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Renata Soraia Duarte Barbosa

Probiotics and prebiotics: focus on psychiatric disorders

Probióticos e prebióticos nas doenças psiquiátricas: a evidência atual

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Probiotics and prebiotics: flows on psychiatric disorders

ORIENTADOR

Professora Doutora Maria Augusta Vieira Coelho

COORIENTADOR (se aplicável)

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Title: Probiotics and prebiotics: focus on psychiatric disorders

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Abstract: The gut-brain axis and microbial dysbiosis may play a role in the basis of brain disease processes, including psychiatric diseases. The gut microbiota can be considered a potential therapeutic target using probiotics and prebiotics.

This systematic review aims to describe the existing evidence which may justify the clinical use of probiotics and prebiotics in psychiatric patients.

The studies included were clinical trials using probiotics or prebiotics in humans diagnosed with a psychiatric disease. Thirteen articles were included out of 212 articles retrieved from PubMed and bibliographic sources.

Probiotics seem to benefit symptoms of major depressive disorder and Alzheimer's disease. No benefits were found for schizophrenia. Probiotics showed a reduction in rehospitalization in patients with acute mania. Early administration of probiotics reduced the risk of development of attention deficit hyperactivity disorder and Asperger Syndrome; however, results were controversial regarding the severity of Autism Spectrum Disorders manifestations.

Despite some limitations, results in human patients support the use of probiotics and prebiotics in specific psychiatric disorders.

Key words: psychiatric disorders; microbiota; gut-brain axis; probiotics; prebiotics.

INTRODUCTION

In recent years, microbiota research has suffered a huge development due to its proven impact on health and disease.[1,2] The gut microbiota (GM) is a diverse community of bacteria in the human gastrointestinal (GI) tract living in symbiosis with the human host.[3] In fact, the gut is inhabited by 1×10^{13} to 1×10^{14} microorganisms - more than 10 times the number of cells in the human body,[1,3] with *Firmicutes* and the *Bacteroidetes* as the most predominant phylotypes.[3,4] The individuality of the microbial populations in the gut and the existence of a core healthy microbiota profile is still controversial.[3,5] Several studies have shown a link between GM and brain function, describing the concept of a gut-brain axis to represent the bidirectional communication between these two organs.[4,6-8] Most recent scientific studies suggests that the gut microbiota affects some aspects of brain function and behavior, including emotional behavior and related brain systems with significant implications for human health and daily living.[9] Moreover, the gut-brain axis may play an important role in the biological and physiological basis of neurodevelopmental and neurodegenerative disorders,[4,10] influencing several key pathways in the endocrine (cortisol), immune (cytokines) and neural (vagus and enteric nervous system) systems.[1,3] In this way, microbial dysbiosis may influence the onset and progress of several neurological disease processes, including psychiatric diseases.[3,10] The GM may be a novel therapeutic target in these illnesses, with potential for treatment using certain antibiotics, microbiota transplantation and diet modulation with pre- and probiotics.[4] Probiotics are defined as live microorganisms that, when administered in adequate amounts, benefit the host's health.[11] These products frequently include lactic acid-producing bacteria that belong to the *Lactobacillus* and *Bifidobacterium* genera.[12]

Probiotics seem to have an advantageous effect in the prevention of urinary tract infections in fertile women as well as in allergic diseases such as atopic eczema and infantile diarrhea.[13] Prebiotics refer to non-digestible fibers, such as oligosaccharides, that promote growth and improve the functioning of the probiotics in the GI tract by acting as a specific substract.[11,14] Prebiotics seem to have a beneficial role in the treatment of bowel constipation, colon cancer and inflammatory bowel disease.[5] The term psychobiotics has emerged to emphasize this therapeutic effect of probiotics and/or prebiotics on mental disorders.[14]

The fact remains that medications used in the treatment of many mental disorders may not be effective or even tolerated by patients. Alternate therapies using pre- or probiotics may be of benefit. Nonetheless, further investigation is needed, particularly regarding the composition of microbiota and how diet and pre- or probiotics influence the microbiota. This new field may bring possibilities of new and inexpensive treatments.[2]

Both studies in animal models and healthy volunteers have evaluated the effect of pro- or prebiotics in psychiatric symptoms. [12,15-19] However, experimental studies testing the effect of these products in patients diagnosed with specific psychiatric conditions are limited and somewhat controversial. The aim of this systematic review is to answer the question: what is the real clinical evidence of pro- and prebiotics in humans with psychiatric disorders?

METHODS

This systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20]

Inclusion criteria

Studies were considered for inclusion only if they were clinical trials. The target population in these studies must have been diagnosed with a psychiatric disease at the beginning or at the end of the trial. The clinical course of the disease had to have been evaluated with questionnaires or checklists. Neither a randomization process nor comparison groups were required for inclusion. Studies comparing use of prebiotics/probiotics compared with a placebo control or other active intervention were included. Outcomes such as symptom improvement, safety, adverse effects and duration of the intervention were considered.

Exclusion criteria

All studies with no experimental intervention in humans were excluded (animal models, reviews, commentaries, notes, study protocols or observational studies). Case-reports were not included. Clinical trials which only described psychiatric symptoms, with no specific diagnosis at the beginning or at the end of the intervention were considered ineligible. Irrelevant articles were excluded at the title/abstract level of screening. Length of follow-up was not defined as part of the eligibility criteria.

Search strategy

The final literature search was on September 7th 2018 using the PubMed database. The objective of this search was to include all articles relating mental disorders and probiotics and/or prebiotics. The search query was:

(“Mental Disorders”[Mesh] OR "Anxiety Disorders" OR “Anxiety Disorder” OR “Obsessive-compulsive disorder” OR “Obsessive-compulsive disorders” OR “Phobic

disorders” OR “Phobic disorder” OR “Dissociative Disorder” OR “Dissociative Disorders” OR "Bipolar Disorders" OR "Bipolar Disorder" OR "Cyclothymic Disorder" OR (“Depressive Disorders” OR “Depressive Disorder” OR “Major Depressive Disorder” OR “Postpartum Depression” OR “Dysthymic Disorder”) OR “Anorexia Nervosa” OR “Bulimia Nervosa” OR “Dementia” OR "Autism Spectrum Disorders" OR "Autism Spectrum Disorder" OR "Autistic Disorder" OR “Asperger Syndrome” OR "Neurodevelopmental Disorders" OR "Neurodevelopmental Disorder" OR “Attention deficit disorder” OR “Conduct disorder” OR “Conduct disorders” OR "Personality Disorder" OR “Personality Disorders” OR "Schizophrenia Spectrum and Other Psychotic Disorders" OR “Schizophrenia” OR “Paranoid Disorders” OR “Paranoid Disorder” OR "Somatoform Disorder" OR "Somatoform Disorders" OR "Psychiatric symptoms"[All Fields] OR "Psychological outcomes"[All Fields])

AND

("probiotics"[Mesh] OR "probiotic"[All Fields] OR "prebiotic"[All Fields] OR "prebiotics"[Mesh] OR "psychobiotics"[All Fields] OR (("microbiota"[MeSH Terms] OR "microbiota"[All Fields]) AND ("probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields])) OR (("microbiota"[MeSH Terms] OR "microbiota"[All Fields]) AND ("prebiotics"[MeSH Terms] OR "prebiotics"[All Fields] OR "prebiotic"[All Fields]))).

The query obtained 209 results. Only Portuguese or English articles were assessed for eligibility. Bibliographies of relevant papers were screened and three additional studies were included.

Quality of evidence was assessed using the Jadad Scale, which considers the quality of randomization, the quality of blinding and motives for withdrawal/dropouts. [21]

RESULTS

209 results were identified through the database search. When the bibliographies of relevant papers were screened, three more studies were considered relevant. There were no duplicates. All the records were screened and excluded based on abstract/title and language, with 32 full-text articles assessed for eligibility. A PRISMA flow diagram (Figure 1) demonstrates the procedure taken to select the papers used in this systematic review.

Of the 13 included studies assessing the effect of prebiotics and probiotics on clinical aspects in patients diagnosed with psychiatric conditions, three studied schizophrenia, three studied major depressive disorder (MDD), one studied acute mania, five studied autism spectrum disorders (ASD) and one studied Alzheimer's disease (AD).

The results of the quality assessment using the Jadad scale are presented in Table 1. The 11 randomized controlled trials (RCTs) included had a score between two and five points while two quasi-experimental studies included did not score any points.

Details of the studies may be seen in Table 2, summarizing the psychiatric conditions and criteria for diagnosis (when applicable), characterization of the sample and intervention and the outcomes assessed for each study.

1. Schizophrenia

The three articles[22-24] mentioned in this section evaluate different aspects of the same RCT. In this study, 58 patients diagnosed with schizophrenia or schizoaffective disorder based on Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) completed a 14-week trial of adjunctive probiotic (n=31) versus placebo (n=27) therapy. The schizophrenia symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS). The impact of probiotic treatment and yeast seropositivity on bowel discomfort as well as systemic immunomodulatory effects of probiotic supplementation were also assessed.

1.1 Probiotic effect on PANSS

At the end of the trial,[22-24] there were no significant differences between the groups with regards to the PANSS total score (p = 0.25) nor were any differences found using the PANSS positive (p = 0.90), negative (p = 0.08), or general psychopathology scale scores (p = 0.44).

According to the authors, there was an improvement in positive psychiatric symptoms in males treated with probiotics who were seronegative for *Candida albicans* compared to those who were seropositive (an effect significantly associated with elevated total PANSS scores). This improvement was significant between the beginning of the study and the 13-week time point (T-test, t=1.8, p≤0.04).[23]

1.2 Probiotics and yeast antibodies on bowel difficulties

The study by Dickerson et al.[22] showed that the probiotic group reported less difficulty in bowel movements along the trial (p = 0.003).

Another study[23] demonstrated that probiotics significantly reduced *C. albicans* antibodies during the study period in males ($p \leq 0.001$). The authors found that, in both males and females, *C. albicans* IgG levels were consistently elevated in patients with GI conditions compared to those without GI distress. *C. albicans*-seropositive males receiving the placebo had significantly higher bowel discomfort over time than the seronegative males ($p \leq 0.03$). Antibody levels for *Saccharomyces cerevisiae* did not significantly change based on treatment group or sex. However, *C. albicans* IgG levels reduced significantly over time in the group receiving probiotics, but not in the placebo group.

1.3 Systemic immunomodulatory effects of probiotics

This RCT showed a significant reduction of acute-phase reactant von Willebrand factor levels in patients diagnosed with schizophrenia ($p=0.047$).[22] The authors did not find significant differences in levels of other immune markers such as monocyte chemotactic protein 1, macrophage inflammatory protein 1 beta, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, tumor necrosis factor receptor 2, ferritin and C reactive protein.

2. Major Depressive Disorder

In the study by Akkashed et al.[25], patients diagnosed with MDD based on DSM-IV criteria completed an 8-week trial receiving either probiotic (n=20) or placebo (n=20). The authors aimed to assess variations in the Beck Depression Index (BDI) and in metabolic parameters such as fasting plasma glucose, markers of insulin metabolism, lipid concentrations, serum high sensitivity C-reactive protein and biomarkers of

oxidative stress including total antioxidant capacity and total glutathione levels. The results were analyzed using an intention to treat approach.

Another RCT[26] in major depressive patients (n=110) evaluated the changes in BDI score, comparing the effect of 8-week supplementation with probiotics (n=38), prebiotics (n=36) and placebo (n=36). They also assessed the effect of supplementation on the kynurenine/tryptophan ratio and tryptophan/branch chain amino acids ratio in these patients as a secondary outcome. The results were analyzed using an intention to treat strategy.

The study by Majeed et al.[27] included patients (n=40) diagnosed with MDD and irritable bowel syndrome in a 90-day intervention period, allocated to probiotic (n=20) or placebo group (n=20). They aimed to evaluate the safety and efficacy of the probiotic in MDD and irritable bowel syndrome, using the Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, Centre for Epidemiological Studies-Depression scale and irritable bowel syndrome quality of life questionnaire.

2.1 Probiotics and prebiotics in depression

Patients who received probiotic supplements had significantly decreased BDI scores (P=0.05) compared with the placebo group in a study by Akkasheh et al.[25]

Kazemi et al.[26] found a significant decrease in the BDI score over 8 weeks in the probiotic group compared to the placebo (p = 0.008). However, the decrease in the BDI score caused by the prebiotic was not significant compared to the placebo (p=0.39) or the probiotic groups (p = 0.26).

Furthermore, a study by Majeed et al.[27] favors the probiotic over placebo in patients diagnosed with depression and irritable bowel syndrome, according to the changes in

Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, Centre for Epidemiological Studies-Depression scale and irritable bowel syndrome quality of life scores ($p < 0.01$).

2.2 Metabolic and inflammatory biomarkers in depression

The only significant change in metabolic parameters in the probiotic supplemented group found in the Akkasheh et al.[25] study occurred in serum insulin, which decreased ($p=0.05$).

Kazemi et al.[26] found a significant decrease in the kynurenine/tryptophan ratio ($p=0.036$) and in tryptophan/branch chain amino acids ratio ($p=0.031$) in the probiotic group.

The study by Majeed et al.[27] showed that from the baseline to the end of study, the level of serum myeloperoxidase was significantly reduced ($p < 0.01$) in patients receiving probiotics.

Significant differences in fasting plasma glucose or lipid profile levels (namely LDL cholesterol) were not found in two of the studies included.[25,27]

3. Acute Mania

The only article assessing acute mania included patients diagnosed with bipolar I or schizoaffective disorder, bipolar type (manic or mixed state) (n=66).[28] The trial lasted for 24 weeks with patients allocated to probiotic (n=33) or placebo (n=33) arms. This study aimed to test whether the probiotic would prevent rehospitalization by assessing the time to rehospitalization and changes in psychiatric symptom severity. The symptoms were assessed with Young Mania Rating Scale, Montgomery-Asberg

Depression Rating Scale and Brief Psychiatric Rating Scale. The relationship between the rehospitalizations and inflammation was also evaluated through an inflammation score. The results were analyzed using an intention to treat approach.

3.1 Probiotics and rehospitalizations for acute mania

The total number of rehospitalizations was 32, with 24 in the placebo group and 8 in the probiotic group (p = 0.009). All rehospitalizations were due to worsening psychiatric symptoms.

Furthermore, in the individuals in the probiotic group, rehospitalization lasted for a mean of 2.8 days, while in the placebo group it lasted for an average of 8.3 days (p = 0.017).

The Brief Psychiatric Rating (p <0.0001) and the Young Mania Rating scales (p < 0.0001) showed significant improvements in both probiotic and placebo groups throughout the trial, but not the Montgomery-Asberg Depression Rating scale (p>0.1). Thus, no significant differences between the placebo and probiotic groups were present.

3.2 Inflammation score

Stratified for level of inflammation, the effect of probiotics in preventing all rehospitalizations was increased in individuals with higher levels of inflammation according to an unspecified score described by Dickerson *et al.*[28]

4. Autism spectrum disorder

Regarding the effect of pre- or probiotics on ASD, five experimental studies were included, with one related to prebiotics and four related to probiotics.

Grimaldi et al[29] included children (n=26) with a formal diagnosis of ASD in a ten-week clinical trial with a six-week prebiotic feeding period. The effect of the prebiotic treatment was evaluated using the Autism Treatment Evaluation Checklist (ATEC), Autism Spectrum Quotient, Empathy and Systemizing Quotient and Spence Children Anxiety Scale-Parent version. Furthermore, the authors used food diaries to divide the subjects according to their primary diets in an attempt to assess the effect of unrestricted or exclusion diets (for example, gluten and casein-free diets). The impact of the prebiotic on the bacterial composition of fecal and urine samples was also evaluated.

In a prospective 13-year follow-up study by Partty et al.,[30] the future diagnosis of attention deficit hyperactivity disorder (ADHD) and Asperger Syndrome (AS) after an early probiotic intervention was assessed. The mothers of the children received probiotic (n=40) or placebo (n=35) daily for four weeks before expected delivery. After delivery, the capsule contents were given either directly to the children, or continuously to the mothers, if breast-feeding, over six months. Differences in GM between children at several timepoints (3, 6 and 24 months and 13 years of age) were also studied.

Shaaban et al.[31] tested the effect of probiotic supplementation in autistic symptoms in children (n=30) using ATEC as well as GI symptoms through the Gastrointestinal Severity Index after three months of treatment.

Patients diagnosed with ASD who had GI distress (n=33) were included in a ATEC-based survey to assess ASD signs and symptoms before and after 21 days of treatment with probiotics.[32] The authors also evaluated the stool frequency before and after the

intervention. Neither of these studies included a process for randomization or blinding, nor did they include a control/placebo group.

The double-blind, placebo-controlled, crossover-designed study by Parracho et al.[33] included children diagnosed with ASD (n=17). Nine children from group I received placebo for three weeks followed by probiotic for three weeks, while eight children from group II received probiotic for three weeks and then placebo for three weeks. The psychological impact in those who completed the 12-week study was evaluated using Development Behaviour Checklist completed by parents or caregivers. This checklist evaluated disruptive/antisocial behaviour, self-absorbed behaviour, communication, anxiety problems and social-relating problems. The Total Behaviour Problem Score was also calculated. The intestinal microbiota was analyzed using fluorescence *in situ* hybridization, while gut function was assessed by parents or caregivers' diaries.

4.1 Prebiotics and diet in ASD

There was a significant improvement in social behavior scores after the prebiotic intervention in ASD children following exclusion diets.[29]

Additionally, lower levels of abdominal pain ($p<0.05$) were reported in children following exclusion diets. GM composition from ASD children with unrestricted diets before and after the prebiotic administration was different according to a redundancy analysis ($p<0.038$). After six weeks of intervention, a significant difference was also found in GM composition of ASD children following exclusion diet ($p<0.008$).[29]

The urine and fecal analysis showed several differences in metabolic profiles. After prebiotic supplementation, the urine from ASD children patients contained greater

amounts of creatinine, creatine, dimethylglycine, dimethylalanine, carnitine, citrate, adipate and trimethylamine-N-oxide than those taking placebo. Regarding the fecal sample analysis, the prebiotic group showed decreased levels of amino acids and lactate.[29]

4.2 Probiotics, GM and the risk of future neuropsychiatric disorders

The results from the Partty et al. study [30] showed that by the age of 13 years, six children were diagnosed with ADHD or AS in the placebo and none in the probiotic group (p = 0.02, controlled for gender). The same study showed that at the age of 13 neither fluorescence *in situ* hybridization nor quantitative polymerase chain reaction analysis showed statistically significant differences in GM composition between the children who later developed ADHD or AS and the healthy children.

4.3 Probiotics and psychiatric symptoms in ASD

Shaaban et al.[31] showed that in the probiotic supplementation group, the total ATEC scores (in all four categories) and the severity of ASD symptoms were significantly decreased (p value = 0.0001).

In the West et al.[32] study, 88% reported a decreased ATEC score from 72.8 prior to treatment to 58.3 following treatment ($p<0.05$). There were significant decreases following treatment initiation in all four ATEC categories: speech/language/communication ($P<0.05$), sociability ($P<0.05$), sensory/cognitive awareness ($p<0.05$) and health/physical/behavior ($P<0.05$).

On the contrary, the study by Parracho et al.[33] did not find differences in Total Behaviour Problem scores between the two feeding periods. There was no significant

359 difference in the median scores for the five domains evaluated between probiotic and
360 placebo feeding.
361
362 **4.4 Probiotics and GI symptoms in ASD**
363 The study by Shaaban et al.[31] showed a significant reduction in the total
364 Gastrointestinal Severity Index score after probiotic supplementation ($p<0.0001$), with
365 a significant reduction in the scores of constipation ($p<0.01$), flatulence ($p<0.037$),
366 abdominal pain ($p<0.002$) and stool consistency ($p<0.023$). These improved symptoms
367 were strongly correlated with improvements in autism manifestations after probiotic
368 supplementation ($r=0.674$, $p=0.001$).
369 Another study[32] also revealed that probiotics may ameliorate bowel movements.
370 When considering the fourth ATEC category (health/physical/behavior) which includes
371 questions measuring the severity of diarrhea and constipation, 48% of the respondents
372 reported decreases in diarrhea severity and 52% reported decreases in constipation
373 severity.
374 The study by Parracho et al[33] did not find a significant association between the
375 treatments and the number of bowel movements. No significant differences were
376 found between probiotic and placebo in terms of abdominal pain, intestinal bloating or
377 flatulence.
378
379 **5. <u>Alzheimer's Disease</u>**
380 Only one RCT evaluated the effects of probiotics on AD patients (n=52).[34] The
381 intervention lasted for 12 weeks and assessed cognitive function of patients in the
382 probiotic (n=26) and placebo (n=26) groups using the Mini-Mental State Examination.

Biomarkers of oxidative stress, inflammation and metabolic profiles were measured, namely, plasma total antioxidant capacity, total glutathione, malondialdehyde concentrations, serum high sensitivity C-reactive protein concentrations, plasma nitric oxide, concentrations of fasting plasma glucose, serum triglyceride, total cholesterol, LDL, HDL, and circulating levels of serum insulin. The homeostatic model of assessment for insulin resistance, homeostatic model assessment for B-cell function and the quantitative insulin sensitivity check index were calculated. The results were analyzed using an intention to treat approach. [34]

5.1 Probiotic supplementation on cognitive function

After the 12-week intervention in patients diagnosed with AD, there was a statistically significant improvement in Mini-Mental State Examination score in the probiotic group compared to control ($p < 0.001$). [34]

5.2 Probiotic supplementation on metabolic status

The authors found changes in high sensitivity C-reactive protein with a significant reduction in the probiotic group compared to control group ($p < 0.001$). The homeostatic model of assessment for insulin resistance ($p = 0.002$), homeostatic model assessment for B-cell function indexes ($p = 0.001$), triglyceride levels ($p = 0.003$) and VLDL concentrations ($p = 0.003$) were also significantly decreased in the probiotic group. Furthermore, the quantitative insulin sensitivity check index was significantly increased in the probiotic subjects in comparison to their control ($p = 0.006$). [34]
In contrast, there were no significant differences in the levels of plasma total antioxidant capacity and nitric oxide between the probiotic and placebo groups. [34]

DISCUSSION

To the authors´ knowledge, this is the first systematic review assessing the effect of pre- and probiotics on clinical aspects of psychiatric diseases which only included studies in patients who had or came to have a specific diagnosis. In this critical review, important clinical aspects were summarized regarding the possible impact of probiotics and prebiotics in psychiatric symptoms, the possible mechanisms involved and the positive influences they may have on the burden of disease.

Physical health depends highly on mental health and it is well-known that psychiatric diseases have a huge global burden.[35,36] Therapeutic alternatives could be beneficial especially in cases of refractory psychiatric diseases, severe adverse reactions to drugs or associated comorbidities.

Effects of probiotics and prebiotics in psychiatric disorders

Schizophrenia is a devastating disease, the pathophysiology and optimal therapies of which are still under investigation. Several risk factors for the development of schizophrenia may be linked to the intestinal tract, with a possible interaction between non-genetic factors, such as diet and exposure to infectious agents, and predisposing genes in its pathogenesis.[10] Schizophrenia is associated with alterations of the systemic immune system including low-grade chronic inflammation and T-cell activation.[37] Inflammatory marker levels appear to be correlated with the severity of the disease. [10] Many of the genetic loci related to this disease are known to modulate inflammation and the immune response. [37,38]

Regarding the symptoms of schizophrenia, the controlled trial included in this systematic review did not show beneficial results.[22-24] In spite of this, the authors

showed that probiotics may be beneficial in the significant portion of schizophrenia patients with GI problems.[22] Also, this experiment highlights possible influences of epithelium integrity, such as C. *albicans* exposure, and how these can be used as tools for diagnosis and treatment in the future.[23] The results suggest an association between C. *albicans* seropositivity and worsened positive symptoms. [23] The administration of probiotics may help normalize *C. albicans* antibody levels and associated gut discomfort in male patients, while also improving positive symptom scores. [23]

Manic and depressive episodes influence the polarity and diagnosis of bipolar disorder. Studying the microbiota composition and the effect of pre- and probiotics in these patients is complicated due to mood alterations during the disease course.[39]
The only clinical trial included in patients with acute mania showed that adjunctive administration of the probiotic reduced the risk of rehospitalization for psychiatric reasons following hospitalization for mania.[28] The probiotic was also associated with shorter hospital stays after rehospitalization. Although there was a significant improvement in symptoms during the trial, this improvement was not significantly different between the probiotic and placebo groups.
Furthermore, the effect of probiotic treatment was increased in individuals with elevated levels of systemic inflammation.[28]

MDD is a recurrent, incapacitating, and potentially life-threatening illness.[40] The use of probiotics in animal studies has consistently shown an impact on anxiety and depressive-like behaviors, however, less is known about the effects of probiotics on depression or anxiety symptoms in humans.[7,41,42] Alterations in microbiota seem to

454 influence behavior and immune challenges which also influence anxiety and
455 depressive behaviors, modulating serotoninergic and GABAergic signaling systems in
456 the central nervous system.[7]
457 All three studies on patients diagnosed with depression showed a significant benefit in
458 symptoms when probiotics were administered, which was not found with the
459 administration of prebiotics or placebo. [25-27] From the study including patients with
460 depression and irritable bowel syndrome, clear conclusions about patients diagnosed
461 with MDD alone cannot be made.[27]
462
463 Regarding ASD, out of the five studies included, only one tested the effect of a
464 prebiotic intervention, while the other four tested the probiotic effect on these
465 diseases.
466 Although diagnosis has increased rapidly over the last decade,[43] ASD are a wide group
467 of disorders caused by a complex interaction between genetic and environmental
468 factors which are still largely undefined.[8] Aside from behavioral problems and
469 cognitive impairments, GI symptoms are also common manifestations in these
470 patients.[44,45] In fact, it was estimated that children with ASD were four times as likely
471 to experience GI symptoms as children without ASD. [44,46] These GI symptoms suggest a
472 possible failure in normal symbiotic relationships between the host and its microbes
473 (dysbiosis),[43,47] but the causal mechanism of these symptoms is not well understood.[8]
474 Furthermore, individuals with ASD who have GI symptoms, compared to those without
475 GI symptoms, seem to have significantly higher measures of anxiety, irritability, and
476 social withdrawal.[8] Interestingly, restricted diets (such as gluten-free and/or casein-
477 free diets) have been associated with reduced GI disorders and improved behavior.[45]

Therefore, changes in diet appear to have an influence on the microbiota and the use of probiotics and prebiotics should be considered.[8,44] These substances may be important not only in groups with GI symptoms, but also in the ASD population due to shared immunologic and intestinal abnormalities (such as gut inflammation, imbalanced microbiota, as well as permeability and absorption disorders).[8,47]

One of the studies[29] included in this systematic review showed that combined intervention of a prebiotic with an exclusion diet could benefit these patients more than either approach alone.

The prospective follow-up trial[30] studied early administration of probiotics four weeks before expected delivery in pregnant women and in their infants until six months of age. The intervention reduced the risk of development of ADHD and AS by mechanisms not directly associated with GM composition, as no significant distinctive characteristics between the children with or without disease were identified.

Also, another study[31] revealed that after probiotic supplementation, the microbiota of ASD patients showed increases in colony counts of *Bifidobacteria* and *Lactobacilli* levels as well as a significant improvement in autism and GI symptoms when compared to baseline. This improvement in GI symptoms were strongly correlated with improvements in autism manifestations, which suggests a strong association between them. This questions whether the effect of probiotics on ASD symptoms is direct and independent of GI symptoms. On the contrary, a different study[33] did not find significant differences between probiotics and placebo feeding in ASD patients in any of the scores evaluated.

Finally, AD is the most common type of dementia, and presently there is no ideal drug available for its complete cure.[48,49] The interaction of environmental factors and genetic background are considered relevant in the pathogenesis of AD,[48] which makes supplementation with probiotics an interesting therapeutic intervention.

Only one RCT included in this systematic review studied AD, with probiotics showing a significant improvement in clinical aspects of the disease using Mini-Mental State Examination scores. [34]

There is a gap in this subject between animal studies, which appear to find an established involvement of GM in modulating pathophysiological aspects of dementia, and clinical trials, which lack a comprehensive profiling of GM composition and functionality. [49-51] These patients often have multiple age-related diseases, may be dependent on third parties and medicated with numerous drugs. All of these aspects can influence the patient's performance in the clinical trial as well as their microbiota and their capacity to give informed consent. [50] This therapeutic approach should be studied as it is possible that the human gut may play a role in the pathogenesis of neurological disorders characterized by amyloidogenic features (including AD) through modulation of intestinal lipopolysaccharides and amyloids.[52] Additionally, alterations of the GM and increased gut permeability might lead to an overall increase in systemic inflammation, neuroinflammation and dysfunction of specific brain regions correlated with AD pathogenesis such as the cerebellum and hippocampus.[52] Because of these reasons, future AD therapies may involve probiotics as a tool not only for treatment, but also as prophylaxis.

Controlled studies on the effects of pre- or probiotics in psychiatric diseases are still very limited and controversial. Further investigation is needed to justify their clinical use in patients with psychiatric disorders.

An advantage analyzed in many of the included studies is that most adverse effects reported with the use of probiotics were infrequent and mild.[22,28,31] These adverse effects rarely justified the withdrawal of the participants, and predominantly consisted of diarrhea, nausea, fever, weakness and abdominal pain.[26,27,29,31]

Underlying mechanisms and effects of pre- or probiotic use

In several studies, probiotics seem to influence several molecules including neurotransmitters and hormones, thereby assuming an important role in different pathways, particularly in inflammation.[22,25,26] Inflammation parameters seem to have a role in the clinical aspects of these diseases and pre- and probiotics seem to have beneficial impact.[8,10,37]

Probiotics appear to have a positive impact in metabolic aspects of schizophrenia, a disorder in which even antipsychotic-naïve individuals show an increased incidence of metabolic dysfunction.[10]

Furthermore, probiotic supplementation significantly reduced levels of von Willebrand factor, a protein considered positively correlated with cardiovascular risk in schizophrenia patients. Several studies have indeed showed that plasma levels of von Willebrand factor are elevated in schizophrenia-spectrum group compared to healthy controls[53,54] and that second-generation antipsychotics are incapable of reducing these levels.[24] Probiotics also affect the regulation of cytokine production in macrophages, T helper cells and intestinal epithelial cells.[24]

548 Additionally, the administration of probiotics showed a beneficial effect in insulin
549 function and oxidative stress, significantly decreasing the body mass index in ASD
550 patients. [25,27,31]
551 In patients with depression, supplementation with probiotics significantly decreased
552 the serum kynurenine/tryptophan ratio, compared with placebo and prebiotic
553 supplementation, showing influence on the serotonin pathway.[26] Tryptophan and
554 branch chain amino acids seem to have an important role in the gut-brain axis because
555 through the release of essential amino acids participating in immune and inflammatory
556 responses, the GM is capable of influence the brain. [3,4,38,52]
557 The investigation of these pathways and involved molecules could be useful to
558 discover prognostic biomarkers in these diseases.
559
560 **Quality of evidence and limitations**
561 There are several limitations that stand out among the studies included in this
562 systematic review. The majority of these studies, but not all, reported the safety,
563 tolerability and ethical approval of the experiments. In some studies, researchers
564 described that instructions about the best way of consuming the probiotics, avoiding
565 possible confounders (such as changes in therapy or exercise habits), were given, [25-
566 27,29,34] while others did not describe these precautions. Four studies did not detail the
567 diagnostic criteria used to select the patients.[26,29, 31, 32] And only two justified the
568 dosage of the intervention.[25,34] Although many studies used validated questionnaires,
569 a questionnaire cannot objectively show what the patient feels, even more so when
570 the answers are given by parents or caregivers. This shows the need to find objective

markers of improvement, maybe even using the microbiota and the microbiome as diagnostic and prognostic markers.

Another limitation of the studies included is the fact that many of them showed conflicts of interest which may bias the reported results.[27,29,32]

Sometimes, different antipsychotic treatments were used within each group of patients, which could affect their microbiota and their response to probiotics.[22] Also, the intervention should not be done at different times throughout the year between patients due to seasonal changes.[26] Aside from this, the duration of the trials could be considered insufficient and the sample sizes too small.[22,26,31]

Regarding the study by Dickerson et al, [28] it should be reflected that the rehospitalization outcome may not necessarily represent worsening symptoms, seeing as not all patients with aggravated symptoms may have been hospitalized, and may instead be treated as outpatients. The authors also used an inflammation score which is not described in the article.

An additional problem in many of the studies included is that when more than one strain of probiotic is used it is unsure if the effect was caused by one or all of them, or even if there was a synergic effect.[23-25,28,31] Furthermore, the unblinding, the lack of a placebo or control group, patients receiving behavioral therapy during the intervention or the caregivers refusing to administer probiotics could also be considered limitation.[31]

Particularly in the study by West et al., [32] the recruitment of participants (children and their parents) may be biased as they were selected from an organization defending that autism is only caused by environmental causes. Furthermore, the statistical data in this study was difficult to interpret because no p-values were presented.

Overall, the evidence of the studies included is variable due to the inclusion of clinical trials that are not RCTs in an attempt to reflect all the evidence currently available in the literature.

Regarding the limitations of the present systematic review, the number of articles included was not ideal, since this is a new area of research and the controlled studies on the effects of pre- or probiotics in psychiatric diseases is very limited. The inclusion and exclusion criteria applied could have been more restricted. Only studies with diagnoses based on validated classifications and with validated questionnaires applied should have been included.

Future research and studies

More studies with studying the same prebiotics and probiotics, including only one strain in each intervention, using a representative sample of patients with comparable characteristics would be informative. It is also important to consider the environmental factors that can influence the effect of pre- and probiotics including vitamin D, variations of diet, fluid intake and seasons of the year. In this way, it would be possible to select the most adequate pre- or probiotic for each individual (according to age, gender and specific characteristics of the disorder), administered in the safest manner with the most adequate dosage and duration of intake.

The studies should be undertaken in patients in the same stages of the disease and in patients undergoing the same antipsychotic treatment, so groups could be more comparable. More sensitive methods should be used to monitor molecular pathway markers. The inclusion of control groups in future trials is also important. It is also essential to rigorously define the study population and consider the subtypes of

symptoms in each disease. Furthermore, one must be aware that the clinical trials in certain patient populations may raise some ethical and methodological issues, especially in children and the elderly.

CONCLUSION

Whether changes in microbiota has an impact in psychiatric conditions is still unproven, but the targeting and modulation of microbiota seems to have a potential therapeutic role in these disorders. [4,10,37] Probiotics appear to benefit symptoms of MDD and AD, while also decreasing rehospitalization rates in patients with acute mania. The early administration of probiotics seems to reduce the risk of development of ADHD and AS.

Pre- and probiotics appear to be useful as an adjunctive therapy due to beneficial properties in other aspects of psychiatric diseases including the metabolic pathways involved. The tolerability and safety of these products also seem to be an advantage. In fact, conclusions for direct improvement in psychiatric symptoms with the use of prebiotics and probiotics cannot be made as current evidence is not sufficiently robust, but the findings are encouraging for further studies. Pre- or probiotics do not seem to lead to the cure of these diseases, but may help to proportionate a better quality of life for psychiatric patients. The potential benefits of this therapy relative to non-psychiatric symptoms is a reminder that these disorders are associated with a wide range of health problems.

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806 **TABLES AND LEGENDS**

807 **Table 1.** Quality assessment of included trials using Jadad scale.

	Described as randomized: yes (+1) no (0)	Method of randomization: appropriate (+1) inappropriate (-1) not described (0)	Described as double-blind yes (+1) no (0)	Method of double-blinding: appropriate (+1) inappropriate (-1) not described (0)	Description of withdrawals and dropouts: yes (+1) no (0)	Final Jadad score (maximum of 5)
Dickerson et al. (2014)	**+1**	**0**	**+1**	**0**	**0**	**2**
Severance et al. (2017)	**+1**	**0**	**+1**	**0**	**0**	**2**
Tomasik, et al. (2015)	**+1**	**0**	**+1**	**0**	**+1**	**3**
Akkasheh et al. (2016)	**+1**	**+1**	**+1**	**+1**	**+1**	**5**
Kazemi et al. (2018)	**+1**	**+1**	**+1**	**+1**	**+1**	**5**
Majeed et al. (2018)	**+1**	**+1**	**+1**	**0**	**+1**	**4**
Dickerson et al. (2018)	**+1**	**+1**	**+1**	**+1**	**+1**	**5**
Grimaldi et al. (2018)	**+1**	**+1**	**+1**	**0**	**+1**	**4**
Partty et al. (2015)	**+1**	**0**	**+1**	**0**	**+1**	**3**
Shaaban et al. (2017)	**0**	**0**	**0**	**0**	**0**	**0**
West et al. (2013)	**0**	**0**	**0**	**0**	**0**	**0**
Parracho et al. (2010)	**+1**	**+1**	**+1**	**+1**	**+1**	**5**
Akbari et al. (2016)	**+1**	**+1**	**+1**	**0**	**+1**	**4**

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814 **Table 2**. Characteristics of studies included in systematic review.

Study	Study design	Psychiatric condition	Sample size	Intervention period	Intervention (probiotic or prebiotic)	Assessed outcomes
Dickerson et al. (2014) [22]	RCT	Schizophrenia or schizoaffective disorder based on DSM-IV	N=58; probiotic (n=31); placebo (n=27	14 weeks	Probiotic: *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* Bb12	Psychiatric symptoms (evaluated with PANSS) and bowel function
Severance et al. (2017) [23]	RCT	Schizophrenia or schizoaffective disorder based on DSM-IV	N=58; probiotic (n=31); placebo (n=27)	14 weeks	Probiotic: *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* Bb12	Impact of probiotic treatment and yeast seropositivity measured through *Candida albicans* and *Saccharomyces cerevisiae* antibody levels on bowel discomfort and psychiatric symptoms.
Tomasik et al. (2015) [24]	RCT	Schizophrenia or schizoaffective disorder based on DSM-IV	N=58; probiotic (n=31); placebo (n=27)	14 weeks	Probiotic: *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* Bb12	Systemic immunomodulatory effects of probiotic supplementation
Akkasheh et al. (2016) [25]	RCT	MDD based on DSM-IV criteria	N=40; probiotic (n=20); placebo (n=20)	Eight weeks	Probiotic: *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum.*	Variations in BDI and metabolic parameters (fasting plasma glucose, markers of insulin metabolism, lipid concentrations, serum hs-CRP) and biomarkers of oxidative stress (total antioxidant capacity and total glutathione levels).
Kazemi et al. (2018) [26]	RCT	Major depressed patients	N=110 probiotic (n=38); placebo (n=36); prebiotic (n=36)	Eight weeks	Probiotic: *L. helveticus* R0052 and *B. longum* R0175 ; prebiotic: galactooligosaccharide	Variations in BDI, kynurenine/tryptophan ratio and tryptophan/branch chain amino acids ratio
Majeed at al. (2018)[27]	RCT	Patients who fulfilled the Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders and DSM for MDD.	N=40 probiotic (n=20); placebo (n=20).	90 days	Probiotic: *Bacillus coagulans* MTCC 5856	Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, Centre for Epidemiological Studies-Depression scale and irritable bowel syndrome quality of life questionnaire.
Dickerson et al. (2018) [28]	RCT	Bipolar I or schizoaffective disorder, bipolar type (manic or mixed state) (DSM-IV)	N=66 probiotic (n=33); placebo (n=33)	24 weeks	Probiotic: *Lactobacillus* GG and *Bifidobacterium lactis* strain Bb12 crystalline cellulose	Time to rehospitalization and changes in psychiatric symptom severity (Young Mania Rating Scale, Montgomery-Asberg Depression Rating Scale and Brief Psychiatric Rating Scale)
Grimaldi et al. (2018)[29]	RCT	ASD	N=26 prebiotic (n=13);	Six weeks	Prebiotic: Bimuno® galactooligosaccharide	Effect of prebiotic treatment (through ATEC, Autism Spectrum Quotient, Empathy

			placebo (n=13)			and Systemizing Quotient and Spence Children Anxiety Scale-Parent version) and bacterial composition of fecal and urine samples
Partty et al. (2015) [30]	RCT	ADHD and AS	N=75 probiotic (n=40) placebo (n=35)	Four weeks + Six months	Probiotic: *Lactobacillus rhamnosus* GG	Future diagnosis of ADHD and AS (based on ICD-10) and differences in GM composition
Shaaban et al. (2017)[31]	Pre-post trial	Autism based on DSM-V criteria	N=30	Three months	Probiotic: *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* and *Bifidobacteria longum*)	ASD signs and symptoms (ATEC) and GSI
West et al. (2013)[32]	Pre-post trial	Patients diagnosed with ASD who had GI distress	N= 33	21 days	Probiotic: *Lactocillus acidophilus*, *Lactobacillus casei*, *Lactobacillus delbruecki, Bifidobacteria longum, Bifidobacteria bifidum*	ASD signs and symptoms (ATEC) and stool frequency
Parracho et al. (2010)[33]	Crossover RCT	Children diagnosed with ASD	N=17	Three weeks	Probiotic: *Lactobacillus plantarum* WCFS1	GM composition (through FISH analysis), gut function (assessed with parents or caregivers' diaries), development Behaviour Checklist and total Behaviour Problem Score
Akbari et al. (2016)[34]	RCT	Alzheimer's disease patients (NINCDS-ADRDA criteria and the National Institute on Aging-Alzheimer's Association revised criteria)	N= 60; probiotic (n=30); placebo (n=30)	12 weeks	Probiotic: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum,* and *Lactobacillus fermentum.*	Cognitive Function (Mini-Mental State Examination) and metabolic status (plasma total antioxidant capacity, total glutathione, malondialdehyde concentrations, hs-CRP concentrations, plasma nitric oxide, concentrations of fasting plasma glucose, serum triglyceride, total cholesterol, LDL, HDL and levels of serum insulin)

815 ADHD, attention deficit hyperactivity disorder; AS, Asperger syndrome; ASD, Autism Spectrum
816 Disorders; ATEC, Autism Treatment Evaluation Checklist; BDI, Beck Depression Index; DSM, Diagnostic
817 and Statistical Manual of Mental Disorders; FISH, fluorescence *in situ* hybridization analysis; GM, Gut
818 microbiota; GSI, Gastrointestinal severity index; hs-CRP, high sensitivity C-reactive protein; ICD,
819 International Classification of Diseases; MDD, Major depressive disorder; NINCDS-ADRDA, National
820 Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related
821 Disorders Association; PANSS, Positive and Negative Syndrome Scale; RCT, Randomized controlled trial.

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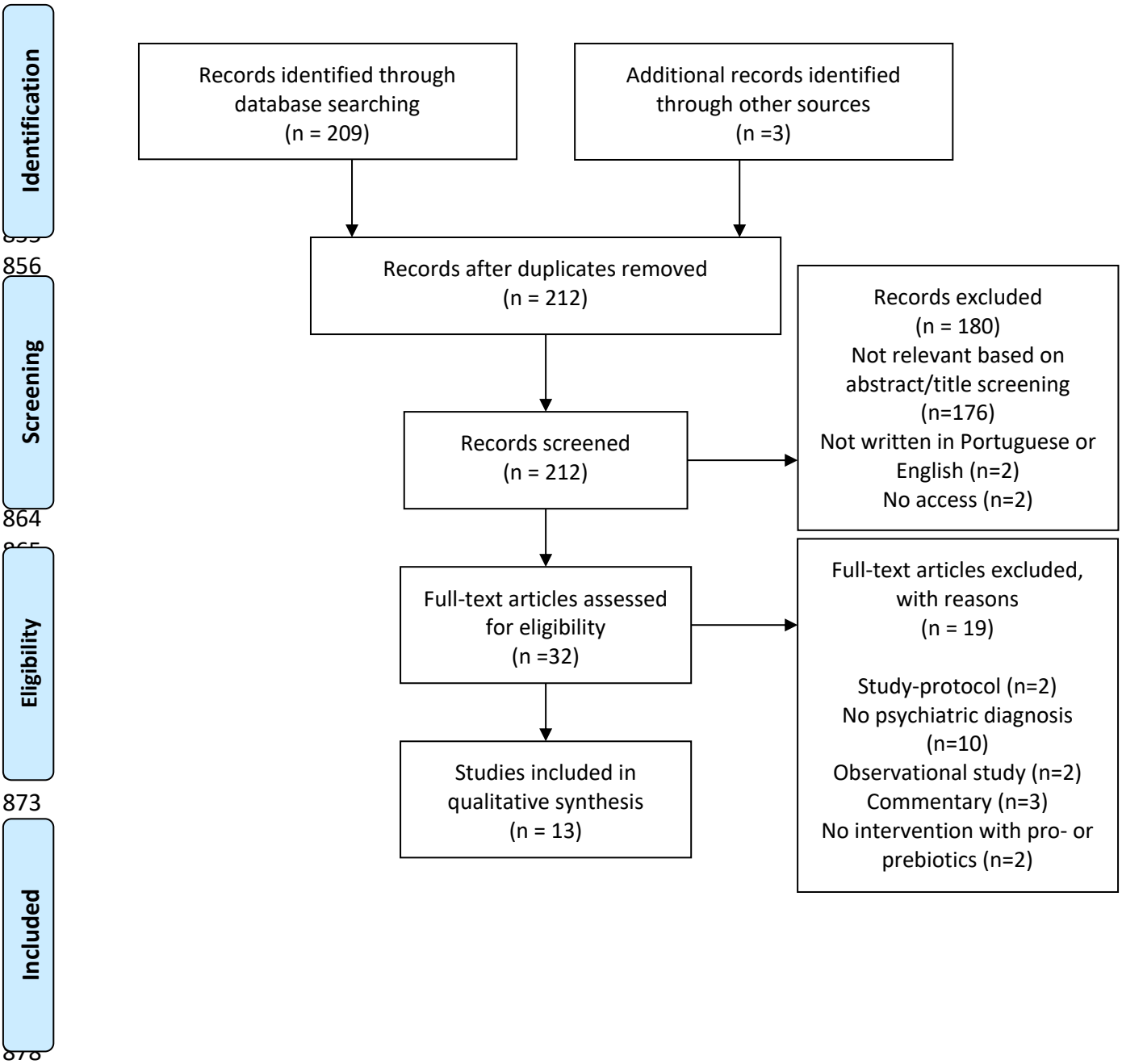
FIGURE LEGEND

Figure 1. Flowchart diagram of literature search process.

Figure 1.


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 209)
Additional records identified through other sources (n =3)
Records after duplicates removed (n = 212)
Records screened (n = 212)
Records excluded (n = 180)
Not relevant based on abstract/title screening (n=176)
Not written in Portuguese or English (n=2)
No access (n=2)
Full-text articles assessed for eligibility (n =32)
Full-text articles excluded, with reasons (n = 19)
Study-protocol (n=2)
No psychiatric diagnosis (n=10)
Observational study (n=2)
Commentary (n=3)
No intervention with pro- or prebiotics (n=2)
Studies included in qualitative synthesis (n = 13)

ANEXOS

Anexo 1. Normas da revista *Nutrition Reviews*

Instructions to authors

Article types

Nutrition Reviews publishes review articles in both the narrative and systematic review formats. Systematic reviews must address a clearly defined research question that is articulated in the abstract; they must also follow recognized approaches to the literature selection, analysis, and conclusions, as outlined in accepted guidelines, such as PRISMA or MOOSE. Scoping reviews that investigate the available literature on a topic in order to determine if more research is required, or if there is sufficient available literature for a full review, fall outside of the journal's scope and are not considered for publication. Submissions in the following article categories are welcome:

Lead Article: Comprehensive review of a broad topic;

- *Special Article:* Comprehensive review focused on a niche topic, a specific aspect of a broad topic, or new methods in nutrition science;
- *Nutrition in Clinical Care:* Presentation of clinically relevant brief reviews of evidence-based information and tools to facilitate translation into clinical practice;
- *Emerging Science:* Discussion of an important current study or group of studies in nutrition research presented in the context of the larger body of research on that topic;
- *Nutrition Science ↔ Policy:* Review of the interaction between scientific research and national and international health and nutrition policy;
- *Letter to the Editor:* Addition to the discourse regarding certain topics covered in recent issues of the journal.

Systematic reviews may be submitted for any category except Emerging Science and Letter to the Editor. Articles in the categories of Lead Article, Special Article, Nutrition in Clinical Care, Emerging Science, and Nutrition Science ↔ Policy are subject to peer review. Letters to the Editor are published at the discretion of the editors.

Terms of consideration

All manuscripts submitted to the journal must be original works of authorship that are not under simultaneous consideration elsewhere and do not infringe the intellectual property rights of any individual or organization. All previously published information, whether by the authors themselves or other individuals, groups, or entities, must be appropriately cited. The final version must have been read and approved by all of the individuals named as authors. The work must present novel information that differs substantially from that presented in works published by the authors previously. Authors should attest to these terms in their cover letter.

Authorship and originality

To qualify for authorship, individuals must meet all of the following criteria: 1) contributed significantly to the work's conception, design, data collection (as applicable), or data interpretation and analysis; 2) participated in the writing or critical revision of the article in a manner sufficient to establish ownership of the intellectual content; and 3) read and approved the version of the manuscript being submitted. All authors share responsibility for ensuring the manuscript complies with the journal's style requirements and terms of consideration. Any requests for changes to author

names, or order of appearance, that are received post submission will need to be approved in writing by all authors.

Funding and sponsorship

All sources of funding for the article's research, preparation, and publication should be noted in the article's Acknowledgments section under the subheading "Funding" and be acknowledged in the cover letter. The full name of the funding agency should be provided and grant numbers should be supplied. If grants or other funding were given to specific authors, the relevant individuals should be identified by their initials in parentheses. The role any sponsor played in the study design, data collection and analysis, manuscript preparation and revision, and publication decisions should be made clear in the Funding declaration in the Acknowledgments section. Authors should also indicate whether they received complete access to data pertaining to the publication that was owned by the sponsor.

Competing interests

All authors are required to disclose relevant competing interests by noting them in the Acknowledgments section of the manuscript under the subheading "Declaration of Interest." Guidelines regarding what constitutes a competing interest are included in the Declaration of Interest form. Completed Declaration of Interest forms for each author should be uploaded as Supporting Information at the time of manuscript submission.

Manuscript preparation

Cover letter. The cover letter should address the following topics: description of the work and its novelty; authorship; and originality. The description of the work should clearly indicate what novel contribution the submitted article makes to the existing literature. A statement should indicate that all listed authors meet the criteria for authorship (see *Authorship and Originality* entry above) and that no individual meeting these criteria has been omitted. Regarding originality, the following should be declared or, if untrue, explained: 1) the submitted article represents the original work of the authors; 2) the article is not currently under consideration elsewhere, nor has it been previously published in the same or substantially similar form; and 3) no copyright to any other work was breached in the manuscript's creation.

Manuscript format. Manuscripts should be prepared electronically using word-processing software, preferably Microsoft Word. Article pages should be formatted as double-spaced and left-justified text with 1-inch margins and 12-point type. Pages and lines must be numbered.

Length restrictions. Articles in any category must be formatted as indicated in the *Manuscript format* guidelines section and may not exceed 50 double-spaced pages in length, including references and illustrative material. Each article should provide a focused, concise, and objective investigation of a clearly defined topic.

Supporting information. The option to publish certain material as "Supporting Information" in an online-only format is provided. Authors are encouraged to make use of this option to accommodate material that may be of interest to the reader but is not integral to the work itself. Examples would include extensive summary tables and appendices. It is particularly important that the main text of an article include everything

essential for a complete understanding of the review and that the main text stand alone from the Supporting Information. Readers should not need to toggle between documents to obtain or understand information. If references are included in Supporting Information documents, they should be listed at the end of each document and appear in a numerical sequence pertaining solely to that document.

Cover page. The following information should be included on the cover page:

- *Article type.* Choose one of the article types in which the journal specializes. Editors may change this designation if they find the article is better suited to another category.
- *Title.* The title of the article should be short (200 characters or less), specific, and accurately describe the topic of the work. Abbreviations and acronyms should not be used unless they are widely recognized and generally understood, e.g. HIV, DNA. Articles and phrases such as "the use of," "the treatment of," and "a report of" should be avoided.
- *Author names.* Please list the first name, middle initial(s), and last name of each author in descending order of their contributions to the article. Individuals who provided technical or administrative support should be recognized in the Acknowledgments section.
- *Author affiliations.* The names of all authors affiliated with a particular institution should be listed directly above the affiliation. Each affiliation should include the department, institution, city, state (spelled out, if applicable), and country.
- *Corresponding author.* The name, complete mailing address, telephone and e-mail address should be provided for the author responsible for correspondence.
- *Abstract.* An abstract clearly outlining the topic and primary objective of the review, methods of data sourcing and extraction, data synthesis (as applicable), and conclusions

must be included with each article. The length should not exceed 170 words for Lead, Special, and Nutrition Science ↔ Policy papers or 125 words for Emerging Science and Nutrition in Clinical Care papers. Abstracts exceeding these word limits will be shortened during copyediting. References, tables, and figures should not be cited in the abstract.

- *Key words.* At least three to five key words or phrases should be provided.

Sections and headings

Narrative reviews. Each manuscript should contain the following sections in addition to the abstract:

Introduction (directly following the abstract)

Conclusion (at the end of the text)

Acknowledgements (after the Conclusion)

Funding and sponsorship (as part of the Acknowledgments)

Declaration of interest (as part of the Acknowledgments)

References (after the Acknowledgments).

Between the Introduction and Conclusion, headings and subheadings are at the discretion of the author. They should be used to organize the text and guide the reader.

Systematic reviews. Articles of this type should be prepared in accordance with relevant, existing guidelines (e.g., PRISMA, MOOSE) and be structured accordingly. If the guidelines used include a checklist, the completed checklist should be uploaded as Supporting Information during the manuscript submission process. Questions regarding the acceptability of chosen guidelines can be sent to the journal's editorial office via e-mail (nutritionreviews@ilsi.org).

Abbreviations and acronyms. Abbreviations and acronyms should not be used unless they are widely recognized and generally understood, e.g. BMI, FDA. These should only be used for terms used more than four times in the text. If that criterion is met, the term should be spelled out on first use followed by the abbreviation or acronym in parentheses. The abbreviated form should be used consistently thereafter, except in section headings, where it should continue to be spelled out.

References. The number of references cited should be tailored to the material being reviewed and be from reputable sources. As a general rule, articles in the Lead, Special, and Nutrition Science ↔ Policy categories do not typically include more than 200 references, while articles in the Emerging Science and Nutrition in Clinical Care categories do not typically have more than 120.

References should be numbered sequentially upon first appearance in text, tables, and figures. They should be typed as superscripts and placed after commas and periods but before colons and semicolons. When citing a series of consecutive numbers, provide the first and last with a dash between them (e.g., [5–7]). When referring to a group of authors in the text, the format "Smith et al.[23]" should be used.

References cited only in figure or table legends should be numbered according to the first mention of the graphic in the text and should be cited in the text at that point. Reference to unpublished work or personal communications should be avoided but, when essential, should be identified in the text as "unpublished data" or "personal communication from …", not in the reference list. To ensure long-term accessibility, internet citations should only be used if that is the sole source of the information.

The reference list should be formatted according to AMA style. For each citation, sufficient information must be provided to allow a reader to know in what medium the material appeared and to access the information. Please list all authors if there are six or fewer; for seven or more authors, list the first three followed by "et al." Examples of AMA style are as follows:

Journal article: Gordon KB, Papp KA, Hamilton TK, et al, for the Efalizumab Study Group. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA. 2003;290:3073–3080.

Chapter in a book: Dybul M, Connors M, Fauci AS. Immunology of HIV infection. In: Paul WE, ed. Fundamental Immunology. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:1285–1318.

Entire book: Gibson GR, Rastall RA. Prebiotics: Developments and Application. Hoboken, NJ: Wiley; 2006.

Government bulletin: Guidance on Labeling of Foods That Need Refrigeration by Consumers. College Park, MD: Office of Food Labeling, US Food and Drug Administration; 1997. Docket No. 96D-0513.

Internet citation: American College of Surgeons. National Trauma Data Bank Report 2006, Version 6.0. Chicago, USA. Available at: http://www.facs.org/trauma/ntdb/ntdbannualreport2006.pdf. Accessed on October 22, 2007.

Tables and illustrations. Tables and illustrations should be numbered in the sequence in which they appear in the text. They should appear in sequence after the reference list.

Tables. All tables should be included in the text file after the reference list. Each table should be constructed using the table functions of the word-processing program being used. A title should appear at the top of each table. A column heading should appear in the top cell of each column. Within the table, each data set should appear in a single cell; the return key should not be used within any cell. Text should be justified to the left. Numerical data should be justified to the decimal point. Capitalization should be restricted to the first letter of the legend, the first letter in each cell, and applicable abbreviations or acronyms. Abbreviations used in the table should be spelled out in a footnote. When citing prior studies in tables please use the following format: Smith et al. (1998)[21].

Illustrations. All artwork should be submitted in digital format in separate files saved using the following convention: surname of first author_figure number (e.g., Smith_figure 1). Figure legends should be cited in the manuscript after the reference list but should not appear in the figures themselves. Charts and graphs downloaded from the Internet are not acceptable. Line artwork (vector graphics) should be saved in Encapsulated PostScript (EPS) format and bitmap files (halftones or photographic images) in Tagged Image Format (TIFF), with a resolution of at least 300 dpi at final size. Do not send native file formats. More detailed guidance for submitting electronic artwork can be found at the Author Resource Centre. A free tool for converting files to other formats can be located at the Zamar website.

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