INPLASY PROTOCOL

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Review Stage at time of this submission: Data analysis.

Conflicts of interest:
None.

Efficacy of probiotics on multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: This study is to systematically evaluate the efficacy of probiotics supplementation on mental health, biomarkers of inflammation, oxidative stress and insulin resistance in patients with multiple sclerosis.

Condition being studied: Multiple sclerosis is an autoimmune and inflammatory demyelinating disease characterized by spinal cord syndrome, brainstem or cerebellar syndrome cognitive impairment and optic neuritis (Sand, 2015). Existing studies have found that gut microbiota plays an important role in autoimmunity, and gut microbial dysbiosis is known to be correlated with pathogenesis of multiple sclerosis (Kadowaki, et al., 2020). Probiotics, as live microorganisms, are able to interact with the gut microbiota and provide beneficial effect and probiotic supplementation have shown some beneficial effects on multiple sclerosis in animal and clinical study (Kouchaki et al., 2018), which could be potentially considered to become a new therapeutic treatment for autoimmune diseases. However, the systematic meta-analysis regarding the effectiveness of probiotics on parameters of mental health, inflammatory factors, markers of insulin resistance and oxidative stress remains uncertain. It is a worthy question to examine the efficacy of the probiotics in the treatment of multiple sclerosis.

INTRODUCTION

Review question / Objective: This study is to systematically evaluate the efficacy of probiotics supplementation on mental health, biomarkers of inflammation, oxidative stress and insulin resistance in patients with multiple sclerosis.

Rationale: Emerging findings are revealing that some species of bacteria in gut may worsen or improve patients with multiple sclerosis (Cekanaviciute et al.2017; Cosorich et al. 2017), and growing studies have been published on the beneficial effects of probiotics on multiple sclerosis. However, the evidence regarding the appropriate strains, doses, and intervention time in humans with multiple sclerosis as well as the effectiveness of probiotics remains uncertain.

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METHODS

Search strategy: The study only selects clinical randomized controlled trials of probiotics supplementation for multiple sclerosis. We will search each database from the built-in until August 2020. The mainly searches MEDLINE/PubMed, Web of science, Cochrane Central Register of Controlled Trials, and Embase. We also included a search of the following databases: ClinicalTrials.gov (https://clinicaltrials.gov/). Grey literature was searched using the OpenGrey database (http://www.opengrey.eu/). Additionally, reference lists of the included studies were handsearched to identify relevant trials. We will use MeSH Term: multiple sclerosis; Sclerosis, Multiple; Sclerosis, Disseminated; Disseminated Sclerosis; MS (Multiple Sclerosis); Multiple Sclerosis, Acute Fulminating; Probiotics; cultured milk products; Yogurt; yeast dried; Yeasts; Bifidobacterium; Lactobacillus; Synbiotics; probiotic; fermented product; fermented dairy product; randomized controlled trial; randomized; placebo.

Participant or population: The inclusion criteria were people with ages between 18 and 60, course of disease relapsing-remitting MS (RRMS), identified according to McDonald criteria and an expanded disability status scale (EDSS) score≤4.5.

Intervention: In the intervention group, persons received a probiotic capsule daily.

Comparator: The patients in the placebo group received capsules containing maltodextrine or starch, the carrier of the probiotic bacteria. The probiotic and placebo capsules were resembled in color, shape, size, packaging, smell and taste.

Study designs to be included: Clinical randomized controlled trials

Eligibility criteria: Eligibility criteria for searches and meta-analysis were specified using the PICO criteria included：（1）Study design：Randomized controlled trials；（2）Population：people with ages between 18 and 60, course of disease relapsing-remitting MS (RRMS), identified according to McDonald criteria and an expanded disability status scale (EDSS) score≤4.5; (3) Intervention: Probiotic or synbiotic, orally or enterally administered, with no restriction on strains, doses, and frequency and duration of administration, provided information was reported; (4) Comparison: Control group or placebo group; (5) Primary outcomes: changes in parameters of mental health (EDSS,

Expanded disability status scale; BDI, Beck depression inventory; DASS, Depression anxiety and stress scale; GHQ, General health questionnaire). Secondary outcomes: changes in intestinal microbiota composition; inflammatory, metabolic, and oxidative stress markers certified by biochemical tests.

Information sources: The study only selects clinical randomized controlled trials of probiotic supplementation for multiple sclerosis. Four electronic databases were searched from inception to Augusty 2020: MEDLINE/PubMed, Web of science, Cochrane Central Register of Controlled Trials, and Embase. We also included a search of the following databases: ClinicalTrials.gov (https://clinicaltrials.gov/). Grey literature was searched using the OpenGrey database (http://www.opengrey.eu/). Additionally, reference lists of the included studies were handsearched to identify relevant trials.

Main outcome(s): The primary outcomes include parameters of mental health (EDSS, Expanded disability status scale; BDI, Beck depression inventory; DASS, Depression anxiety and stress scale; GHQ, General health questionnaire), inflammatory factors (IL-6, hs-CRP), markers of insulin resistance (Insulin, HOMA-IR, QUICKI) and oxidative stress (TAC, GSH, MDA).

Data management: We will import all retrieved studies into EndNote and then remove any duplicates. Two researchers (Wang and Zhang) will first scan the title and abstract then the full articles will be read when the abstracts lack of the information. The articles will be screened according to the pre-established inclusion and exclusion criteria. Any disagreement will be resolved through discussion, or underwent third party adjudication. The statistical analysis of this meta-analysis was conducted by RevMan software version.

Quality assessment / Risk of bias analysis: The revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was applied to evaluate the individual studies, considering its five dimensions: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Wang and Zhang completed the risk-of-bias evaluation in an independent fashion. After completion of the first coding, the tables were compared and all disagreements were discussed with all the authors of the manuscript and reanalyzed until consensus was achieved.

Strategy of data synthesis: The random-effects meta-analysis with the inverse-variance method was used to compare the effects of intervention vs placebo on the outcomes of interest. Standardized mean difference was applied for parameters of mental health and mean difference was applied for other outcomes. Changes within groups from baseline were used to assess the intervention effect. Where modifications were not reported, mean changes were calculated as the postintervention mean minus the pre-intervention mean. A P value of <0.05 was considered significant. Heterogeneity among the included studies was determined using the chi-square test (P < 0.1) and an I2test, where an I2value >50% indicated moderate to high heterogeneity.

Subgroup analysis: None.

Sensibility analysis: In the direct comparison, if there is a large heterogeneity and the number of studies included is enough, we will use the method of meta regression for sensitivity analysis, otherwise we will exclude the studies one by one for sensitivity analysis.

Language: English only.

Country(ies) involved: China.

Keywords: multiple sclerosis, meta-analysis, probiotics, randomized controlled trial.

Dissemination plans: This systematic review and meta-analysis will be published in a peer-reviewed journal.

Contributions of each author:

Author 1 - Chuanqi Chu - Writing the introduction, discussion and conclusions. Revised and approved the final draft.

Author 2 - Leilei Yu - Methodology and results. Revised and approved the final draft.

Author 3 - Chen Wang - The author provided statistical expertise and made the quantitative analysis. Revised and approved the final draft.

Author 4 - Chengcheng Zhang - The author provided statistical expertise and made the quantitative analysis. Revised and approved the final draft.

Author 5 - Fengwei Tian - The author will read, provide feedback and approve the final manuscript.