antidepressants medications within three month of study commencement; intake of antioxidant vitamin supplements, pre, pro and synbiotic supplements and other forms of probiotics (including probiotic yogurt, kefir, and other fermented foods) and antibiotics within one month of study commencement.		**Comparator:** Placebo **Additional supplement:** None		
Heidarzadeh-Rad et al.[10] 2020 Iran	**Study design:** RCT **Dates of recruitment:** July 2016 – Apr 2018 **Inclusion Criteria**: Diagnosed with major depressive disorder, aged between 20 years and 50 years, had a current diagnosis of mild to moderate melancholic depression for at least 1 month, and were taking one of the following anti-depressant medications: fluoxetine, citalopram, amitriptyline, or sertraline. **Exclusion Criteria:** any sensitiv-ity reaction to prebiotic and	**Intervention 1 (Probiotic)** n= 25 (females:20) Mean age (SD): 37.8 (7.9) **Intervention 2 (Prebiotic)** n= 25 (females:20) Mean age (SD): 36.6 (8.4) **Control** n= 25 (females:15) Mean age (SD): 36.0 (8.5)	**Type:** *Lactobacillus helveticus* R0052 (CNCM strain I-1722) and *Bifidobacterium longum* R0175 (CNCM strain I-3470) **Probiotic Dosage:** ≥10 x 10^9 CFU per sachet **Additional supplement:** None **Probiotic Duration:** 8 weeks **Prebiotic Type:** 80% galactalogosaccharide (GOS) powder **Additional supplement:** None **Prebiotic Duration:** 8 weeks	• BDI	• After 8 weeks, the change in BDI scores from baseline were significantly different between probiotic and placebo, but not for probiotic and prebiotic, or prebiotic and placebo.

	probiotic compounds, refusal to cooperate, any serious changes in diet routine and lifestyle during the study, any changes in medication or its dosage, long term (at least 1 week) inflammatory disease requiring anti-inflammatory pharma-cotherapy, pregnancy or lactation, antibiotic intake during the study, history of cancer, diabetes, pancreatitis, or thyroid, kidney, liver, respiratory, or cardiovascular disorders, diagnosis of nutritional allergy by a medical professional, regular consumption of probiotic products within 2 months of study start, dietary supplement intake such as vitamins, antioxidant and/or omega-3's at least 4-6 weeks before the study, alcohol consumption (alcoholism according to Di-agnostic and Statistical Manual of Mental Disorders-IV criteria), smoking (at least 5 cigarettes per day during last 6 months or pipe or hookah at least once in last month), opiate addiction or substance abuse, history of heart attack or stroke, following a specific diet, using hormonal		**Comparator:** Placebo **Additional supplement:** None		

	drugs and who participated in another study in the 2 months preceding the study.				
Inoue et al.[11] 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 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.	**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 **Comparator:** Placebo **Additional supplement:** None	• PHQ-9	• No statistically significant effect due to treatment identified.
Jamilian et al.[12] 2018 Iran	**Study design:** RCT **Dates of recruitment:** Dec 2017 – Mar 2018 **Inclusion Criteria:** Women with PCOS based on the Rotterdam	**Intervention:** n= 30 (females: 30) Mean age (SD): 26.0 (5.3) **Control:**	**Type:** *Lactobacillus acidophilus, L. reuteri, L. fermentum, Bifidobacterium bifidum* **Probiotic Dosage:** 8 x 10^{9} CFU/day	• 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)

	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 hyperplasia, and rogen-secreting tumors, hyperprolactinemia, thyroid dysfunction, diabetes at enrollment.	n=30 (females:30) Mean age (SD): 25.6 (3.8)	**Additional supplement:** 200 µg selenium **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		
Kazemi et al.[13] 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	**Intervention (Prebiotic):** n= 37 (females:) Mean age (SD): 37.35 (7.97)	**Type:** *Lactobacillus helveticus* R0052, *Bifidobacterium longum* R0175 **Probiotic Dosage:** ≥10x10^9 CFU, frequency not specified **Additional supplement:** None **Prebiotic Type:** Galactooligosaccharide	• BDI	• Probiotics improved BDI score compared to placebo while prebiotics had no statistically significant effect

	amitriptyline for 3 months or 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 month); any addiction to opiates; history of heart attack or stroke; following	**Intervention (Probiotic):** n=38 (females: 27) Mean age (SD): 36.15 (7.85)	**Prebiotic Dosage:** 5g sachet, frequency not specified **Additional supplement:** None **Prebiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None		

	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 trial.	**Control:** n= 36 (females:24) Mean age (SD):36 (8.47)			
Kelly et al.[14] 2017 Ireland	**Study design:** RCT- Crossover **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 a diet or taking a medication that would interfere with the objectives of the study, pose a safety risk or confound the	**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 **Comparator:** Placebo: **Additional supplement:** None	• BDI	• No statistically significant effect due to treatment identified.

	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				
Kim et al.[15] 2021 Korea	**Study design:** RCT **Dates of recruitment:** Mar 2018 – Mar 2019 **Inclusion Criteria:** Over 65 years old and to consent to be randomly assigned and refrain from consuming any other dietary supplements, which include other probiotics, yogurts with live, active cultures or supplements, and immune-enhancing supplements, during the period of the study. **Exclusion Criteria:** Use of antibiotics, anti-inflammatory medications, gastrointestinal	**Intervention** n= 27 (females: 17) Mean age (SD): 71.11 (5.02) **Control** n= 26 (females:10) Mean age (SD): 72.00 (3.36)	**Type:** *Bifidobacterium bifidum* BGN4, *B. longum* BORI **Probiotic Dosage:** 1 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• GDS-Korean	• No statistically significant effect due to treatment identified.

	medicine within the past 3 months; and with regular intake of probiotics within the past 3 months. Participants who are incapable of living independently based on activities of daily living and instrumental activities of daily living score.				
Kouchaki et al.[16] 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. **Exclusion Criteria:**	**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

	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.				
Lee et al.[17] 2021 South Korea	**Study design:** RCT **Dates of recruitment:** Jul – Sept 2018 **Inclusion Criteria:** College students over 20 years of age, with 20 or more natural teeth, and volatile sulfur compound levels ≥ 1.5 ng/10mL (concentration standard for volatile sulfur compounds that causes discomfort to others) **Exclusion Criteria:** Subjects currently being treated for systemic diseases that may cause halitosis; diagnosed with rhinitis or sinusitis and gastritis; showing adverse reactions to lactose or milk products; regularly using probiotic products or supplements; had taken antibiotics within the last month; has dry mouth, with multiple dental caries or severe	**Intervention:** n= 34 (females:10) Mean age (SD): 23.44 (2.88) **Control:** n= 28 (females:13) Mean age (SD): 23.75 (3.42)	**Type:** *Weissella cibaria* **Probiotic Dosage:** 1.0 x 10^8 CFU/g in 800mg tablet **Additional supplement:** None **Probiotic Duration: 8** weeks **Comparator:** Placebo **Additional supplement:** None	• Korean CES-D	• No statistically significant effect due to treatment identified.

	periodontal disease; has communication difficulties from hearing or vision problems; uses correction devices after orthodontic treatment; or has tongue problems.				
Lahtinen et al.[18] 2020 Finland	**Study design:** RCT **Dates of recruitment:** Aug 2015 – July 2017 **Inclusion Criteria:** Adult patients (18-73 years old), diagnosed by an experienced gastroenterologist to have IBS and remaining symptomatic despite receiving conventional treatments. **Exclusion Criteria:** Unable to provide written informed consent, had an organic gastrointestinal diagnosis such as inflammatory bowel disease or if they were pregnant.	**Fecal Microbiota Transplant** n= 23 (females:12) Mean age (SD): 47.3 (16.8) **Control Autologous Transplant** n= 26 (females: 17) Mean age (SD): 46.3 (14.3)	**Donor:** A single universal donor, a young adult male who was in good general health and normal weight was used as the faecal donor. He had been delivered through vaginal childbirth, had not had antibiotics during the previous year, and he was not a health care worker **Dosage:** single colonoscopy with 30 grams of faecal material administered into the caecum **Additional supplement:** None **Follow-up:** 52 weeks **Comparator:** Autologous sample (participant's own stool) **Additional supplement:** None	• BDI	• There were no significant changes in the reported depression scores after the FMT between the placebo and FMT groups or between the time points within the groups
Lew et al.[19] 2018	**Study design:** RCT	**Intervention:** n= 52 (females:40)	**Type:** *Lactobacillus plantarum* P8	• DASS42 – D	

Malaysia	**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 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.	Mean age (SD): 31.03 (10.8) **Control:** n= 51 (females:39) Mean age (SD): 32.1 (11.4)	**Probiotic Dosage:** 2.0 x 10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		• No statistically significant effect due to treatment identified.
Lyra et al.[20] 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	**Low Dose Intervention:** n=129 (females: 94) Mean age (SEM): 47.1 (13.3) **High Dose Intervention:** n=131 (females: 104)	**Type:** *Lactobacillus acidophilus* NCFM (NCFM not defined) **Probiotic Dosage:** Low dose: 10^9 CFU/day High dose: 10^{10} CFU/day	HADS-D	• No statistically significant effect due to treatment identified.

	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 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	Mean age (SEM): 47.2 (12.5) **Control:** n=131 (females: 94) Mean age (range): 49.4 (SEM: 12.9)	**Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		

	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.[21] 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 Func-	**Intervention:** n= 20 (females:17) Mean age (SD): 40.36 (10.28) **Control:** n= 20 (females:17)	**Type:** *Bacillus coagulans* **Probiotic Dosage:** 2 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 90 Days	• HAM-D • MADRS • CES-D	• Significant change (p=0.01) due to probiotic was observed for the Hamilton Rating Scale for Depression, Montgomery- Åsberg Depression Scale, and Centre for Epidemiological Studies-Depression Scale.

	tional IBS for the last 3 months with symptom onset at least 6 months prior to 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 medication (prescription and over the counter), including vitamins and	Mean age (SD): 43.88 (9.85)	**Comparator:** Placebo **Additional supplement:** None		

	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.[22] 2019 Italy	**Study design:** RCT **Dates of recruitment:** Nov 2016 – Jun 2017 **Inclusion Criteria:** Between ages 18 – 35. **Exclusion Criteria:** Psychiatric or	**Intervention:** n= 18 (females:7) Mean age (SD): 21.61 (2.2) **Control:** n= 15 (females:5)	**Type:** *Lactobacillus fermentum* LF16 (DSM26956), *L. rhamnosus* LR06 (DSM 21981), *L. plantarum* LP01 (LMG P-21021), *Bifidobacterium longum* BL04 (DSM23233) **Probiotic Dosage:**	• BDI-2 • LEIDS-R	• No significant between-group difference found for BDI-2 • Overall score for LEIDS-R not calculated or tested for significance

	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.	Mean age (SD): 21.67 (2.19)	4 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None		
Messaoudi et al.[23] 2011 France	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** healthy 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,	**Intervention:** n= 26 (females:19) Mean age (SD): 42.4 (7.5) **Control:** n= 29 (females:22) Mean age (SD):43.2 (8.5)	**Type:** *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 **Probiotic Dosage:** 3 x 10^9 CFU per stick; 1 stick/day **Additional supplement:** None **Probiotic Duration:** 30 Days **Comparator:** Placebo **Additional supplement:** None	• HADS-D	• No statistically significant effect due to treatment identified.

	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 than twenty cigarettes; Pregnant women and subjects who had participated in another clinical study over the past 2 months				
Miyaoka et al.[24] 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-	**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

	noradrenalin reuptake inhibitor medications, including fluvoxamine, paroxetine, escitalopram, sertraline, duloxetine, and milnacipram. **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.				
Moloney et al.[25] 2021	**Study design:** Crossover RCT **Dates of recruitment:** NR	**Intervention/Control:** n=8 (females:0)	**Type**: *Bifidobacterium longum* 1714	• BDI-2 • HADS-D	

Ireland	**Inclusion Criteria:** Ability to give written informed consent, be between 18 and 30 years of age; be male; be in generally good health as determined by the investigator **Exclusion Criteria:** Being less than 18 and greater than 40 years of age; having a significant acute or chronic illness; having a condition 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 – subjects should have a wash-out period of 4 weeks; current prebiotic or probiotic use – subjects should have a wash-out period of 4 weeks; excessive use of vitamin D supplementation; not being fluent in English; having dyslexia or dyscalculia; being a current or past smoker; being considered to be poor attendees or unlikely for any reason to be able to comply with the trial; using treatment involving experimental drugs – participation in a trial should be completed not less than 30 days	Mean age (SD):20.7 (0.28) **Control/Intervention:** n=12 (females:0) Mean age (SD): 20.7 (0.28)	**Probiotic Dosage:** $1x10^9$CFU/day **Additional supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None		• No statistically significant effect due to treatment identified.

	prior to this study; and having a malignant disease or any concomitant end-stage organ disease				
Moludi et al.[26] 2019 Iran	**Study design:** RCT **Dates of recruitment:** April 2018 – Oct 2018 **Inclusion Criteria:** Admitted with diagnosis of myocardial infarction who underwent percutaneous coronary intervention with stable conditions **Exclusion Criteria:** Refusal to participate or low ejection fraction (<35%), unsuccessful percutaneous coronary intervention.	**Intervention:** n= 22 (females: 2) Mean age (SD): 56.7 (9.1) **Control:** n= 22 (females: 1) Mean age (SD): 57.1 (7.8)	**Type:** *Lactobacillus rhamnosus* **Probiotic Dosage:** 1.6 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI-2	• Significant improvement in BDI-2 scores due to probiotic
Moludi et al.[27] 2021 Iran	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Subjects aged 18-85 years old with coronary artery disease who agreed to participate in the study **Exclusion Criteria:** End-stage renal disease, undergoing	**Intervention (Probiotic):** n= 24 (females: 9) Mean age (SD): 51.3 (12.7) **Intervention (Prebiotic):** n=24 (females: 12) Mean age (SD): 52.2 (12.8)	**Probiotic Type:** *Lactobacillus rhamnosus* **Probiotic Dosage:** 1.9 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 8 weeks	• BDI-2	• Co-supplementation of probiotics and inulin in CAD subjects for 8 weeks had beneficial effects on depression. Adding inulin to probiotic supplements improved outcomes more effectively than two supplements separately

	corticosteroid, immunosuppressive, anti-inflammatory, or anti-depressant drugs; a history of dietary supplements including Pre/Pro-biotics, antioxidants, or vitamins at least two months prior were excluded from the study	**Intervention (Synbiotic):** n=24 (females: 9) Mean age (SD): 49.1 (11.2) **Control:** n= 24 (females: 8) Mean age (SD): 51.8 (12.2)	**Prebiotic Type:** Inulin **Prebiotic Dosage:** 15g/day **Additional supplement:** None **Synbiotic Type:** Combination of probiotic and prebiotic interventions **Additional supplement:** None **Comparator:** Placebo **Additional supplement:** None		
Ostadmohammadi et al.[28] 2019 Iran	**Study design:** RCT **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	**Intervention:** n= 30 (females: 30) Mean age (SD): 24.4 (4.7) **Control:** n= 30 (females: 30) Mean age (SD): 25.4 (5.1)	**Type:** *Lactobacillus acidophilus, 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	• BDI	• Vitamin D and probiotic co-administration for 12 weeks significantly reduced BDI scores

	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.		**Additional supplement:** None		
Östlund-Lagerström et al.[29] 2016 United States	**Study design:** RCT **Dates of recruitment:** 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	**Intervention:** n= 125 (females:71) Mean age (SD): 72.6 (5.8) **Control:** n= 124 (females:81) Mean age (SD): 72 (5.6)	**Type:** *Lactobacillus reuteri* **Probiotic Dosage:** 1 x 10^8 CFU/day **Additional supplement:** None **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None	• HADS-D	• No statistically significant effect due to treatment identified.

Papalini et al.[30] 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 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	**Intervention:** n= 29 (females:29) Mean age (SEM): 21 (0.4) **Control:** n= 29 (females:29) Mean age (SEM): 22 (0.5) **Control:** n= 20 (females: 12) Mean age (SD): 21.5 (10.1)	**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 **Probiotic Dosage:** 5 x 10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI • LEIDS-R	• No statistically significant effect due to treatment identified.

	testing session; MRI compatibility				
Patterson et al.[31] 2020 Finland	**Study design:** RCT **Dates of recruitment:** Apr 2018 – Oct 2018 **Inclusion Criteria:** if they gave voluntary, written informed consent to participate in the study, were either male or female aged between 18-45 years (inclusive), had a body mass index (BMI) between 18.5 – 29.9 kg/m2, a medical examination at Visit 2 indicated they were healthy (in the opinion of the Principal Investigator (PI)), had the ability to comprehend the full nature and purpose of the study including possible risks and side effects, agreed to comply with the protocol and study restrictions, were available for all study visits, had easy access to the internet and females provided a negative urine	**Intervention:** n=55 (females: NR) Age: 23.73 (4.27) **Control:** n= 58 (females: NR) Age: 23.25 (4.2)	**Type:** *Lacticaseibacillus paracasei* Lpc-37 **Probiotic Dosage:** 1.75 x 10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 5 weeks **Comparator:** Placebo **Additional supplement:** None	• DASS42-D	• No statistically significant effect due to treatment identified.

	pregnancy test and were using effective contraception. **Exclusion Criteria:** diagnosed with one or more DSM-IV axis 1 disorder, had a significant acute or chronic coexisting illness, were currently taking (from Visit 1 onwards) or previously took (last four weeks prior to Visit 1) psychoactive medication(s), were currently taking (from Visit 1 onwards) medication or dietary supplements that would interfere with the objectives of the study (in the opinion of PI), were undergoing recent (last four weeks prior to Visit 1) or ongoing antibiotic therapy, consumed daily concentrated sources or probiotics / prebiotics within two weeks of Visit 1 or ongoing, were females either pregnant or lactating or had pregnancy planned during the intervention period, were not fluent in the German language, had self-reported dyslexia, previously had a history of alcohol, medication or drug abuse, were self-declared illicit drug users for three weeks prior to Visit 1 and during the intervention period, had any				

	contraindication to any substance in the investigational products, were hypertensive, had unstable or uncontrolled hyper- or hypothyroidism, previously participated in the Trier Social Stress Test (TSST), smoked > five cigarettes per day, were an employee of either DuPont Nutrition & Biosciences or daacro, participated in another study with any investigational product within 60 days of Visit 1 and during the intervention period, were uncooperative and/or noncompliant (in the opinion of PI) or were under legal supervision.				
Pinto-Sanchez et al.[32] 2017 Canada	**Study design:** RCT **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)	**Intervention:** n=18 (females: 12) Median age (IQR): 46.5 (30-58) **Control:** n= 20 (females: 12) Median age (IQR): 40.0 (26-57)	**Type:** *Bifidobacterium longum* **Probiotic Dosage:** 1 x 10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None	• HADS-D	• No statistically significant effect due to treatment identified.

	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 trial.				
Qi et al.[33] 2020 China	**Study design:** RCT **Dates of recruitment:** Jan 2017 – Dec 2018 **Inclusion Criteria:** Patients attending audio-vestibular testing, between 18 and 50 years old, providing written informed consent, and have sufficient cognitive abilities as well as language proficiency to complete the assessments and questionnaires. 1) migraine based on the International Classification of Headache Disorders 3rd edition (IHS,	**Intervention:** n=103 (females: 89) Mean age (range): 32 (18-50) **Control:** n=101 (females: 85) Mean age (range): 33 (19-49)	**Type:** *Lactobacillus casei* Shirota **Probiotic Dosage:** 2×10^{10} CFU/day **Additional supplement:** None **Probiotic Duration:** 4 months **Comparator:** Placebo **Additional supplement:** None	• BDI	• Significant improvement due to intervention (p=0.04)

	2018); (2) five or more episodes of moderate to severe vestibular symptoms lasting between 5 min and 72 h (spontaneous vertigo, positional vertigo, visually-induced vertigo, head motion-induced vertigo and head motion-induced dizziness with nausea); (3) half of episodes are associated with at least one of the three migrainous features: (a) headache with at least two of the following four characteristics including unilateral location, pulsating quality, moderate or severe intensity and aggravation by routine physical activity, (b) photophobia and phonophobia and (c) visual aura; (4) alternative causative factors ruled out through appropriate assessments. **Exclusion Criteria**: (1) bilateral vestibular dysfunction; (2) report of mere spontaneous episodic dizziness that was not provoked/worsened by movements; (3) past histories of moderate neurological or orthopaedic deficits; (4) use of probiotics supplement within 2 months prior to this study				

Rahimlou et al.[34] 2020 Iran	**Study design:** RCT **Dates of recruitment:** Oct 2018 – June 2019 **Inclusion Criteria:** relapsing-remitting multiple sclerosis according to the original or 2005 revised McDonald criteria, EDSS score of ≤4.5, and confirmed by MRI; age 18-50. **Exclusion Criteria:** Unwillingness to participate, acute or severe phase of multiple sclerosis, pregnancy, taking antibiotics, any product or supplement containing probiotics, anti-inflammatory drugs over the past 1 month, taking oral or systemic glucocorticoids or adrenocorticotropic hormone, omega 3 or other antioxidant supplements within 30 days prior to inclusion, a history or presence of severe depression and arthrosis, suicide attempt or current suicidal ideation, history of gastroenteritis and bowel surgery over the past month, inflammatory bowel disease, rheumatoid arthritis, systemic lupus, type 1 diabetes and other autoimmune diseases;	**Intervention:** n=32 (females: 26) Mean age (SD): 42.2 (12.0) **Control:** n=33 (females: 21) Mean age (SD): 39.9 (8.8)	**Type:** *Bacillus subtilis* PXN 21, *Bifidobacterium bifidum* PCN 23, *Bifidobacterium breve* PXN 25, *Bifidobacterium infantis* PXN 27, *Bifidobacterium longum* PXN 30, *Lactobacillus acidophilus* PXN 35, *L. delbrueckii* ssp. *Bulgaricus* PXN 39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57, *Lactococcus lactis* ssp. *Lactis* PXN 63, *Streptococcus thermophilus* PXN 66 **Probiotic Dosage:** 4×10^9 CFU/day **Additional supplement:** None **Probiotic Duration:** 6 months **Comparator:** Placebo **Additional supplement:** None	• BDI-2	• Significant improvement reported due to intervention (p=0.049).

	treatment with interferon in the past month and with other medications in the previous three months.				
Raygan et al.[35] 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.[36] 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	**Intervention:** n= 27 (females:16) Mean age (SD): 64.8 ± 8.3 **Control:** n=27 (females: 17)	**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:**	• BDI	• Probiotic and selenium co-supplementation significantly improved BDI score in intervention compared to control

	the 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.	Mean age (SD): 62.4 (13.1)	200 µg/day Selenium **Probiotic Duration:** 12 weeks **Comparator:** Placebo **Additional supplement:** None		
Roman et al.[37] 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 other studies, pregnant or breastfeeding, severe intestinal disease, psychiatric disorder other than depression and/ or anxiety	**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 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• No statistically significant effect due to treatment identified.
Romijn et al.[38]	**Study design:** RCT	**Intervention:**			

2017 New Zealand	**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 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	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 statistically significant effect due to treatment identified.
Rudzki et al.[39] 2019 Poland	**Study design:** RCT **Dates of recruitment:** June 2014 – March 2016	**Intervention:** n=30 (female: 23) Mean age (SD): 39.13 (9.96)	**Type:** *Lactobacillus plantarum* (strain 299v) **Probiotic Dosage:** 10×10^9 CFU/capsule twice/day	• HAM-D	• No statistically significant effect due to treatment identified.

	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, glucocorticosteroids	**Control:** n=30 (female: 20) Mean age (SD): 38.9 (12)	**Additional supplement:** SSRI **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** None		

Saccarello et al.[40] 2020 Italy	**Study design:** RCT **Dates of recruitment:** Sept 2018 – Oct 2018 **Inclusion Criteria:** men and women aged 18-60 years with signed and dated written informed consent; diagnosis of recurrent mild-to-moderate depressive disorders according to ICD-10/F33 criteria; Z-SDS raw score between 41 and 55; and ability to comply with the requirements of the entire study **Exclusion Criteria:** Pregnant or breast-feeding women, presence of ≥ 1 psychiatric disturbances (alcoholism, substance abuse, or dependency disorder; bipolar disorder; schizophrenia; or other personality disorder), treatment with psychotropic drugs (antipsychotics, anxiolytics, hypnotics, or sedatives), or oral consumption of food supplements (only multivitamins, salts, and trace elements were accepted)	**Intervention:** n=45 (females: 38) Mean age (SD): 48.6 (10.7) **Control:** n=44 (females: 35) Mean age (SD): 47.5 (11.9)	**Type:** *Lactobacillus plantarum* **Probiotic Dosage:** 1×10^9 CFU/ day **Additional supplement:** S-adenosylmethionine 200mg **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None	• Zung SDS	• Significant improvement reported due to intervention (p=0.0165)
Salami et al.[41] 2019 Iran	**Study design:** RCT **Dates of recruitment:**	**Intervention:** n=24 (females: 18)	**Type:** *Bifidobacterium infantis, B. lactis, Lactobacillus reuteri,*	• BDI	• Significant improvement in intervention group

	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.	Mean age (SD): 34.79 (1.06) **Control:** n=24 (females: 18) Mean age (SD): 36.54 (1.44)	*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		compared to control (p =0.026)
Sanchez et al.[42] 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 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	**Intervention:** n=62 (female: 38) Mean age (SD): 35 (10) **Control:** n=63 (female: 39) Mean age (SD): 37 (10)	**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) **Synbiotic Duration:** 24 weeks **Comparator:** Placebo **Additional supplement:** None	• BDI	• Synbiotic offered a significant decrease in BDI score ($p<0.05$).

	Exclusion Criteria: NR				
Sawada et al.[43] 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 statistically significant effect due to treatment identified.
Sawada et al.[44] 2019 Japan	**Study design:** RCT **Dates of recruitment:** Sept 2016 – Dec 2016 **Inclusion Criteria:** 18-22 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	**Intervention:** n=24 (females: 0) Mean age (SD): 19.8 (1.4) **Control:** n=25 (females: 0) Mean age (SD): 20.1 (1.1)	**Type:** *Lactobacillus gasseri* CP2305 (CP2305) mixed in sport drink containing sweetener, acidifier, flavorings, vitamin C, and minerals (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	• HADS-D	• Significant reduction in intervention group compared to control

	period; allergic to milk and soybean		**Comparator:** Placebo **Additional supplement:** None		
Shahrbabaki et al.[45] 2020 Iran	**Study design:** RCT **Dates of recruitment:** Oct 2017 – Oct 2018 **Inclusion Criteria:** diagnosis of type 1 bipolar disorder based on DSM-5 criteria, were age 18-65 years, not consuming any medication or discontinuing it within 2 weeks prior to the study, and not receiving ECT since 4 weeks prior to the study. **Exclusion Criteria:** pregnancy and breast feeding, alcohol and drug use, suicide risk, use of probiotics and supplements over a period of 2 months before the start of the study, chronic diseases (cardiovascular, kidney, liver, lung, AIDS and cancer), active infection, schizophrenia, and other psychiatric disorders, and seizure, which were detected by 2 psychiatrists.	**Intervention** n=19 (females: not reported) Mean age (SD): 38.9 (9.83) **Control** n=19 (females: not reported) Mean age (SD): 35.0 (8.18)	**Type:** *Bifidobacterium bifidum, B. lactis, B. langum, and Lactobacillus acidophilus)* **Probiotic Dosage:** 1.8×10^9 CFU per capsule, per day **Additional supplement:** Lithium oxide, with a maximum dose of 900 mg per day, sodium valproate, with a maximum dose of 1200 mg per day, and, if necessary, risperidone. **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement:** Lithium oxide, with a maximum dose of 900 mg per day, sodium valproate, with a maximum dose of 1200 mg per day, and, if necessary, risperidone.	• HAM-D	• No statistically significant effect due to treatment identified.
Silk et al.[46] 2009 United Kingdom	**Study design:** Crossover RCT **Dates of recruitment:** Jan 2006 - Dec 2006	**Intervention 1:** n= 16 (females: NR) Mean age (range): NR	**Type:** Trans-galactooligosaccharide **Prebiotic Dosage:** 3.5 g or 7.0 g per each dry powder/ day	• HADS-D	• No statistically significant effect due to treatment identified.

	Inclusion Criteria: 18-80 years old, diagnosed with IBS; and not organic gastrointestinal disease, including inflammatory bowel disease **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	**Control 1:** n= 16 (females: NR) Mean age (range): NR **Intervention 2:** n= 14 (females: NR) Mean age (range): NR **Control 2:** n= 14 (females: NR) Mean age (range): NR	**Additional supplement:** None **Prebiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None		
Simren et al.[47] 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 laboratory test clinical	**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 **Probiotic Duration:** 8 weeks	• HADS-D	• No statistically significant effect due to treatment identified.

	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; pregnant or lactating or planning to become pregnant during the study period		**Comparator:** Placebo **Additional supplement:** No		
Slykerman et al.[48] 2017 New Zealand	**Study design:** RCT **Dates of recruitment:** Dec 2012 – Nov 2014	**Intervention:** n=193 (female: 193) Mean age (SD): 33.5 (4.24)	**Type:** *Lactobacillus rhamnosus* (HN001) **Probiotic Dosage:** HN001, 6×10^9 CFUs/day	• EPDS	• Mothers in the probiotic treatment group reported significantly lower depression scores than

	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	**Control:** n=187 (female: 187) Mean age (SD): 33.7 (4.44)	**Additional supplement:** None **Probiotic Duration:** 12 months **Comparator:** Placebo **Additional supplement:** None		those in the placebo group (-1·2, 95% CI (-2·4, -0·1), p=0.035)
Smith-Ryan et al.[49] 2019 United States	**Study design:** RCT **Dates of recruitment:** Sep 2016 – Jan 2018 **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,	**Intervention:** n=15 (female: 15) Mean age (SD): 30.5 (7.7) **Control:** n=18 (female: 18) Mean age (SD): 30.2 (10.0)	**Type:** *Bifidobacterium bifidum* W23*, B. lactis* W51*, B. lactis* W52*, Lactobacillus acidophilus* W37*, L. brevis* W63*, L. 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	• HADS-D	• No statistically significant effect due to treatment identified.

	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		**Synbiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None		
Steenbergen et al.[50] 2015 Netherlands	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** non-smoking young adults, with no reported cardiac, renal, or hepatic conditions, no 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	**Intervention:** n=20 (female: 15) Mean age (SD): 20.2 (2.4) **Control:** n=20 (female: 17) Mean age (SD): 19.7 (1.7)	**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) **Probiotic Dosage:** $2.5x10^9$ CFUs/g, 2g/day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None	• LEIDS-R • BDI-2	• Probiotic significantly improved LEIDS-R ($p<0.001$). • No evidence of significant improvement in BDI due to probiotic
Vaghef-Mehrabany et al.[51] 2019 Iran	**Study design:** RCT **Dates of recruitment:** Jun 2018- Sept 2018 **Inclusion Criteria:** female, 20-50 years old; diagnosed with MDD	**Intervention:** n= 31 (females: 31) Mean age (SD): 37.45 (6.77) **Control:**	**Type:** Inulin **Prebiotic Dosage:** 10 g/ day **Additional supplement:** None **Prebiotic Duration:** 8 weeks	• HAM-D • BDI-2	• No statistically significant effect due to treatment identified.

	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 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	n=31 (females: 31) Mean age (SD): 40.0 (8.66)	**Comparator:** Placebo **Additional supplement:** None		
Vidot et al.[52] 2019 Australia	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** Adult patients with hepatic cirrhosis and a history of hepatic encephalopathy who attended a liver clinic. Participants were required to be on daily lactulose therapy, abstinent from alcohol and intravenous drug use for at least 3 months prior to study entry, and if on methadone, were required to be dose-stable	**Intervention (Synbiotic):** n= 12 (females: 1) Mean age (SD): 56.7 (7.5) **Control (Placebo):** n=12 (females: 1) Mean age (SD): 54.1 (6.7)	**Type:** *Lactobacillus paracasei* ssp. *paracasei, L. plantarum, Leuconostoc mesenteroides, Pediococcus pentosaceus,* oat bran, pectin, resistant starch, inulin **Dosage:** $10x10^{11}$ CFU/sachet of each species, 2.5g of each prebiotic. **Additional supplement:** None **Duration:** 8 weeks **Comparator:** Placebo	• DASS21-D	• No statistically significant effect due to treatment identified.

	for a minimum of 3 months prior to study entry. **Exclusion Criteria:** Celiac disease or a history of gluten sensitivity; current use of a probiotic or if they were taking rifaximin, or if random blood glucose levels were ≥15mMol/L.		**Additional supplement:** None		

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.[53] 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 statistically significant effect due to treatment identified.	• Insufficient detail reported
Cremon et al.[54] 2018	**Study design:** RCT – Cross over **Dates of recruitment:** NR	**Intervention:** n=20 (females: 11)	**Type:** *Lactobacillus paracasei* CNCM I-1572 (LCDG)	• HADS-D	• No statistically significant effect	

Italy	**Inclusion Criteria:** 18- 65 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 relevant organic, systemic, or metabolic disease as assessed by medical history,	Mean age (SD): 37.35 (11.25) **Control:** n=20 (females: 15) Mean age (SD): 44.55 (12.98)	**Probiotic Dosage:** 24 billion viable cells of the bacterial strain LCDG each capsule 2/day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None		due to treatment identified.	• Insufficient detail reported

	appropriate consultations, and laboratory tests; or abnormal laboratory values deemed clinically significant on the basis of predefined values					
Dickerson et al.[55] 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 available for follow-up visits **Exclusion Criteria:** Substance or medically induced symptoms of mania at hospital admission; HIV infection or other immunodeficiency condition;	**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 statistically significant effect due to treatment identified.	• Insufficient detail reported

	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.					
Kato-Kataoka et al.[56] 2016 Japan	**Study design:** RCT **Dates of recruitment:** Oct 2012-Jan 2013 **Inclusion Criteria:** Medical students **Exclusion Criteria:** Over 30 years of age, habitual smoking, taking medication, mental and other diseases, and milk allergy or other allergies for 3 months prior to enrolment.	**Intervention (Probiotic):** n=24 (females:10) Mean age (SD): 23.0 (0.4) **Control-non fermented milk:** n=23 (females:11) Mean age (SD): 22.7 (0.4)	**Type:** Fermented milk with *Lactobacillus casei* strain Shirota **Probiotic Dosage:** >1.0x10^9 CFU/mL **Additional supplement:** None **Probiotic Duration:** 8 weeks **Comparator:** Placebo **Additional supplement: None**	• HADS-D • Zung SDS	• Outcome at end of treatment duration not reported.	• Outcome at end of intervention period not reported
Nishida et al.[57] 2017 Japan	**Study design:** RCT **Dates of recruitment:**	**Intervention:** n= 16 (females: 5)	**Type:** Heat killed *Lactobacillus gasseri* strain CP2305	• Zung-SDS • HADS-D	• No statistically significant effect	

	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)	**Para-probiotic Dosage:** 1 x 10^{10} bacterial cells/day **Additional supplement:** None **Para-probiotic Duration:** 5 weeks **Comparator:** Placebo **Additional supplement:** None		of intervention on HADS-D • Zung-SDS outcomes not reported	• Insufficient detail reported
Rao et al.[58] 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, severe CFS such that they were largely bedridden, patients meeting criteria for psychiatric disorders	**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 statistically significant effect due to treatment identified.	• Insufficient detail reported

	other than depression and/or anxiety					
Smith et al.[59] 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 statistically significant effect due to treatment identified.	• Prebiotic intervention
Tillisch et al.[60] 2013 United States	**Study design:** RCT **Dates of recruitment:** NR **Inclusion Criteria:** 18-55 years 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	**Intervention:** n= 12 (females: 12) Mean age (SD): NR **Control- nonfermented milk:** n= 11 (females: 11) Mean age (SD): NR	**Type:** Fermented milk product with probiotic: *Bifidobacterium animalis* subsp *Lactis*, *Streptococcus thermophiles, Lactobacillus 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	• HADS-D	• No statistically significant effect due to treatment identified.	• Insufficient detail reported

	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- no intervention:** n= 13 (females: 13) Mean age (SD): NR	**Additional supplement:** None **Probiotic Duration:** 2 weeks **Comparator:** Placebo **Additional supplement:** None			
Whorwell et al.[61] 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 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	**Intervention 1- BIFIDO6:** n=90 (females: 90) Mean age (SD): 40.8 (1.10) **Intervention 2- BIFIDO8:** 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)	**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 each capsule 1/ day **Additional supplement:** None **Probiotic Duration:** 4 weeks **Comparator:** Placebo **Additional supplement:** None	• HADS-D	• No statistically significant effect due to treatment identified.	• Insufficient detail reported

	immunodeficiency; had undergone any abdominal surgery, with the exception of hernia repair or appendectomy					
Wong et al.[62] 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); 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	**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 bacteria each capsule 4/ day **Additional supplement:** None **Probiotic Duration:** 6 weeks **Comparator:** Placebo **Additional supplement:** None	• HADS-D	• No statistically significant effect due to treatment identified.	• Insufficient detail reported

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;

Section 6: 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[53]	Prebiotic	IBS	HADS-D	4	Some Concerns	38	41	No statistically significant difference due to intervention
Cremon, 2018[54] (crossover)	Probiotic	IBS	HADS-D	4	Some Concerns	20	20	No statistically significant difference due to intervention
Dickerson, 2018[55]	Probiotic	Bipolar I; or Schizoaffective Disorder; or Bipolar Type Manic or Mixed	MADRS	24	Some Concerns	33	33	No statistically significant difference due to intervention
Kato-Kataoka, 2016[56]	Probiotic	Medical Students	Zung SDS, HADS-D	8		23	24	Not reported at end of intervention period
Nishida, 2017[57]	Para-probiotic	Medical Students	Zung SDS, HADS-D	5	High	16	16	No statistically significant difference in HADS-D; Zung SDS not reported
Rao, 2009[58]	Probiotic	Chronic Fatigue Syndrome	BDI	8	High	16	19	No statistically significant difference due to intervention
Smith, 2005[59] (crossover)	Prebiotic	Volunteers	HADS-D	2	High	142	142	No statistically significant difference due to intervention
Tillisch, 2013[60]	Probiotic	Healthy Women	HADS-D	2	High	24	12	No statistically significant difference due to intervention
Whorwell, 2006[61]	Probiotic	IBS	HADS-D	4	High	270	92	No statistically significant difference due to intervention
Wong, 2015[62]	Probiotic	IBS	HADS-D	6	High	22	20	No statistically significant difference due to intervention

Section 7: Risk of bias

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

First Author (Year)	Bias from Randomization	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
Browne et al.[2] (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Chahwan et al.[3] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Chong et al.[4] (2019)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Chung et al.[5] (2014)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Cremon et al.[54] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Dawe et al.[6] (2020)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Dickerson et al.[55] (2018)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Haghighat et al.[9] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Heidarzadeh-Rad et al.[10] (2020)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Inoue et al.[11] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Jamilian et al.[12] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Kato-Kataoka et al.[56] (2016)	Some Concerns	Some Concerns	Low Risk	Low Risk	High Risk	High Risk
Kazemi et al.[13] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Kelly et al.[14] (2017)	Some Concerns	High Risk	Low Risk	Low Risk	Some Concerns	High Risk

Kim et al.[15] (2020)	Low Risk	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns
Kouchaki et al.[16] (2016)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Lee et al.[17] (2021)	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
Lew et al.[19] (2018)	Low Risk	Some Concerns	High Risk	Low Risk	Some Concerns	High Risk
Lyra et al.[20] (2016)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Majeed et al.[21] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Marotta et al.[22] (2019)	Low Risk	Some Concerns	Some Concerns	Low Risk	Some Concerns	High Risk
Messaoudi et al.[23] (2011)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Miyaoka et al.[24] (2018)	High Risk	Some Concerns	Low Risk	High Risk	Some Concerns	High Risk
Moloney et al.[25] (2021)	Some Concerns	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Moludi et al.[26] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Moludi et al.[27] (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ostadmohammadi et al.[28] (2019)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Östlund-Lagerström et al.[29] (2016)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Papalini et al.[30] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Patterson et al.[31] (2020)	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk
Pinto-Sanchez et al.[32] (2017)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns

Appendix 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

Qi et al.[33] (2020)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Rahimlou et al.[34] (2020)	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
Rao et al.[58] (2009)	Some Concerns	High Risk	High Risk	Low Risk	Some Concerns	High Risk
Raygan et al.[36] (2018)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Raygan et al.[35] (2019)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Roman et al.[37] (2018)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Romijn et al.[38] (2017)	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
Rudzki et al.[39] (2019)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Saccarello et al.[40] (2020)	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk
Salami et al.[41] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Sawada et al.[43] (2017)	Some Concerns	Low Risk	Some Concerns	Low Risk	Some Concerns	High Risk
Sawada et al.[44] (2019)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Shahrbabaki et al.[45] (2020)	Some Concerns	Some Concerns	Low Risk	Some Concerns	Low Risk	Some Concerns
Simren et al.[47] (2010)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Slykerman et al.[48] (2017)	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk
Steenbergen et al.[50] (2015)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Tillisch et al.[60] (2013)	Some Concerns	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk
Whorwell et al.[61] (2006)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	High Risk

Appendix 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

Wong et al.[62] (2015)	High Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk
Prebiotics						
Azpiroz et al.[53] (2017)	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Heidarzadeh-Rad et al.[10] (2020)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Kazemi et al.[13] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Moludi et al.[27] (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Silk et al.[46] (2009)	Some Concerns	Some Concerns	Some Concern	Low Risk	Some Concerns	High Risk
Smith et al.[59] (2005)	High Risk	Some Concerns	High Risk	Some Concerns	Some Concerns	High Risk
Vaghef-Mehrabany et al.[51] (2019)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Synbiotics						
Ghorbani et al.[7] (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Hadi et al.[8] (2019)	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
Haghighat al.[9] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Moludi et al.[27] (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sanchez et al.[42] (2017)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Smith-Ryan et al.[49] (2019)	Some Concerns	Some Concerns	Low Risk	Low Risk	Some Concerns	Some Concerns
Vidot et al.[52] (2019)	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	High Risk
Para-probiotics						
Nishida et al.[57] (2017)	Some Concerns	High Risk	Low Risk	High Risk	High Risk	High Risk
Fecal Microbiota Transplant						

Lahtinen et al.[18] (2020)	High Risk	Low Risk	Some Concerns	Low Risk	Some Concerns	High Risk

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Appendix 1, as supplied by the authors. Appendix to: Hofmeister M, Clement F, Patten S, et al. The effect of interventions targeting gut microbiota on depressive symptoms: a systematic review and meta-analysis. *CMAJ Open* 2021. DOI:10.9778/cmajo.20200283.

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