

INPLASY PROTOCOL

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None declared.

Effects of different stages of Alzheimer's disease on intestinal flora — a systematic evaluation and network meta analysis scheme

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Review question / Objective: The relationship between intestinal flora and the early, middle and late stages of AD was studied retrospectively to explain the change law of intestinal flora in each stage of AD. The relationship between intestinal flora and various stages of AD was studied retrospectively. Explain the changes of intestinal flora in each stage of AD. The purpose of this study is to use a high-quality system to evaluate the changes of intestinal flora in the three stages of AD (preclinical stage, mild cognitive impairment stage and dementia stage), and to analyze the composition of intestinal flora, the abundance of opportunistic pathogenic bacteria and the abundance of beneficial symbiotic bacteria by NMA method. According to the advantages and disadvantages of exponential effect, the indexes of intestinal bacteria in different stages of AD were sorted, and the best evidence of the relationship between AD and intestinal flora in different stages was selected. This protocol is helpful to understand the impact between the early, middle and late stage of AD and intestinal flora. The understanding of the relationship between AD and intestinal flora may provide information and new treatment options for the phased treatment of AD. Our review will better review the relationship between intestinal microflora and different stages of AD, explain the different effects of different stages of ad on intestinal microflora, the change law of intestinal microflora in different stages of AD, and provide new insights and possible phased treatment schemes for the treatment of intestinal microflora in patients with AD and then change the process of ad to a certain extent.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 October 2021 and was last updated on 25 October 2021 (registration number INPLASY2021100093).

INTRODUCTION

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Condition being studied: Alzheimer's disease (AD) is a complex senile central nervous system degenerative disease, which is the most common type of dementia. The main clinical manifestation is the gradual aggravation of cognitive impairment, from memory loss, recent forgetting to severe memory loss. Ad can be divided into three stages according to nin-aa diagnostic criteria (2011). The typical histopathological feature of ad is the accumulation of abnormal protein aggregates, including amyloid plaques- Amyloid (a) Brain magnetic resonance imaging (MRI) of AD patients also showed atrophy of temporal lobe system, reduction

of hippocampal volume, enlargement of sulcus and stenosis of gyrus. Intestinal flora is one of the most important immune defense lines of the human body. The dynamic balance of intestinal microorganisms plays a very important physiological and pathological role in the human body. The microbiota will produce a variety of nerve and immune regulatory substances, which can locally act on intestinal secretory cells and regulate the function of the central nervous system. The pressure signal from the brain passes through the efferent nerve The conduction of (vagus nerve) and HPA axis changes the composition of microbiota and gastrointestinal function. Emerging studies have shown that metabolites produced by intestinal microbiota can regulate the differentiation, maturation and activation of microglia and astrocytes, which mediate a variety of neurophysiological processes, including neurodevelopment, neurotransmission and CNS immune activation. Intestinal endocrine cells (EEC) The secreted mediators in contact with vagal neurons can transmit information directly to the brain, allowing the brain to respond to various mechanical, chemical and hormonal stimuli from the intestinal microbiota. The imbalance of intestinal microbiota can cause the increase of harmful substances (such as amyloid and TMAO), causing the increase of intestinal mucosal barrier and BBB (blood-brain barrier) Become transparent, activate peripheral immune response, cause amyloid plaque formation, and promote the pathological progress of AD. Probiotics are considered as a potential method for the treatment of AD. FA produced by probiotics has antioxidant and anti-inflammatory effects, which can inhibit amyloid protein in a dose-dependent manner. Some probiotic strains (*Lactobacillus plantarum* wcf1, *Escherichia coli* nissle and *Bifidobacterium infantis*) have been proved to enhance the intestinal barrier function by up regulating the tight junction of intestinal epithelial cells - Amyloid (a) Peptides, endotoxin and other substances are not easy to activate peripheral immune response and delay the emergence of ad pathological features such as amyloid plaque and neuritis.

Therefore, taking intestinal flora as the object, studying the pathogenesis of AD may solve the shortcomings of many candidate ad drugs explored so far, and may become the main method for the treatment of ad in the future.

METHODS

Search strategy: Comprehensive search includes databases in Chinese and other languages, such as PubMed, ScienceNet, EBSCO, Ovid, Cochrane Library, CNKI, CBM, EMBASE, Wanfang And Chinese sci-tech journal database and Chinese biomedical database. A pre-designed search strategy was used to search for clinical studies of Alzheimer's disease and intestinal flora. The search results were independently analyzed by two researchers, extracted according to the preset table, and evaluated according to the quality evaluation tool recommended in the Cochrane system evaluator manual.

Participant or population: Inclusion: Patients with Alzheimer's disease
Exclusion: Persons with serious physical diseases, drug abuse history, blood diseases, pregnancy and lactation will be excluded.

Intervention: At present, the first-line drugs for the treatment of ad include acetylcholinesterase inhibitors: donepezil, galantamine, kabalatin and rivastatin, and NMDA receptor antagonist: memantine. According to the typical clinical symptoms of AD and the diagnostic criteria, AD patients were divided into three groups: preclinical stage, mild cognitive impairment and dementia stage. The number of intestinal flora of the four groups was measured before drug treatment, and the mean value of each group was taken to compare with the number of intestinal flora of the normal population. After administration and treatment, measure the number of intestinal flora in each group, take the mean value, and compare it with the mean value of flora before treatment and normal flora, that is, longitudinal comparison. The comparison objects will be normal people without Alzheimer's

disease and patients with AD before and after treatment.

Comparator: Probiotics are considered to be a potential method for the treatment of AD. FA produced by probiotics has antioxidant and anti-inflammatory effects, which can inhibit amyloid protein in a dose-dependent manner. Some probiotic strains (*Lactobacillus plantarum wdfs1*, *Escherichia coli nissle* and *Bifidobacterium infantis*) have been proved to enhance the intestinal barrier function by up regulating the tight junction of intestinal epithelial cells - Amyloid (a) Peptides, endotoxin and other substances are not easy to activate peripheral immune response and delay the emergence of pathological features of ad such as amyloid plaque and neuritis. So far, there is no systematic review and meta-analysis on the relationship between AD and intestinal flora at different stages. In order to better study the relationship between intestinal microbiota and preclinical, mild cognitive impairment and dementia, and obtain the target of prevention or treatment. Our goal is to further reveal the close relationship between microbiota brain gut axis and the change law of intestinal flora in the three development stages of AD, so as to improve the treatment and phased prevention and treatment of AD.

Study designs to be included: Studies on the correlation between Alzheimer's disease and intestinal flora will be included in the systematic review. The included literature has no restrictions on language type, use of blind method or allocation concealment requirements. As long as the included research is approved by local institutions, we will include the research into the scope of the research. We will include clinical studies, case-control studies and cross-sectional studies. However, comments, brief investigations, case reports and letters will be excluded. The inclusion criteria were determined according to diagnostic.

Eligibility criteria: The design of inclusion and exclusion criteria in this study makes five main principles based on the

participant intervention comparator study (Picos) design search principle. Studies on the correlation between Alzheimer's disease and intestinal flora will be included in the systematic review. The included literature has no restrictions on language type, use of blind method or allocation concealment requirements. As long as the included research is approved by local institutions, we will include the research into the scope of the research. We will include clinical studies, case-control studies and cross-sectional studies. However, comments, brief investigations, case reports and letters will be excluded. The inclusion criteria were determined according to diagnostic criteria, intervention and results. These patients suffered from Alzheimer's disease regardless of race, age and gender. The diagnostic criteria of Alzheimer's disease should comply with NINCDS-ADRDA diagnostic criteria for Alzheimer's disease (1984), nincds-adrda-r research criteria for the diagnosis of Alzheimer's disease (2007), nia-aa diagnostic criteria (2011), the fifth edition of diagnostic and Statistical Manual of mental diseases (dsm-5) and iwg-2 criteria. Persons with serious physical diseases, history of drug abuse, blood diseases, pregnancy and lactation will be excluded.

Information sources: The retrieval strategy is operated by Cxs and WHR, and the differences are solved through discussion with the third reviewer (GMZ). We will search in PubMed, ScienceNet, EBSCO, Ovid, Cochrane Library, CNKI, China biomedical literature database (CBM), excerpted medical database (EMBASE), Wanfang, China Science and technology journal database and China biomedical database. The retrieval time is from the establishment of the database to January 10, 2022. The following search terms will be used, such as "Alzheimer's disease", "preclinical AD", "MCI" (mild cognitive impairment), "dementia" and "intestinal microbiota". In addition, we will track relevant references in the literature. When a complete report cannot be obtained or the data is incomplete, we will contact the corresponding author and try our best to

ensure the comprehensiveness of the preliminary search and prevent the loss of valuable research data.

Main outcome(s): Explain the changes of intestinal flora in each stage of Alzheimer's disease, so as to improve the treatment and phased prevention of AD. To retrospectively study the relationship between intestinal flora and various stages of Alzheimer's disease, and further explain the close relationship between brain intestinal axis.

Quality assessment / Risk of bias analysis: The quality and bias risk assessment included the quality of research methodology, which was independently assessed by two researchers (Cxs and WHR) using Cochran's rob tool. If the results are different, third-party researchers are invited to help discuss and analyze the bias. According to the quality evaluation standard of Cochrane System Review Manual, the research quality evaluation uses Revman quality tool to evaluate the integrity of the method including registered articles, including whether the random method is correct, whether it is allocated for concealment, whether it is used for analysis, and whether the result data is complete. According to the appropriate standard in Cochrane intervention system evaluation manual, the research is divided into low risk High risk and unknown risk. The cross-sectional study will be evaluated by the evaluation method of Joanna Briggs Institute. Finally, we will use Revman and Stata to collect data for analysis.

Strategy of data synthesis: First, the researchers used Revman software to analyze the direct comparison results of the literature. Secondly, for the indirect comparison results, the researchers used Addis software for data consolidation and statistical analysis, and drew the network relationship diagram and sequence diagram of various intervention measures. The netmeta program is started by R programming language, and the MCMC algorithm is used to realize the mapping of network data analysis and random effect data results.

Subgroup analysis: If substantial heterogeneity is detected, subgroup analysis will be performed to find potential causes. The data of patients of different ages, genders and course of disease can be compared. If the meta-analysis is positive and more than 3 studies are included, the R software is used for sensitive analysis of the statistical results. For each excluded study, meta-analysis was conducted again to compare the results with those before exclusion. If there was no significant change in the comparative analysis, the results were stable, otherwise the results were unstable.

Sensitivity analysis: If substantial heterogeneity is detected, subgroup analysis will be performed to find potential causes. The data of patients of different ages, genders and course of disease can be compared. If the meta-analysis is positive and more than 3 studies are included, the R software is used for sensitive analysis of the statistical results. For each excluded study, meta-analysis was conducted again to compare the results with those before exclusion. If there was no significant change in the comparative analysis, the results were stable, otherwise the results were unstable.

Country(ies) involved: China.

Keywords: senile dementia; AD Intestinal flora; probiotics; META.

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