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Effect of probiotics on depressive symptoms: A meta-analysis of human studies

Kah Kheng Goh[a], Yen-Wenn Liu[b,c], Po-Hsiu Kuo[d,e], Yu-Chu Ella Chung[d], Mong-Liang Lu[a,f], Chun-Hsin Chen[a,f,*]

[a] Department of Psychiatry, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[b] Institute of Biochemistry and Molecular Biology, National Yang-Ming University, Taipei, Taiwan
[c] Microbiome Research Center, National Yang-Ming University, Taipei, Taiwan
[d] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan
[e] Department of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan
[f] Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

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ABSTRACT

Accumulating data show that probiotics may be beneficial in reducing depressive symptoms. We conducted an updated meta-analysis and evaluated the effects of probiotics on depressive symptoms. A systematic search of six databases was performed, and the results were reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses, with the priori-defined protocol registered at PROSPERO (CRD42018107426). In total, 19 double-blind, randomized, placebo-controlled trials with a total of 1901 participants were included in the qualitative synthesis. Participants treated with probiotics showed significantly greater improvement in depressive symptoms than those receiving placebo. The clinical population was stratified by clinical diagnosis into those with major depressive disorder (MDD) and those with other clinical conditions. The beneficial effect of probiotics on depressive symptoms was significant in patients with MDD, but not in those with other clinical conditions and in the general population. In addition, multiple strains of probiotics were more effective in reducing depressive symptoms. In conclusion, altering the gut–brain axis with probiotics may be an approach to improve depression severity. It is essential to verify the efficacy of specific combinations or strains of probiotics for depressive symptoms by conducting studies with a larger sample size in the future.

1. Introduction

Depression is a common mental disorder that may lead to marked disabilities in affected patients and has become a leading cause of global burden of disease (DALYs and Hale Collaborators, 2016). Current pharmacological treatment includes antidepressants, whose mechanisms are based on modulating monoamine neurotransmitters. A recent meta-analysis of randomized clinical trials showed that antidepressants are more effective in relieving depressive symptoms than placebo (Cipriani et al., 2018). However, progressively increasing dropout rates and decreasing remission rates across each study phase in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which reflected real-world practice, suggest that antidepressants may not show optimal results in the real world (Pigott et al., 2010). It is essential to find alternatives to antidepressants to help patients with depression.

Probiotics are defined as live organisms that exert a health benefit when ingested in an adequate amount (Food and Agriculture Organization and World Health Organization Expert Consultation, 2001). Accumulating data indicate that the gut microbiota can influence brain function and behavior, including mood symptoms (Cryan and Dinan, 2012; Forsythe et al., 2016; Rogers et al., 2016). Therefore, consumption of probiotics to alter composition of gut microbiota may be a novel way to treat patients with depression.

Animal studies showed that consumption of probiotics may alter brain functions and reduce anxiety or depression-like behaviors (Desbonnet et al., 2010; Liang et al., 2015; Liu et al., 2016b). For example, Liu et al. found that administration of *Lactobacillus plantarum* PS128 could reduce immobility time in the forced swimming model of depression in mice with early life stress (Liu et al., 2016b). The latest meta-analysis showed that consumption of probiotics can improve mood symptoms in patients with mild to moderate depression, but no

* Corresponding author at: Department of Psychiatry, Wan Fang Hospital, Taipei Medical University, #111, Section 3, Xing-Long Road, Taipei 11696, Taiwan
E-mail address: chunhsin57@gmail.com (C.-H. Chen).

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significant effect on mood symptoms was demonstrated in healthy individuals (Ng et al., 2018). In Ng's meta-analysis, the significant effect of probiotics was shown only in patients with major depressive disorder (MDD) (Akkasheh et al., 2016). As more studies, including two studies in which patients with MDD comprised the study population, have been published after Ng's meta-analysis, we aim to provide an updated meta-analysis evaluating the effects of probiotics on depressive symptoms in patients with MDD and patients with other clinical conditions.

2. Methods

The effect of consumption of probiotics on depressive symptoms in humans was assessed by analyzing double-blind, randomized, placebo-controlled trials in a systematic review and meta-analysis in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) principles (Moher et al., 2009). The proposed protocol (CRD42018107426) was registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO).

2.1. Selection criteria

Double-blind, randomized, placebo-controlled trials of probiotics in humans were included in the analysis. The intervention group was defined as the group with consumption of probiotics, and specific details regarding the probiotic strains and the dosages should be available. The comparison group was defined as the group receiving placebo, which was indistinguishable from the probiotics in appearance and administration route. The scope of the studies was not restricted to the general population or clinical population if measurements of depression severity were able to be completed. Observational studies (case reports, case series, retrospective chart reviews, cross-sectional studies, and open-label studies), studies with incomplete measurement of depression severity (depression subscale data unpublished), studies with incomplete information on probiotic intervention in terms of dosage or strains, studies with outcomes resulted from the same patient samples, and suspended studies were excluded.

2.2. Search strategy

The search strategy was designed and the search was performed by two independent researchers (KK Goh and CH Chen) by using following keywords: [depress* OR mood OR suicide] AND [microbiome OR probiotic OR yeast]; the search was restricted to publications in English; double-blind, randomized, placebo-controlled trials; and human studies. PubMed, Embase, Medline, Cochrane, Web of Science, and ProQuest databases were searched from database inception in August 1998–August 25, 2018. ClinicalTrails.gov (https://clinicaltrials.gov/) and International Clinical Trials Registry Platform (http://apps.who.int/trialsearch) were reviewed to confirm that all clinical studies meeting the inclusion criteria were included. An electronic search was re-performed before the final analysis, and additional studies were retrieved for inclusion. Studies were exported to the EndNote library after systematic literature search of the aforementioned databases. Duplicated studies were excluded, and the remaining studies were screened for relevance by examining the titles. Studies were then reviewed based on their abstracts. Full articles were assessed thoroughly for eligibility based on protocol-specified inclusion and exclusion criteria. Conflictual studies that caused differences between two investigators were discussed thoroughly and resolved through a consensus before entering qualitative and quantitative steps.

2.3. Main outcome measurement

Primary outcomes included all published and validated measurements of depression severity in the double-blind, randomized, placebo-controlled trials. Mean differences in depression scores were selected as continuous outcomes rather than the endpoint values to minimize the possibly of hidden reporting bias due to the difference in depression severity at baseline. Secondary outcomes were the safety profiles of intervention, including the reported discontinuation rate and adverse events.

2.4. Data extraction and quality assessment

Full articles were reviewed independently by two researchers (KK Goh and CH Chen) for inclusion and data extraction. Characteristics of the included studies, study population, interventions, primary outcomes, and secondary outcomes were recorded in a standardized form. The following data were extracted: (a) study characteristics including primary author, publication year, study period, country, context of the study, duration of intervention and follow-up, study design, and case number; (b) study population characteristics including age, sex, race, clinical diagnosis, and conclusion regarding the effects of probiotics on depression; (c) intervention characteristics including probiotic strains, concentration, dosage, prescription pattern, and schedule; (d) primary outcome was mean changes in depression severity; (e) secondary outcomes were discontinuation rate and adverse events. Indirect measurements were conducted according to the principles and guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Higgins and Green, 2011). Inconsistencies and discrepancies were discussed; subsequently, the original article was referred to, and the inconsistencies and discrepancies were resolved through a consensus before included for further analysis. Risk of bias was assessed using the Cochrane Risk of Bias assessment tool (Higgins et al., 2011). In this systematic review, quality of evidence was evaluated using GRADE criteria (Guyatt et al., 2008).

2.5. Data synthesis and statistical analysis

Narrative synthesis of the findings was performed and structured around the primary author, publication year, study design, country, intervention population and context, duration of intervention and follow-up, intervention variables, age, sex, clinical diagnosis, and conclusion of the effects of probiotics on depression symptoms. The intention-to-treat principle was applied for subsequent analyses.

There was limited scope for meta-analysis because of the varying outcomes measured across a small number of existing studies. Hence, we pooled the results using random effects meta-analysis, with standardized mean differences (SMD) calculated for continuous outcomes and risk ratios (RRs) for binary outcomes, and 95% confidence intervals (CI) and two-sided P values were also calculated for each outcome. For outcome measurements in different units across trials, we calculated SMD to combine the outcomes for this meta-analysis. Eligible outcomes from multiple intervention groups in a study were included in our study; the control group was divided evenly into two to three groups with a smaller sample size to overcome the unit-of-analysis error.

This meta-analysis was conducted and performed using Review Manage (RevMan) version 5.3.5 for Mac OS (http://tech.cochrane.org/revman/download). Meta-regression was performed, and publication bias was analyzed using Comprehensive Meta-Analysis Software. Heterogeneity between the studies was assessed using both the χ^2 test and I^2 statistic. χ^2 with $P < 0.05$ and I^2 value greater than 50% indicated substantial heterogeneity between the included studies. Stratified meta-analysis with priori-defined subgroups was applied to explore heterogeneity in the estimated effects between different populations and identify the potential moderators or mediators of the outcomes. The study population in the included studies was stratified into the general population, population with MDD, and population with other clinical diagnoses (without MDD). Multiple meta-regression analyses were performed to interpret heterogeneity and the moderating effects of age, sex, and treatment duration on the outcomes. Multiple sensitivity analyses based on study quality, alternative statistical

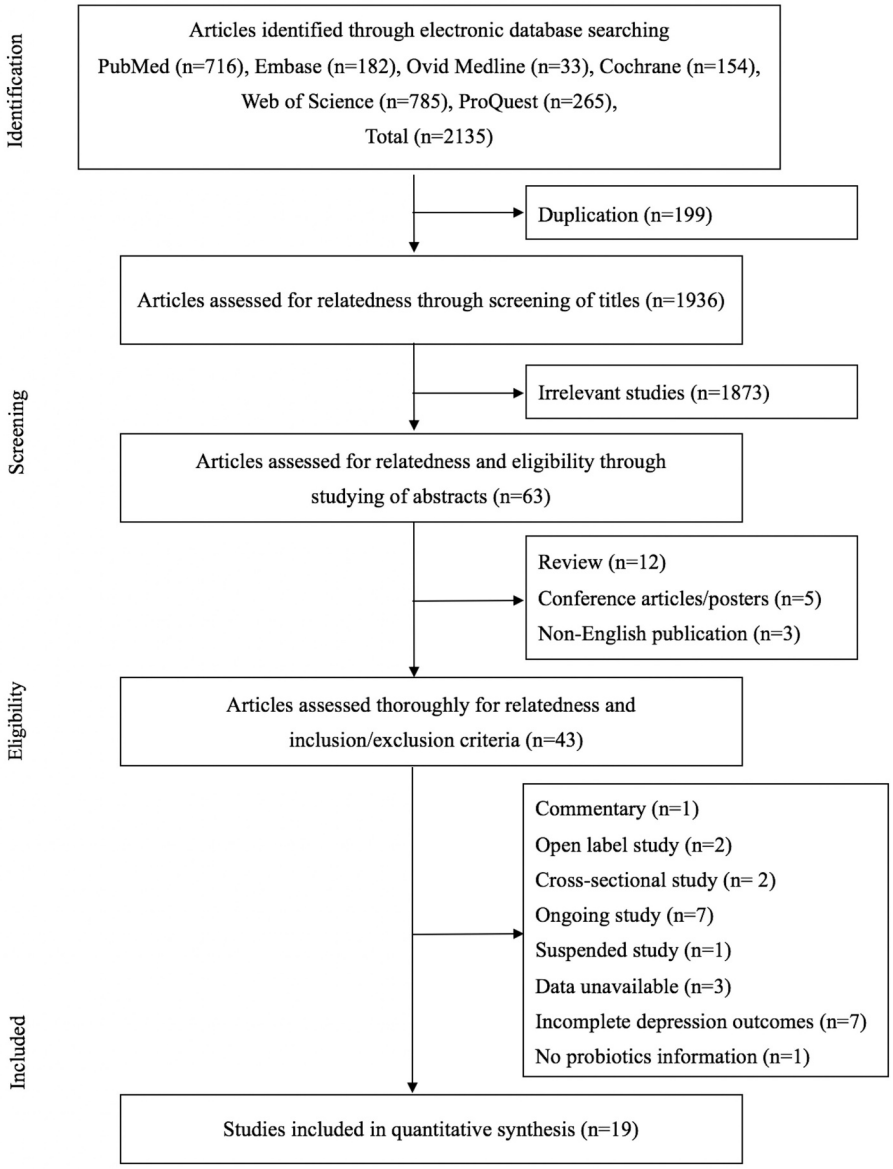

Fig. 1. PRISMA flowchart of included and excluded studies.

approach (fixed effects model), and studies with multiple comparison groups were conducted to examine the robustness of the results. Publication bias was evaluated through funnel-plot asymmetry, Begg and Mazumdar rank correlation, Egger's regression, Fail-safe N test, and Trim and fill method. If the aforementioned analysis yielded conflictual results of publication bias, the Trim and fill method was prioritized (Idris, 2012), and the results were discussed by two investigators (KK Goh and CH Chen).

3. Results

3.1. Identification of eligible studies

Fig. 1 shows the data extraction process. A total of 2135 articles were retrieved through the last electronic database search conducted on August 25, 2018 by using a designed search strategy. Finally, 19 double-blind, randomized, placebo-controlled trials (Akkasheh et al., 2016; Chung et al., 2014; Cipriani et al., 2018; Ghorbani et al., 2018; Kazemi et al., 2019; Messaoudi et al., 2011; Michalickova et al., 2016; Mohammadi et al., 2016; Nishihira et al., 2014; Östlund-Lagerström et al., 2016; Pinto-Sanchez et al., 2017; Raygan et al., 2018a,b; Roman et al., 2018; Romijn et al., 2017; Sashihara et al., 2013; Shinkai et al., 2016; Simren et al., 2010; Slykerman et al., 2017; Steenbergen et al., 2015) were included in qualitative synthesis.

3.2. Study and patient characteristics

The characteristics of 19 double-blind, randomized, placebo-controlled trials in the meta-analysis are summarized in Table 1. All studies were published online between 2010 and 2018. Overall, 1901 participants were randomized to the probiotic intervention group (n = 1030) and the placebo group (n = 871). Overall, the study cohort of 10 studies was recruited from the clinical population, including patients with MDD (n = 3), patients with irritable bowel syndrome (n = 2), patients with diabetes and coronary heart disease (n = 2), patients with depression (n = 1), patients with fibromyalgia (n = 1), and pregnant women (n = 1), and the study cohort of nine studies were recruited from the general population. The study outcomes of the scales designated for measuring depressive symptoms varied among studies (as listed in Table 1). These scales included the Beck Depression Inventory (BDI) (n = 5), Hospital Anxiety and Depression Scale (HADS) (n = 4), Profile Of Mood States (n = 3), Depression Anxiety Stress Scales

Table 1
Characteristics of the 19 included double-blind, randomized, placebo-controlled studies.

Study	Country	Population (Diagnosis criteria of depression) Inclusion criteria	Study duration	Probiotics strain(s) (daily dosage in CFU)	Design	n	Male	Age (mean ± SD)	Outcome measures	Conclusion (depression)
Akkasheh et al. (2016)	Iran	Major depressive disorder (DSM–IV) with HDRS ≥ 15, aged 20–55	8 weeks	*L. acidophilus* (2×10^9), *L. casei* (2×10^9), *B. bifidum* (2×10^9)	Probiotic capsule	20	3	38.3 ± 12.1	BDI[a]	Patients who received probiotic supplements had significantly decreased BDI total score
					Placebo capsule	20	3	36.2 ± 8.2		
Chung et al. (2014)	South Korea	General population[b] of senior citizens with MMSE ≥ 24, 35 ≥ BMI ≥ 16, and GDS–SF <8, aged 60–75	12 weeks	*L. helveticus* fermented milk, bacteria free (*L*HFM 125, 250, 500 mg)	*L*HFM tablet 500 mg	10	9	64.5 ± 2.2	GDS-SF[a]	A significant interaction and time effect for the GDS-SF was observed, however, no significant between-groups differences were observed for the changes in GDS-SF
					*L*HFM tablet 1000 mg	7	2	64.3 ± 4.5		
					*L*HFM tablet 2000 mg	9	5	66.6 ± 5.0		
					Placebo tablets	10	4	64.5 ± 4.5		
Ghorbani et al. (2018)	Iran	Major depressive disorder (DSM–5) with 23 ≥ HDSR ≥ 17, aged 18–55	6 weeks	Familact H® *L. casaei* (3×10^8), *L. acidofilus* (2×10^8), *L. bulgarigus* (2×10^9), *L. rhamnosus* (3×10^8), *B. breve* (2×10^8), *B. longum* (1×10^9), *S. thermophilus* (3×10^8), fructooligosaccharide (100 mg)	Synbiotic capsule + Fluoxetine 20 mg/d	20	6	34.5 ± 4.0	HDRS[a]	Probiotic group had a significantly decreased HDRS score compared to the placebo
					Placebo capsule + Fluoxetine 20 mg/d	20	6	35.5 ± 5.3		
Kazemi et al. (2019)	Iran	Major depressive disorder (ICD–10 code F32) with mild to moderate severity, took sertraline, fluoxetine, citalopram or amitriptyline for 3 months, aged 18–50	8 weeks	*L. helveticus* R0052, *B. longum* R0175 ($\geq 2 \times 10^9$)	Probiotic sachet	38	11	36.2 ± 7.9	BDI[a]	Probiotic supplementation resulted in a significant decrease in BDI score compared to the placebo and prebiotic supplementation
					Placebo sachet	36	9	36.0 ± 8.5		
Messaoudi et al. (2011)	France	General population[b] with HADS–anxiety ≤ 12 or HADS–depression ≤ 12 or HADS total score ≤ 20, aged 30–60	30 days	Probio'Stick® *L. helveticus* R0052, *B. longum* R0175 (3×10^9)	Probiotic stick	26	7	42.4 ± 7.5	HADS[a]	Administration of probiotic formulation significantly alleviated psychological distress in volunteers, as measured by HADS.
					Placebo stick	29	7	43.2 ± 8.5		
Michalickova et al. (2016)	Serbia	General population[b] of athletes with good maximal aerobic capacity under high training load, aged 18–28	14 weeks	*L. helveticus* Lafti® *L*10 (2×10^{10})	Probiotic capsule	20	15	23.5 ± 2.7	POMS	There were no interaction, time or group effects observed for the total mood disturbance, anger, confusion, depression, fatigue and tension scores.

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Population (Diagnosis criteria of depression) Inclusion criteria	Study duration	Probiotics strain(s) (daily dosage in CFU)	Design	n	Male	Age (mean ± SD)	Outcome measures	Conclusion (depression)
					Placebo capsule l	19	14	22.8 ± 2.5		
Mohammadi et al. (2016)	Iran	General population[b] of petrochemical workers, aged 20–60	6 weeks	Probiotic yougurt: *L. acidophilus*LA5, *B. lactis* BB12 ($>1 \times 10^7$) Probiotic capsule: *L. casei* (3×10^3), *L. acidophilus* (3×10^7), *L. rhamnosus* (7×10^9), *L. bulgaricus* (5×10^8), *B. breve* (2×10^{10}), *B. longum* (1×10^9), *S. thermophilus* (3×10^8) + fructo-oligosaccharide Conventional Yogurt: *S. thermophilus* and *L. bulgaricus*	Probiotic yogurt + placebo capsule	25	12	33.2 ± 6.4	DASS[a]	A significant improvement in DASS scores in the probiotic yogurt and the probiotic capsule group.
					Probiotic capsule + conventional yogurt	25	12	31.5 ± 5.8		
					Conventional yogurt + placebo capsule	20	12	33.1 ± 6.1		
Nishihira et al. (2014)	Japan	General population[b], aged 32–76	12 weeks	Probiotic yogurt: *L. gasseri* SBT2055 ($\geq 5 \times 10^8$), *B. longum* SBT2928 ($\geq 1 \times 10^9$), *S. thermophilus* and *L. delbrueckii* subsp. *bulgaricus* Placebo yogurt: *S. thermophilus* and *L. delbrueckii* subsp. *bulgaricus*	Probiotic yogurt	115	35	53.6 ± 11.3	GHQ-28	No significant differences in GHQ-28 score were observed between the test and placebo groups.
					Placebo yogurt	109	34	54.3 ± 10.9		
Östlund-Lagerström et al. (2016)	Sweden	General population[b] of senior citizens, aged ≥65	12 weeks	*L. reuteri* DSM17983 (1×10^8)	Probiotic stick-pack	125	54	72.6 ± 5.8	HADS	Probiotic treatment did not significantly affect depression score.
					Placebo stick-pack	124	43	72.0 ± 5.6		
Pinto-Sanchez et al. (2017)	Switzerland	Irritable bowel syndrome[b] with diarrhea or mixed–stool pattern, HADS 8–14, aged 26–58	6 weeks	*B. longum* NCC3001 (2×10^{10})	Probiotic sachet	22	10	42.8 ± 11.0	HADS[a]	14 patients in probiotic group had reduction in depression scores of 2 points or more on the HADS than in placebo.
					Placebo sachet	22	10	40.8 ± 9.0		
Raygan et al. (2018a)	Iran	Type 2 DM with coronary heart disease[b], aged 45–85	12 weeks	Lactocare® *L. acidophilus* (2×10^9), *L. reuteri* (2×10^9), *L. fermentum* (2×10^9), *B. bifidum* (2×10^9)	Probiotic + selenium pill (200 µg/d)	27	11	64.8 ± 8.3	BDI[a]	Probiotic and selenium co-supplementation decreased BDI compared with the placebo
					Placebo	27	10	62.4 ± 13.1		
Raygan et al. (2018b)	Iran	Type 2 DM with coronary heart disease[b], aged 45–85	12 weeks	*L. acidophilus* (2×10^9), *L. reuteri* (2×10^9), *L. fermentum* (2×10^9), *B. bifidum* (2×10^9)	Probiotic + vitamin D_3 pill (50,000 IU/q2w)	30	16	71.5 ± 10.9	BDI[a]	Vitamin D and probiotic co-supplementation resulted in significant improvements in BDI total score.
					Placebo	30	14	67.3 ± 11.0		
Roman et al. (2018)	Spain	Fibromyalgia[b] with diagnosis ≥ 1 year	8 weeks	*L. rhamnosus* GG, *L. casei*,*L. acidophilus, B. bifidus* (2.4×10^7)	Probiotic capsule	16	1	55.0 ± 2.1	BDI[a]	No beneficial effects were observed in depressive or anxiety symptoms
					Placebo capsule	15	2	50.3 ± 2.0		

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Population (Diagnosis criteria of depression) Inclusion criteria	Study duration	Probiotics strain(s) (daily dosage in CFU)	Design	n	Male	Age (mean ± SD)	Outcome measures	Conclusion (depression)
Romijn et al. (2017)	New Zealand	Depression (QIDS ≥ 11 or DASS-depression ≥ 14) with free of psychiatric medication for 4 weeks, aged ≥ 16	8 weeks	*L. helveticus* R0052, *B. longum* R0175 ($\geq 2 \times 10^9$)	Probiotic sachet	40	8	35.8 ± 14.0	DASS[a]	No significant difference was found between probiotic and placebo groups on any psychological measurements.
					Placebo sachet	39	9	35.1 ± 14.5		
Sashihara et al. (2013)	Japan	General population[b] of athletes with high-intensity training ≥ 5d/w, aged ≤ 30	4 weeks	*L. gasseri* OLL2809 (1×10^{10})	Probiotic tablet	15	15	19.8 ± 0.9	POMS[a]	No significant treatment effects and their interaction effects in all the subscales were observed.
					Probiotic + α-lactalbumin	15	15	19.9 ± 0.9		
					Placebo tablet	14	14	20.2 ± 1.1		
Shinkai et al. (2016)	Japan	General population[b] of senior citizens resided in Tokyo and its suburbs, aged ≥65	20 weeks	*L. pentosus* b240, heat-killed (Low dose 2×10^9) (High dose 2×10^{10})	Probiotic low-dose tablet	92	44	71.0 ± 4.0	POMS	No significant difference was found between the probiotic and placebo groups on any POMS measure.
					Probiotic high-dose tablet	93	48	70.8 ± 3.4		
					Placebo tablet	93	46	70.9 ± 3.8		
Simren et al. (2010)	Sweden	Irritable bowel syndrome[b], aged 18–70	8 weeks	*L. paracasei* F19, *L. acidophilus* La5, *B. lactis* Bb12 ($\geq 5 \times 10^7$))	Probiotic milk	37	11	42.0 ± 15.0	HADS	No significant changes in HADS-depression scores were detected in any groups.
					Placebo milk	37	11	44.0 ± 16.0		
Slykerman et al. (2017)	New Zealand	Pregnancy of 14–16 weeks of gestation[b], aged ≥ 16	6 months	*L. rhamnosus* HN001 (6×10^9)	Probiotic capsule	193	0	33.5 ± 4.2	EPDS[a]	Mothers in the probiotic treatment group reported significantly lower depression scores than those in the placebo group.
					Placebo capsule	187	0	33.7 ± 4.4		
Steenbergen et al. (2015)	Netherland	General population[b] of young adults	4 weeks	Ecologic® Barrier *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and W58 (2.5×10^9)	Probiotic powder	20	5	20.2 ± 2.4	LEIDS-r[a]	Participants with probiotics intervention showed a significantly reduced overall cognitive reactivity to but BDI total score revealed no main effect of time.
					Placebo powder	20	3	19.7 ± 1.7		

Abbreviations: ACR = American College of Rheumatology, ADA = American Diabetes Association, AHA = American Heart Association, BDI = Beck Depression Inventory, BMI = Body Mass Index, DASS = Depression Anxiety Stress Scales, EPDS = Edinburgh Postnatal Depression Scale, GDS-SF = Geriatric Depression Scale-Short Form, POMS = Profile Of Mood States, GHQ-28 = General Health Questionnaire-28, HADS = Hospital Anxiety and Depression Scale, HDRS = Hamilton Depression Rating Scale, LEIDS-r = Leiden Index of Depression Sensitivity-revised, MMSE = Mini-Mental State Examination, QIDS = Quick Inventory of Depressive Symptomatology.

[a] Depression is a primary outcome.

[b] No diagnosis of depression in inclusion criteria.

(n = 2), Hamilton Depression Rating Scale (HDRS) (n = 1), General Health Questionnaire-28 (n = 1), Geriatric Depression Scale-Short Form (n = 1), Edinburgh Postnatal Depression Scale (n = 1), and Leiden Index of Depression Sensitivity revised (n = 1). The mean duration of intervention was 9.89 ± 5.31 weeks (range: 4–24 weeks). Among the MDD studies, patients were treated with antidepressants and probiotics in two studies (Ghorbani et al., 2018; Kazemi et al., 2019) and with probiotics monotherapy in one study (Akkasheh et al., 2016). In non-MDD studies, none of the participants received concomitant antidepressants, except for in one study, which allowed patients to continue their ongoing psychotherapy during the trial (Romijn et al., 2017). Overall, 10 studies showed significant depression improvement after probiotic intervention, whereas the remaining nine studies showed nonsignificant effects of probiotic intervention.

3.3. Quality of included studies and risk of bias assessment

Quality of evidence was examined using GRADE criteria (Guyatt et al., 2008). After assessment, the primary outcome showed high quality evidence, whereas secondary outcomes showed low quality evidence. Using the Cochrane Risk of Bias assessment tool, we assessed the risk of bias of individual studies in the context of the primary outcome and is summarized in Fig. 2.

3.4. Effects of probiotic intervention on depressive symptoms

Participants in the probiotic group had significant improvement in depression (SMD = −0.31; 95% CI, −0.56 to −0.07; P = 0.01; I^2 = 82%) compared with those in the placebo group. The significant effects of probiotics on depressive symptoms remained unchanged after the sensitivity analysis conducted using the fixed effects model, which was restricted to studies without a high risk of bias and to studies with two comparison groups.

3.5. Stratified meta-analysis and meta-regression analysis

Heterogeneity detected during the assessment and meta-analysis procedure resulted from the interaction between subgroups of the studies included. The included studies were stratified into three groups according to the study population (Fig. 3). Probiotics were significantly superior to placebo in improving depressive symptoms in patients with MDD, but not in other clinical populations and the general population. Among the MDD studies, the pooled treatment effects of probiotics on depressive symptoms in patients administered antidepressants (SMD = −0.75; 95% CI, −1.15 to −0.35; P < 0.001) and those not administered antidepressants (SMD = −0.74; 95% CI, −1.38 to −0.10; P < 0.05) were not significantly different (Test for subgroup differences: χ^2 = 0.00, df = 1, P = 0.97).

We summarized probiotics strains used in the included studies in Table 2. A total of 12 studies used the probiotics formulation containing multiple strains, and 7 studies used a single strain for the participants. From Table 2, it is difficult to conclude that any specific strain of probiotics contributed to positive results. Fig. 4 shows the effects of probiotics on depressive symptoms based on the number of strains. The results showed that multiple strains, but not single strain, of probiotics could significantly reduce depressive symptoms.

Moderators were tested in exploratory meta-regression analysis to examine their significance to primary outcomes. Age (P = 0.10), sex (P = 0.11), and the duration of intervention (P = 0.06) showed nonsignificant interactions with the treatment response in the meta-regression analysis.

3.6. Safety profile

Among 19 included studies, only 7 studies reported their discontinuation, including one study with no discontinuation of participants in both arm that was excluded for relative risk calculation. No difference was found in all-cause treatment discontinuation (RR = 0.90; P = 0.62) and discontinuation due to adverse events (RR = 2.01; P = 0.23) between the probiotic and the placebo groups.

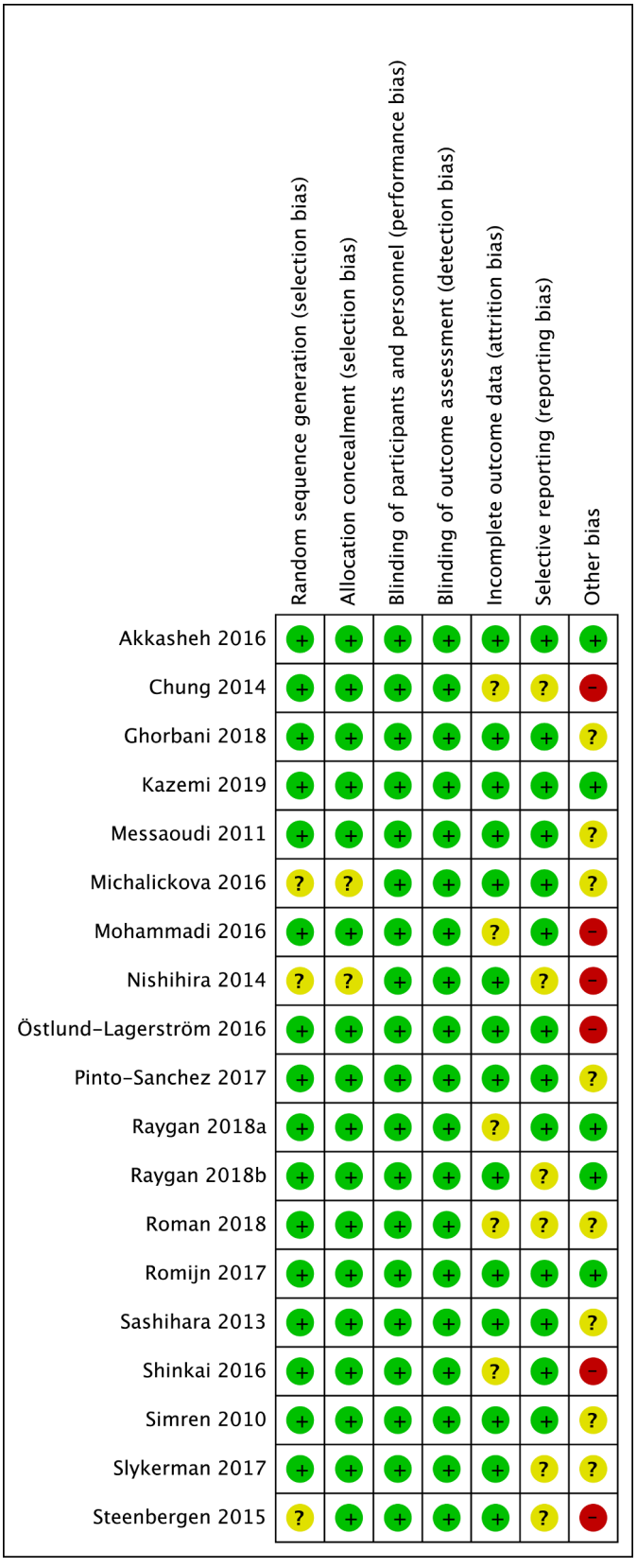

Fig. 2. Risk of bias of included studies.

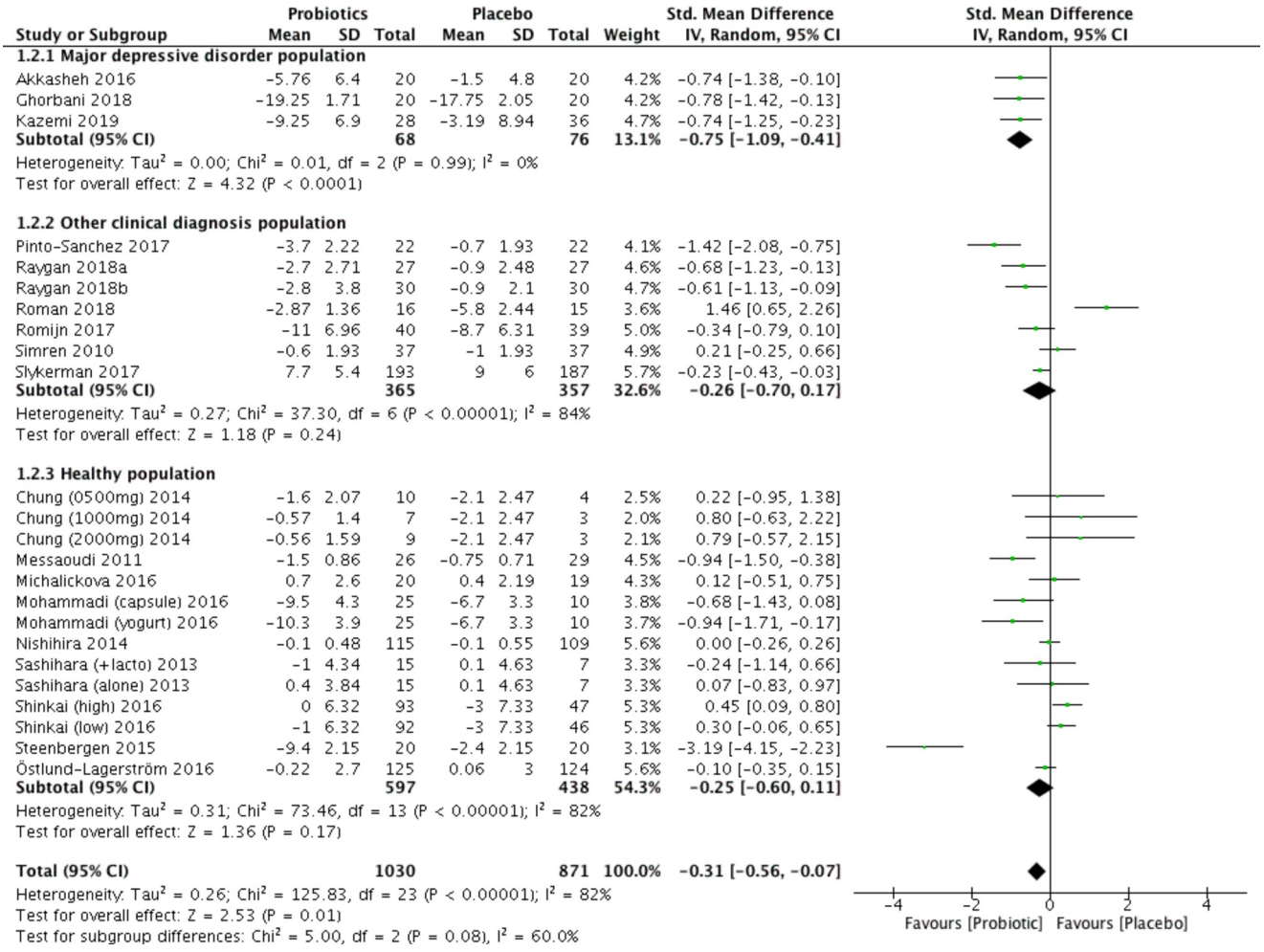

Fig. 3. Subgroup analysis of the effect of probiotics on depressive symptoms in different population groups.

Overall, the probiotic intervention was well-tolerated. No significant differences were observed in adverse events between the two groups, except for a higher incidence of abdominal discomfort in the probiotic group ($P = 0.05$).

3.7. Sensitivity analysis and publication bias

As a priori-defined protocol, multiple sensitivity analyses were conducted to verify and examine heterogeneity between the included studies. The primary outcome remained statistically significant after multiple sensitivity analyses in the fixed effects model as well as when restricted to studies without a high risk of bias and to studies with two comparison groups.

Publication bias was examined both qualitatively (funnel-plot asymmetry) and quantitatively (Begg and Mazumdar rank correlation, Egger's regression, Fail-safe *N* test, and Trim and fill method). Overall, no evidence of publication bias was observed.

4. Discussion

Our current meta-analysis showed that the overall effect of probiotics on depressive symptoms was statistically significant (SMD = −0.31; 95% CI, −0.56 to −0.07; $P = 0.01$). We found that probiotics were effective in reducing depressive symptoms in the clinical population (SMD = −0.40; 95% CI, −0.74to −0.06; $P = 0.02$), which is similar to the findings of Ng's meta-analysis (Ng et al., 2018). Compared with Ng's meta-analysis, we included almost double the number of studies in our meta-analysis and increased the sample size from 1349 to 1901. To ensure superior homogeneity among patients with depression, we further stratified patients by their clinical diagnosis: those with MDD versus those with other clinical conditions, which was not performed in Ng's meta-analysis. In subgroup analyses, the significant effect of probiotics on depressive symptoms only existed in patients with MDD (SMD = −0.75; 95% CI, −1.09 to −0.41; $P < 0.001$), but not in those with other clinical conditions (SMD = −0.26; 95% CI, −0.70 to 0.17; $P = 0.24$) and general population (SMD = −0.25; 95% CI, −0.60 to 0.11; $P = 0.17$). It is unclear why probiotics were effective in patients with MDD, but not in those with other clinical conditions. It is possible that the severity of depression is too mild to show the effectiveness of probiotics in patients with other clinical conditions. However, the severity of depression at baseline was moderate in four of seven studies of patients with other clinical conditions, with BDI scores higher than 20 (Raygan et al., 2018a, b; Roman et al., 2018) and Montgomery–Åsberg Depression Rating Scale scores higher than 25 (Romijn et al., 2017). These outcomes were similar to the severity of depression in two clinical studies of patients with MDD, with BDI scores of 18.2 (Kazemi et al., 2019) and HDRS-17 scores of 22.9 (Ghorbani et al., 2018) (Akkasheh's study did not provide depression scores at baseline). We found that probiotics did not have a significant effect on depressive symptoms in these four studies of patients with other clinical conditions and moderate depression (SMD = −0.10; 95% CI, −0.85 to 0.65; $P = 0.79$). Therefore, the severity of depression cannot explain the different effects of probiotics on depressive symptoms between patients with MDD and those with other clinical conditions. In addition, clinical diagnoses of other clinical conditions in two studies of patients with diabetes and coronary

Table 2
Summary of bacterial strains used in the 19 double-blind, randomized, placebo-controlled studies.

	Probiotics								
	Single / Multiple strains	*L. acidophilus*	*L. brevis*	*L. bulgarigus*	*L. casei*	*L. fermentum*	*L. gasseri*	*L. helveticus*	*L lactis*
Studies with positive results									
Akkasheh et al. (2016)	Multiple	+			+				
Chung et al. (2014)	Single							+	
Ghorbani et al. (2018)	Multiple	+		+	+				
Kazemi et al. (2019)	Multiple							+	
Messaoudi et al. (2011)	Multiple							+	
Mohammadi et al. (2016)	Multiple	+		+	+				
Pinto-Sanchez et al. (2017)	Single								
Raygan et al. (2018a)	Multiple	+				+			
Raygan et al. (2018b)	Multiple	+				+			
Slykerman et al. (2017)	Single								
Studies with negative results									
Michalickova et al. (2016)	Single							+	
Nishihira et al. (2014)	Multiple			+			+		
Östlund-Lagerström et al. (2016)	Single								
Roman et al. (2018)	Multiple	+			+				
Romijn et al. (2017)	Multiple							+	
Sashihara et al. (2013)	Single						+		
Shinkai et al. (2016)	Single								
Simren et al. (2010)	Multiple	+							
Steenbergen et al. (2015)	Multiple	+	+		+				+

	Probiotics									
	L. paracasaei	*L. pentosus*	*L. reuteri*	*L. rhamnosus*	*L. salivarius*	*B. bifidum*	*B. breve*	*B. lactis*	*B. longum*	*S. thermophilus*
Studies with positive results										
Akkasheh et al. (2016)						+				
Chung et al. (2014)										
Ghorbani et al. (2018)				+			+		+	+
Kazemi et al. (2019)									+	
Messaoudi et al. (2011)									+	
Mohammadi et al. (2016)				+			+	+	+	+
Pinto-Sanchez et al. (2017)									+	
Raygan et al. (2018a)			+			+				
Raygan et al. (2018b)			+			+				
Slykerman et al. (2017)				+						
Studies with negative results										
Michalickova et al. (2016)										
Nishihira et al. (2014)									+	+
Östlund-Lagerström et al. (2016)			+							
Roman et al. (2018)				+		+				
Romijn et al. (2017)									+	
Sashihara et al. (2013)										
Shinkai et al. (2016)		+								
Simren et al. (2010)	+							+		
Steenbergen et al. (2015)					+	+		+		

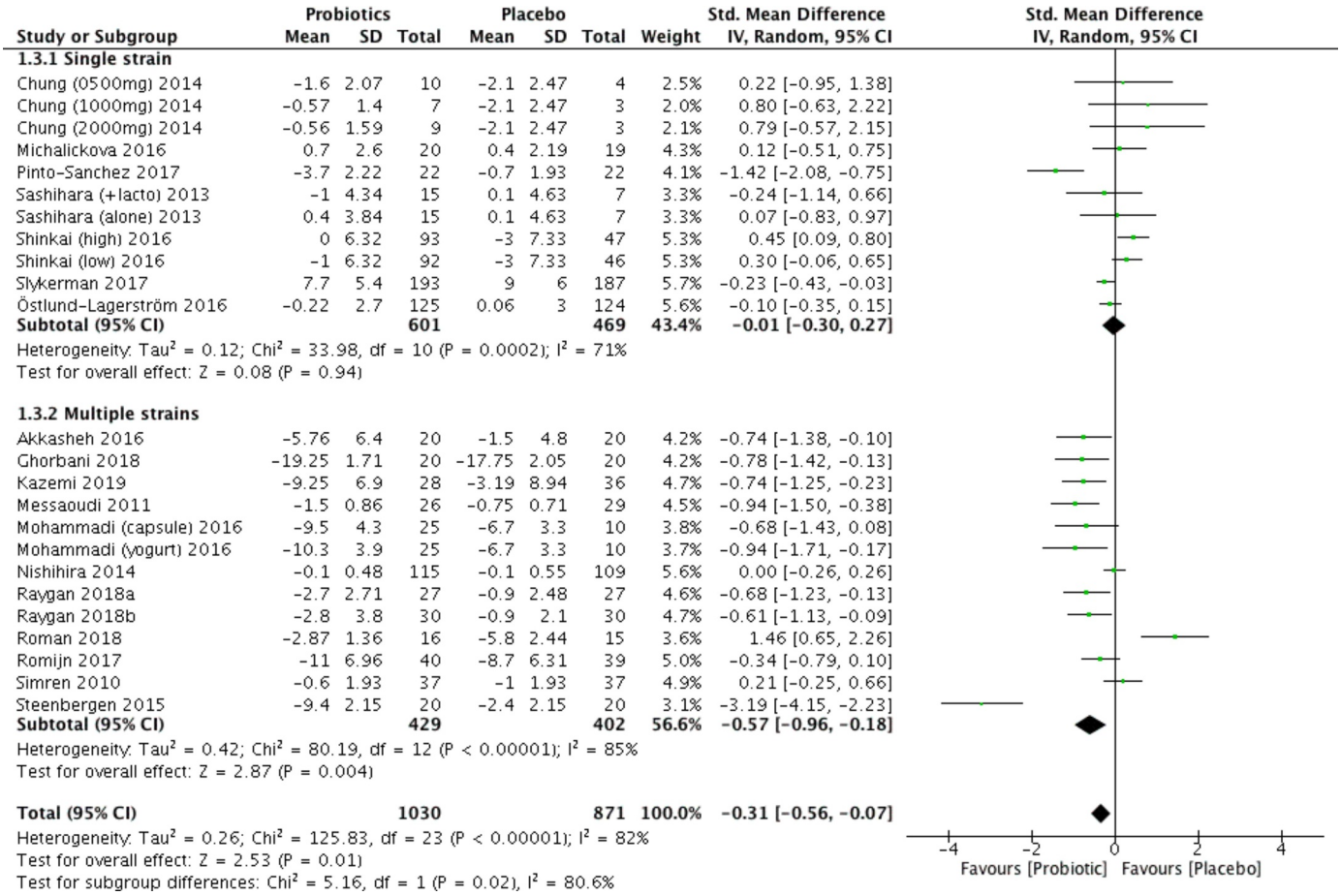

Fig. 4. Subgroup analysis of the effect of probiotics on depressive symptoms based on the number of strains.

heart disease (Raygan et al., 2018a, b), two studies of irritable bowel syndrome (Pinto-Sanchez et al., 2017; Simren et al., 2010), one study of fibromyalgia (Roman et al., 2018), one study of pregnant women (Slykerman et al., 2017), and one study of patients with moderate depressive symptoms without clinical diagnosis (Romijn et al., 2017) were too heterogeneous to stratify the patients into subgroups for further analysis.

As another point of differentiation from Ng's meta-analysis, we stratified strains of probiotics into single strain and multiple strains and analyzed their effectiveness in reducing depressive symptoms. Although we found that multiple strains of probiotics were effective in reducing depressive symptoms, the combinations of species and strains of probiotics were too diverse to identify specific effective strains. The effective strains of probiotics for the improvement of depressive symptoms warrant further exploration.

Multiple mechanisms can explain the possible antidepressant effect of probiotics. First, the hypothalamic–pituitary–adrenal (HPA) axis and inflammatory pathways may account for crucial interactions between probiotics and the brain. Consumption of probiotics attenuated the hyperactivity of the HPA axis (Ait-Belgnaoui et al., 2014; Liu et al., 2016b), normalized the enhanced immune response, and reversed depressive-like behavior in maternal separation rats (Desbonnet et al., 2010; Liu et al., 2016b). Among our included clinical studies, some studies examined changes in inflammation markers, but the results were inconsistent (data not shown). Second, the vagus nerve may be involved in the communication between probiotics and the brain. For example, *L. rhamnosus* can reduce stress-induced corticosterone and anxiety- and depression-related behavior in mice. These behavioral changes were not found in vagotomized mice (Bravo et al., 2011). However, changes in gut microbiota caused by antimicrobials affected the behavior independently of vagus nerve integrity and inflammation (Bercik et al., 2011). Third, short chain fatty acids (SCFAs), which are produced by gut microbes by metabolizing indigestible fibers, may play some roles in the communication between the gut and brain. SCFAs show immunomodulatory properties (Smith et al., 2013), affect host health through the inhibition of histone deacetylases (Stilling et al., 2016), activate G-protein-coupled receptors (Milligan et al., 2017), and facilitate colonic serotonin production (Reigstad et al., 2015). SCFA levels were correlated with depressive and anxiety behaviors in mice with chronic stress after prebiotic treatment (Burokas et al., 2017). Administration of SCFAs alleviated depressive and anxiety behavior in mice with chronic stress (van de Wouw et al., 2018). Fourth, neurotransmitters may be modulated by microbes. For example, gut microbes may affect the metabolism of tryptophan (O'Mahony et al., 2015), which is absorbed from the gut and transported to the CNS for serotonin synthesis. In addition, microbes produce gamma-aminobutyric acid in vitro, but the effect varied among different species (Barrett et al., 2012). In vivo, microbes can alter turnover rates of serotonin and dopamine in the striatum of mice (Liu et al., 2016a). Although significant evidence shows that probiotics may affect brain function in animal studies, the results have not been validated in humans.

The current meta-analysis has some limitations. First, the lack of uniformity in the sample size and population distribution among the included studies may affect the validity and generalizability of the results. The study design varied among the included studies, which may interfere with the results, especially because those studies involved participants with different diagnoses, different microbiomes, different mode of delivery, different treatment durations, and different outcome measurements. We tried to reduce diagnosis heterogeneity by further stratifying populations into three groups based on their clinical

diagnosis, including patients with MDD, and we used multiple sensitivity analyses and post hoc meta-regression to confirm primary outcomes. Additionally, our method of dividing the control group evenly may only partially overcome the unit-of-analysis error. Second, selective publication bias of the studies is another critical issue influencing the treatment effect. At least one suspended study without detail disclosure was noticed when accessing the registered unpublished clinical trials; in other words, studies with unfavorable or negative outcomes may be unpublished and/or uncovered. Third, compared with other clinical populations and the healthy population, the sample size of patients with MDD (probiotics: $n = 68$ and placebo: $n = 76$) was small. More studies are warranted to support the antidepressant effect of probiotics in patients with MDD.

In conclusion, manipulating the gut–brain axis may be an approach to improve depression severity. Our meta-analysis showed that probiotics have antidepressant effects in patients with MDD, but not in those with other clinical conditions or in the general population. Multiple strains of probiotics may be more effective in reducing depressive symptoms than a single strain of probiotics. Because the study sample of patients with MDD is relatively small and the species and strains of probiotic used in clinical trials are diverse, the results are still quite preliminary. Additional studies with larger sample sizes are warranted to verify the efficacy of specific combinations or strains of probiotics in the future.

Data for reference

The datasets generated and analyzed in the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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