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Meta-analysis of the gut-brain axis and mental disorder

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Abstract. The gut-brain axis refers to the bidirectional information communication network between the brain and the gut. Microbiome and gut-brain axis have been implicated in mental disorders and have become the focus of neuroscience research. A meta-analysis was conducted to summarize the evidence regarding this link. A filtering search was performed using Hollis, PubMed, and Google Scholar to identify considered studies and trials. A keyword search identified 5500 articles. Seven provided analytically valuable and eligible data and were finally included for consideration and analysis. The data offered relevant studies on depression or anxiety, Schizophrenia, and Alzheimer's disease. Of the seven papers, four used correlational analysis (n=952) on depression and anxiety, two (n=384) on Schizophrenia, and one (n=80) on Alzheimer's disease. These correlation analyses were designed to investigate the differences in gut microbial abundance between normal individuals and patients with mental disorders. In addition, three studies (n=314) identified a causal link by comparing the changes in mental health status by altering or influencing the gut microbiota. These causal analyses aimed to explore the differences in gut microbial abundance before and after the onset of mental disorders. In this case, mental illnesses were 2.8 to 14 times higher in the experimental groups than in the control groups. The findings support the hypothesis that the health of the gut-brain axis (microbial abundance) is inversely correlated to the incidence of many psychological disorders. However, how the gut-brain axis facilitates the pathogenesis of mental disorders remains to be further studied.

Keywords: The gut-brain axis, mental disorder, microbiota, meta-analysis.

1. Introduction

The gut-brain axis refers to the bidirectional information communication network between the brain and the gut. Microbiome and gut-brain axis have been implicated in mental disorders and have become the focus of neuroscience research. Due to this situation, people face more mental pressure because of the uncertainty and the severe competitive environment [1]. Common mental disorders still remain threatening around the world, profoundly affecting people from different countries and social hierarchies [2]. Hence, Psychologists have investigated indicators and methods to support diagnostic principles of diseases and treatments [3,4]. The gut-brain axis is vital for humans to keep homeostasis, and the microbiota appears as an essential regulator of the gut-brain function [5]. Transformation in the gut-

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brain axis and microbiota mutual effects have been recognized in several rodent models of digestive, mental diseases, and neurological disorders [6,7,8].

Nonetheless, due to the limited sample size and intricate research methods, the relationship between the gut-brain axis and mental disorders still needs to be clarified. For example, in the two articles on depression and anxiety [9,10], two sets of data on anxiety contradicted the results shown by the other data. Thus, this review will focus on a set of studies that are related to the axis and various mental disorders to provide an estimation of their relationships.

2. Methods

We followed the guidelines for conducting and reporting meta-analyses of epidemiological observational studies [11] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [11,12].

2.1. Study Inclusion and Exclusion Criteria

The review was limited to the range of ages between 16 to 65 years of age within the majority of respondents (>50%). The decision to include only experiments conducted in the general adult population represents a shared recognition of the particularities of the child-adolescent and older adults and the need for a separate, targeted review of common mental disorders in these age groups.

Studies were published from 2007 to 2023 that applied research that intended to discover the relationship between various microbiota in the gut-brain axis and different mental disorders and reviews that further discuss their relationships. We mainly kept the review that at least included more than 30 sample sizes. This ensures that studies have sufficient possibility for statistics, which provide steady estimates of the general public. We implemented an empirical approach to conducting an optimized detection method for finding studies that include research about the functions of the gut-brain axis of common mental disorders. This set of papers was used to contribute to evidence-based medicine about mental disorders. In order to optimize the sensitivity and specificity for recognizing relevant articles from three different databases: HOLLIS, PubMed, and Google Scholar. In HOLLIS, we searched keywords “Gut-Brain Axis” and “Mental Disorder” or “Mental Illness” or “Psychosis”. The total results we had were 2911 articles. In PubMed, we searched “Gut-Brain Axis,” “mental disorder,” “mental illness,” and “psychosis”. The total results were 1129. In Google Scholar, we searched “gut-brain axis” and “mental disorder, " and the total results were 1460. All study abstracts acquired in the searches were screened by all the authors in an incipient process to remove the in-conformity articles for inclusion. Before screening all studies, the authors used 400 papers to confirm inclusion criteria, achieving 97% agreement.

2.2. Search Strategy

Figure 1 shows the total quantity of studies acquired from the separate databases using the search strategy. In all, 2681 non-repetitive articles were obtained by using strategy. After a screening of abstracts, 534 full-text articles remained to conduct a more detailed investigation. We deleted articles that were only related to one keyword.

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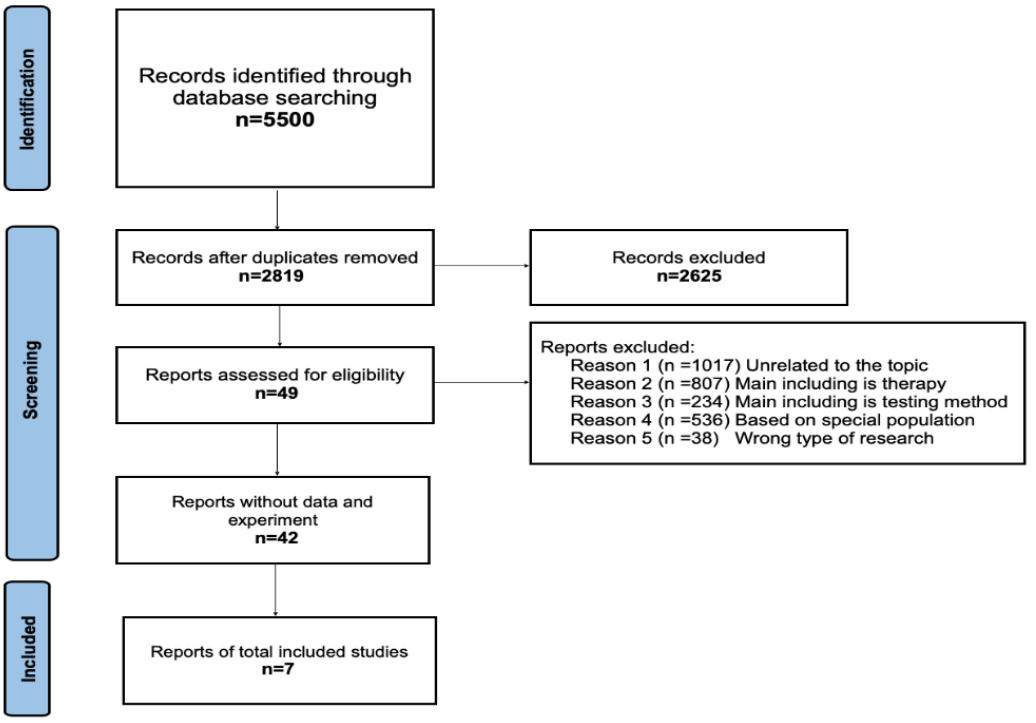

Figure 1. Flowchart of systematic review procedure for identifying studies about the gut-brain axis and mental disorder.

Additionally, articles were deleted if they focused on therapies and testing methods, some including probiotics or drugs, to determine the effect of some treatments. Also, some articles only include ways to test the microbiota in the axis instead of finding the relationship between it and mental disorders. Some are also based on a particular population in unique regions, one gender, or after having particular medicines, which lack the reliability of general relationships. Moreover, after reading the full article, we deleted studies that include cross-sectional studies instead of experiments and lacking data. Thus, the Full-text review ascertained seven articles to include, which reported data related to the studies about gut-brain axis and mental disorders.

We further explored the sensitivity of keywords to finding currently included articles. Of the seven articles, five were identified in HOLLIS, 1 in PubMed, and 1 in Google Scholar.

Table 1. Reference graph of seven articles used in meta-analysis.

Study	Study Design	Setting, Sample	Study Purpose
Duan, Y., et al, 2022.	Experiment	N=61, treatment=31, control=30	To testify the mental state of two groups so that the relationship between mental disorder and the gut-brain axis can be confirmed.
Pei, Y., et al, 2023	Experiment	N=80, treatment=45, control=35	To testify whether cognitive impairments are associated with gut microbial and intestinal barrier dysfunction.
Li, S., et al, 2020	Experiment	N=162, treatment=82, control=80	To provide evidences about the changing of the gut microbiota of schizophrenia patients.
Cardona, D., et al, 2021	Experiment	N=31, treatment=16, control=15	To testify the changing of the gut microbiota is related to mental disorder.

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Table 1. (continued).

Study	Study Design	Setting, Sample	Study Purpose
Park, E., et al, 2021	Experiment	N=784, treatment=295, control=295	To test the relationship of gastrointestinal and behavioral manifestations of intestinal flora disorders and neurosis.
Carpinelli, L., et al, 2023	Experiment	N=76, treatment=38, control=38	To identify the relationship between gastrointestinal symptoms and mental disorders.
Zhang, J. P., et al, 2012	Experiment	N=222, treatment=96, control=126	To provide evidences between the obesity and mental disorder.

3. Results

Figure 1 presents the results of the systematic review. In total, seven studies met the inclusion criteria, and data from seven controlled trials (2012-2023) were considered. Most of these experiments (86%) were from 2020-2023, and very few (14%) were taken from 2012, which shows the data's reliability and provides vital evidence for the research. Data from these experiments provided information on the gut microbiome and the risk of developing mental disorders for 1416 participants. There were four trials (n=952) with nine results for depression and anxiety symptoms, three results from two experiments (n=384) on Schizophrenia, and an investigation on Alzheimer's disease (n=80) with two results. Within these seven studies, three of them (n=314) were used to compare the changes in mental health status by altering or influencing the gut microbiota of the participants. Four other studies (n=1102) explored the association between the gut-brain axis and mental disorders by comparing the gut microbiota of healthy subjects and patients with mental disorders. To sum up, twelve results from seven trials (86%) supported our view ($p<0.05$), with effect sizes ranging from 0.11 to 4.62 across all the studies (To ensure the same standards for comparisons, negative effect sizes in some experiments were taken as absolute values after confirmation).

As to how the variables were defined, we made the following statement in this meta-analysis: The incidence of mental disorders was measured by whether participants experienced significant deterioration in mental status and deepening of mental illness symptoms. The health of the gut-brain axis was evaluated through the abundance of common gut microbes (e.g., bifidobacterium, bacillus) in the subjects and whether there was an abnormal increase or decrease compared to the average population. Psychiatric disorders are assessed by symptoms (such as vision, auditory hallucinations, and cognitive impairment) and test results (SCL-90, MMPI, and MHT scales).

3.1. Depression and Anxiety

Table 2 shows several groups of studies between the gut microbiota and depression and anxiety and presented in the figure of forest plots (Figure 2). These findings provide an understanding of (1) the role of gut microbiota alterations in developing depression and anxiety and (2) The difference in abundance of various gut microbes between patients who have depression or anxiety and healthy subjects. It is worth mentioning that to exclude the influence of living environment and diet on gut microbiota, one of the studies did not consider historical prisoners and only selected the data of prisoners imprisoned for less than one month. Among them, even though most prisoners were not diagnosed with a mental disorder, their rates of depression and anxiety were 14 times higher than those in the control group because of changes in their gut microbiome. Three other studies showed that the use of probiotics (altering the gut microbiome) improved cognition and morbidity in patients with depression and anxiety. The scores of depression and anxiety tests of the subjects with high and low groups of microorganisms in the gastrointestinal tract were compared. The incidence of depression and anxiety is significantly increased in patients with microbial dysbiosis caused by eating disorders.

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Table 2. Meta-analysis about the effect size between gut microbiota and Depression and Anxiety.

Study name	Research topic	Effect size	Sample size (Treatment)	Sample size (Control)	Standard error	Weight
Duan, Y., et al, 2022.	Anxiety	0.48	30	31	0.26	0.06
	Depression	1.24	30	31	0.28	
Cardona, D., et al, 2021	Anxiety	-0.70	16	15	0.37	
	Anxiety	-0.87	16	15	0.38	0.03
	Depression	0.45	16	15	0.36	
	Depression	0.23	16	15	0.36	
Park, E., et al, 2021	Anxiety	-4.62	218	189	0.19	0.82
	Depression	-4.45	236	177	0.18	
Carpinelli, L., et al, 2023	Depression	-3.96	38	38	0.39	0.09

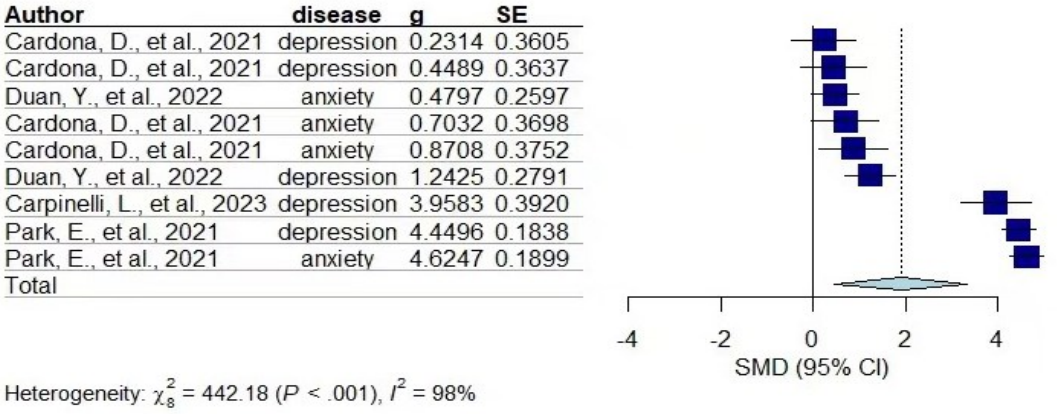

Figure 2. The forest plot of Meta-analysis about the effect size between gut microbiota and Depression and Anxiety.

3.2. Schizophrenia

Table 3 collates two experiments on schizophrenic disorders as presented in the figure of forest plots (Figure 3). They provide (1) data that the gut microbiota of schizophrenia patients is different from that of ordinary people and (2) changes in the composition about gut microbiota of obese patients have different degrees of schizophrenia as their condition improves after treatment. Interestingly, through this series of experiments, these therapies can produce improvement not only in a single patient with schizophrenia. As the gut microbiome changes with treatment, the obesity condition will also slowly disappear. The more severe the disease, the more significant the weight loss.

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Table 3. Meta-analysis about the effect size between gut microbiota and Schizophrenia.

Study name	Research topic	Effect size	Sample size (Treatment)	Sample size (Control)	Standard error	Weight
Li, S., et al, 2020	Schizophrenia	0.36	82	80	0.16	0.42
Zhang, J. P., et al, 2012	Schizophrenia	-0.11	47	126	0.17	0.58
	Schizophrenia	0.76	49	126	0.17	

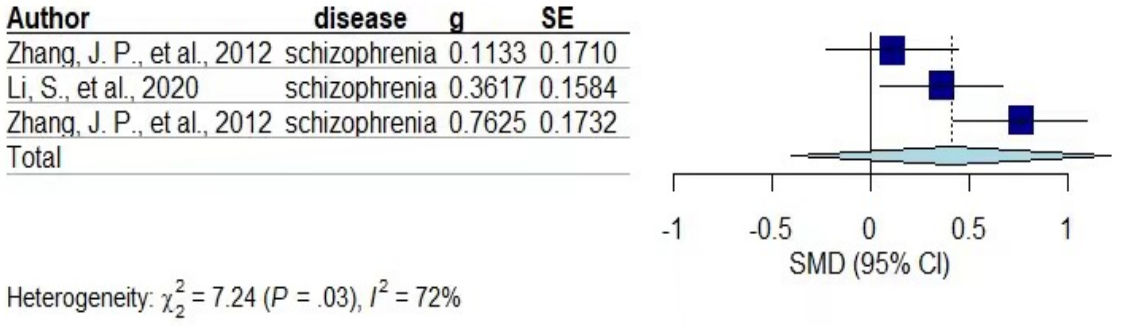

Figure 3. The forest plot of Meta-analysis about the effect size between gut microbiota and Schizophrenia.

3.3. Alzheimer's Disease

Table 4 records a set of comparative experiments on Alzheimer's disease and is presented in the figure of forest plots (Figure 4). This study provided specific data on the changed abundance of four gut microbiota species in AD patients compared to healthy controls. One organism (Dorea) was negatively associated with symptom severity, whereas the remaining three (DAO, DA, ET) were positively associated. Notably, gut barrier function, not only microbial abundance, was more affected by AD (cognitive impairment) and inversely correlated with symptom severity. Therefore, both sides should be considered when predicting GI disease or AD in the future.

Table 4. Meta-analysis about the effect size between gut microbiota and Alzheimer's Disease.

Study name	Research topic	Effect size	Sample size (Treatment)	Sample size (Control)	Standard error	Weight
Pei, Y., et al, 2023	Alzheimer's Disease	-2.32	45	35	0.29	1.00
	Alzheimer's Disease	-2.96	45	35	0.32	

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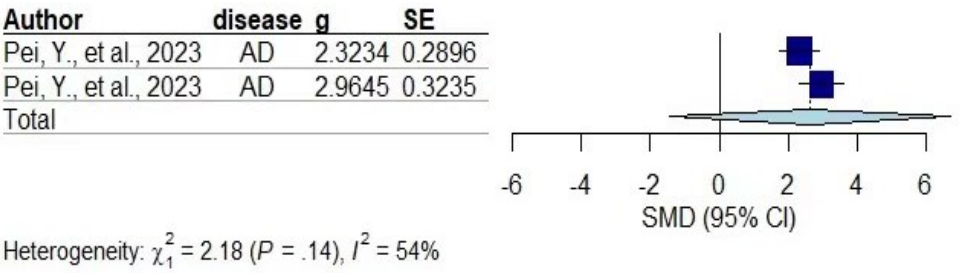

Figure 4. The forest plot of Meta-analysis about the effect size between gut microbiota and Alzheimer's Disease.

4. Conclusion

The articles we have reviewed so far have briefly pointed out that alterations in the constitution and distribution of gut microbiota may lead to increased permeability of the intestinal barrier, and this phenomenon may lead to cytokine storms that may trigger systemic inflammatory activation and immune responses [13]. On this basis, toxic metabolites and pro-inflammatory cytokines from altered microbiota can cross the blood-brain barrier, contributing to changes in the pro-inflammatory state at the brain level. High levels of inflammation in the brain bring about structural changes in glial cells that affect neural pathways and then refer to mental health, which may contribute to the emergence of mental disorders [14].

Studies have revealed the relationship between the gut-brain axis and its microbiota and the incidence of common mental disorders. In this meta-analysis, we obtained some relationships between microorganisms and the onset of mental disorders. For instance, the abundance of actinomycetes is positively related to the onset of schizophrenia. The quantity of Firmicutes was negatively correlated with the incidence of schizophrenia; The levels of 5-HT, DA, and NH are positively associated with the onset of depression [15].

It should be noted that for the unity and disambiguation of forest plots in the following figures, we reasonably take the absolute value and record the negative values in them uniformly according to the different assumptions and research directions of different articles. Table 1 shows nine items of data from four experiments on depression and anxiety. In the first two surveys of prisoners, we excluded data from historical prisoners to minimize the effects of the prison environment and diet. Therefore, although individual prisoners will still have differences due to reasons such as mood, the error in the analysis and calculation of the whole experiment is much smaller. Table 2 shows three data from two experiments on schizophrenia. In the first three surveys of patients with obese-type mental disorders, the data included patients of varying severity and a large number of controls (n=126) to avoid special conditions due to obesity and diet. Other psychiatric disorders with symptoms similar to schizophrenia were also used as references. Table 3 shows two data from an experiment on Alzheimer's disease. As in exceptional cases, survey data from patients with cognitive dysfunction with the same rationale or symptoms were kept for reference in order to reduce effects such as age.

Although our hypothesis that the health of the gut-brain axis (microbial abundance) is inversely correlated to the incidence of mental disorders is supported in this meta-analysis and in the articles we examined (5500), the results of the current computational analysis do not tell us how the gut-brain axis and microbiome specifically affect the onset of mental disorders. The majority (86%) of the research and experiments, in particular, were from 2017 to the present, with a small proportion from 2007 to 2017. This feature probably reflects the difference and progress of research methods in recent years and the necessity of in-depth research. For future research and investigation analysis, the two-way intervention of intestinal and mental disorders should be applied in the clinical medicine part with the deepening of the process. At present, this method has appeared in clinical cases. Thus, this field of study has broad research prospects. Currently, several clinical instances of using the method of treating the

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gut-brain axis to cure the mental disorder already appeared, which represents a bright future for this research field.

In summary, it is necessary to emphasize the limitations of this experiment to a certain extent. Due to the material requirements, the sample size for this meta-analysis is limited. In addition, we did not fully consider variables other than these two that could have affected the results, such as lifestyle habits before the study and underlying psychological states (childhood trauma). Under such a situation, although the relationship between gut-brain axis health and mental disorders incidence is obtained, we still need to conduct further studies. In the future, we will build on this, refer to more articles, and try to explore different hypotheses.

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Hanmo Yang and Shuran Zhang contributed equally to this work and should be considered co-first authors.

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