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What is the association between the microbiome and cognition? An umbrella review protocol

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ABSTRACT

Introduction Cognitive impairment is reported in a variety of clinical conditions including Alzheimer's disease, Parkinson's and 'long-COVID'. Interestingly, many of these clinical conditions are also associated with microbial dysbiosis. This comanifestation of cognitive and microbiome findings in seemingly unrelated maladies suggests that they could share a common mechanism and potentially presents a treatment target. Although a rapidly growing body of literature has documented this comorbid presentation within specific conditions, an overview highlighting potential parallels across healthy and clinical populations is lacking. The objective of this umbrella review, therefore, is to summarise and synthesise the findings of these systematic reviews.

Methods and analysis On 2 April 2023, we searched MEDLINE (Pubmed), Embase (Ovid), the Web of Science (Core Collection), the Cochrane Library of Systematic Reviews and Epistemonikos as well as grey literature sources, for systematic reviews on clinical conditions and interventions where cognitive and microbiome outcomes were coreported. An updated search will be conducted before completion of the project if the search-to-publication date is >1 year old. Screening, data abstraction and quality assessment (AMSTAR 2, A MeaSurement Tool to Assess systematic Reviews) will be conducted independently and in duplicate, with disagreements resolved by consensus. Evidence certainty statements for each review's conclusions (eg, Grading of Recommendations Assessment, Development and Evaluation (GRADE)) will be extracted or constructed de novo. A narrative synthesis will be conducted and delineated by the review question. Primary study overlap will be visualised using a citation matrix as well as calculated using the corrected covered area method.

Ethics and dissemination No participant-identifying information will be used in this review. No ethics approval was required due to our study methodology. Our findings will be presented at national and international conferences and disseminated via social media and press releases. We will recruit at least one person living with cognitive impairment to collaborate on writing the plain language summary for the review.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We designed an exhaustive search of five databases as well as grey literature sources working with an experienced systematic review librarian and Peer Review of Electronic Search Strategies (PRESS).
⇒ We plan a robust critical evaluation of included studies using A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) and augmenting existing quality of evidence statements with de novo Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments when possible.
⇒ The exploratory aim, heterogeneous nature of the research question and the umbrella review methodology preclude quantitative assessments and pooled effect estimates.
⇒ Many interventions impact the microbiome, and further inclusion criteria limits are needed to directly address the research question, we therefore will exclude studies of dietary interventions/exposures unless the stated purpose of the intervention was to modify the microbiome.

INTRODUCTION

Cognitive impairment is a defining characteristic of conditions such as Alzheimer's and Parkinson's disease, but altered cognition is also reported secondarily in a variety of other clinical conditions. Indeed, patients suffering from a number of maladies report varying degrees of cognitive impairment or 'brain fog' including postacute sequelae of COVID-19 or 'long-COVID',[1] cancer-related cognitive impairment (CRCI) or 'chemo-brain',[2] brain injury-associated fatigue and altered cognition,[3] post-treatment Lyme disease syndrome,[4] irritable bowel syndrome,[5] multiple sclerosis,[6] rheumatoid arthritis[7] and lupus.[8] Others have noted the similar cognitive impairment in these disparate conditions[9 10] along with the associated systemic inflammation and microglia activation.[11 12]

Interestingly, many of these clinical conditions are also associated with microbial dysbiosis,[13–19] which is an 'imbalance' of the normal human microbiome. The human microbiome includes the bacteria, viruses and yeast that inhabit the various skin regions and the oral, nasal, vaginal, lung, and, most importantly, gut mucosa.[20] The collective microbiome is an important source of bidirectional host/symbiont signalling, and a healthy and balanced microbial composition may be altered by factors including environment, physiology, lifestyle and pathology.[21 22] Comorbid microbial dysbiosis and altered cognition are associated with poor diet and obesity,[23–25] stroke and Alzheimer's disease,[26] mild cognitive impairment,[27] dementia,[28] brain injury,[29] multiple sclerosis,[30] Lyme disease[4] and postacute sequelae of SARS-CoV-2.[10] Other diseases marked directly by intestinal difficulties and dysbiotic microbiome have also documented cognitive components including coeliac disease,[31] Crohn's disease,[32] Gulf War Syndrome[33] and inflammatory bowel disease.[34]

Despite the comanifestation of cognitive impairment and microbial dysbiosis in these conditions, it is not clear if this is due to a common underlying trigger, or if dysbiosis may be directly causative to the neurologic symptoms through primary or secondary mechanisms.[19 23 35] A number of plausible mechanisms have been proposed by which dysbiosis could affect neurofunction including altered gut permeability (with varied secondary effects), vagus nerve activation, immune function/inflammation (both localised and systemic), altered bioavailability of neuroactive nutrients and metabolites (eg, short-chain fatty acid production, amino acid scavenging, etc) and altered microbial production/scavenging of hormones, neurotransmitters and/or their precursors.[19 22–25]

Although the gut microbiome is generally relatively stable in adults, it can be significantly altered by changes to environment, diet and lifestyle as well as targeted interventions such as antibiotics and faecal microbiome transplant.[16 36] Antibiotics directly target bacteria but do not specifically differentiate between pathogenic and commensal species which can negatively impact microbial ecology.[36] Healthy diet and exercise are each independently shown to alter the gut microbiome and improve cognition.[37–39] Microbiome-targeted diets including prebiotics and probiotics also alter the microbial composition, and have been used to shift the microbial community towards less dysbiosis.[36] Treatments to improve cognitive function targeted at altering a dysbiotic microbiome may provide a viable clinical approach.[23 26 40–42]

In summary, altered cognition and microbial dysbiosis commonly co-occur in a number of clinical conditions. This comanifestation in seemingly unrelated maladies suggests that they could share a common mechanism and potentially present a treatment target. Although a rapidly growing body of literature has documented this comorbid presentation within specific conditions, an overview highlighting potential parallels across healthy and clinical populations is lacking.

The objective of this overview of reviews (umbrella review) is to summarise and synthesise the findings of multiple systematic reviews on this topic in a diverse set of healthy and clinical adult populations. Such a '30 000 foot view' would not only benefit consumers of the research literature in this field, but may also reveal previously unappreciated overlap between seemingly disparate conditions, expose potential mechanisms linking cognitive impairment and microbial dysbiosis and identify potential treatments to reduce cognitive symptoms in a variety of conditions.

Specifically, we seek to (1) characterise and compare microbial dysbiosis associated with altered cognition in various clinical cognitive conditions/complaints, and (2) characterise and compare microbial changes associated with interventions that improve cognition.

METHODS

Inclusion Criteria and Protocol Registration

This protocol was informed by guidance from the Joanna Briggs Institute.[43]

Systematic reviews of *clinical conditions* that assess both microbial and cognitive change will be considered for inclusion. This includes conditions characterised by cognitive decline such as Alzheimer's and Parkinson's disease. Systematic reviews of *interventions* that assess both microbial and cognitive change will be considered for inclusion. This includes both targeted microbial interventions (eg, fecal–microbial transplant, antibiotics, prebiotics and probiotics) as well as interventions that secondarily alter the microbiome (eg, exercise, diet and medications). Studies on adult individuals with complaints/diseases involving cognition will be included. Examples include Alzheimer's disease, Parkinson's and subjective complaints of 'brain fog'. Studies involving populations with cognitive complaints that are side effects of medications such as 'chemo-brain'/CRCI will be included. Because many conditions may have secondary cognitive manifestations, inclusion will be limited to conditions characterised by cognitive decline such as Alzheimer's, Parkinson's and mild cognitive impairment, unless the article delineates a focus/study of the cognitive impacts of the condition (eg, a study of the association of the microbiome and 'chemo-brain' in cancer treatments). Adults will be defined by study authors or if >80% of the population is >17 years of age. Paediatric and non-human animal studies will be excluded. Studies describing the microbiome of cohorts of individuals with cognitive complaints/disorders will be included even if there is no control group. We will include systematic reviews that report on microbiome alteration interventions including probiotics, prebiotics, synbiotics and antibiotics even if specific microbiome data are not reported. Dietary interventions will be excluded unless the stated purpose of the intervention is to modify the microbiome.

Search strategy

On 2 April 2023, we searched the Pubmed interface of the MEDLINE medical literature database, the Ovid interface for the EMBASE database, Web of Science, the Cochrane Library of Systematic Reviews and the Epistemonikos database. An updated search will be conducted before completion of the project if the search-to-publication date is >1 year old. Search strategies for all of these databases can be found in the attached online supplemental appendix. Other information sources, including for the grey literature, will consist of a web-crawler search (Google Scholar), registry search (PROSPERO), citation harvest and discussion with content experts. The webcrawler-based search will be conducted according to published guidance.[44 45] To ensure adequate coverage of the topic, we will augment the search with vector score searching and cocitation and bibliographic coupling of included studies. Vector score searching underlies Pubmed's 'Similar Articles Tool' and is based on text weighting across the >30 million MEDLINE citations.[46] We will use cocitation and bibliographic coupling to build and visualise a force-directed graph of articles related to included studies. Cocitation and bibliographic coupling will be completed using the Connected Papers tool which is based on the Semantic Scholar Paper Corpus (>80 million scientific articles). There are no language or date restrictions on the search, nor restriction on article type (ie, posters, abstracts and unpublished manuscripts will be included). Key elements of articles of interest in languages other than English will be initially translated using Google Translate and confirmed, when possible, with native speakers. Our electronic search strategy was peer reviewed by a medical librarian experienced in systematic reviews following Peer Review of Electronic Search Strategies (PRESS) guidance.[47] All systematic reviews on our research questions regardless of whether or not they explicitly identify themselves as systematic reviews will be included. We define systematic reviews as studies with a clearly reported research question, a systematic search of at least two databases and a systematic data synthesis.

Study selection

Screening will be conducted in two stages: title/abstract and full text. All screening will be done independently and in duplicate with disagreements tracked by software (EppiReviewer), and resolved by consensus or adjudication by a senior reviewer. All citations from the database search will be screened. Up to 200 citations from Webcrawler searching will be screened per published guidance.[45] All citations identified by content experts, systematic review registry and citation harvesting will be screened. Citations in a format that can be uploaded to a citation manager (eg, .ris, .nbib) will be screened using EppiReviewer. We will utilise a machine learning classifier from the University of York for Systematic Reviews, 'trained' on the DARE systematic review database. During full-text review, reasons for exclusion will be noted.

Assessment of methodological quality

The quality assessment of the systematic reviews will be assessed using the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) critical appraisal instrument.[48] The AMSTAR 2 instrument uses 16 items to assess the quality of included systematic reviews. Among them, seven are items from the critical domains, domains thought to be of the highest importance when assessing the credibility of a systematic review. The critical domains require information from a systematic review regarding protocol registration, comprehensiveness of literature search, justification for excluding studies from the review, risk of bias assessment of included studies, appropriateness of statistical methods for meta-analysis, consideration of the risk of bias during the interpretation of the overall results and consideration of the potential impact of publication bias in the review. We will follow published guidance and will rate the credibility of the systematic review as high if there is no or one non-critical weakness, moderate if there is more than one non-critical weakness, low if there is one critical flaw with or without non-critical weaknesses or three or more non-critical weaknesses and critically low if there is more than one critical flaw with or without non-critical weaknesses.

AMSTAR 2 ratings will be conducted independently and in duplicate using EppiReviewer, with disagreements tracked in EppiReviewer, and resolved via consensus or senior author adjudication. If Grading of Recommendations Assessment, Development and Evaluation (GRADE) or other evidence certainty statements were included in eligible reviews, we will report them. If not, we will attempt to conduct our own GRADE assessment based on the published information in the review. If a risk of bias assessment was used by the systematic review authors (eg, Cochrane Risk of Bias Tool), this will be reported

Table 1 Quality assessment

Unit of analysis	Instrument	Extraction vs evaluation
Underlying primary studies	Eg, Cochrane Risk of Bias Tool	Extracted from systematic reviews
Overall evidence base of outcomes within included systematic reviews	Eg, GRADE	Extracted from systematic reviews if available, independent evaluation if possible
Included systematic reviews	AMSTAR 2	Independent evaluation

AMSTAR 2, A MeaSurement Tool to Assess systematic Reviews; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

as well. In this way, we will report on both the quality of the evidence syntheses and on the underlying primary evidence base (table 1).

Data collection

All extraction/abstraction will be done independently and in duplicate with disagreements resolved by consensus or adjudication by a senior reviewer. Data extraction will include information about the systematic reviews (eg, authors, title, number of included studies, number of participants and publication year), search strategies (eg, names of databases searched, database search date and date of last search update), population (eg, age, sex, setting and disease state), interventions (eg, intervention type, dose and frequency), comparators (eg, comparator type, dose and frequency), outcomes reported (not exclusive to cognition or microbiome outcomes), length of follow-up, risk of bias and information about the primary studies (eg, authors, title, study design, publication year and country of publication). Details regarding clinical and methodologic heterogeneity, such as age, location, study design, etc, will be extracted, as will metrics of statistical heterogeneity (eg, I^2) if a meta-analysis was conducted. We will use the ARHQ's Systematic Review and Data Repository (SRDR+) software for data extraction.[49] We will attempt to contact the systematic review authors to clarify any missing outcome data.

Data summary

A narrative synthesis of the included reviews will be conducted and delineated by the review question. We will tabulate included systematic review details in a Characteristics of Studies table. We will report all systematic reviews that meet inclusion criteria regardless of overlap. However, we will highlight those which are of the highest methodologic quality, the most recent and the most comprehensive in terms of our research questions.

Primary study overlap will be shown using a citation matrix as well as calculated using the corrected covered area method (Pieper 2014) using a priori overlap thresholds (0%–5%—slight, 6%–10%—moderate, 11%–15%—high and >15%—very high).

We will report on statistical heterogeneity (ie, I^2) on a systematic review level if it was calculated by the included systematic reviews. We will consider non-statistical heterogeneity on the umbrella review level. Specifically, in terms of clinical heterogeneity, we plan to report our findings by disease state and intervention type. In terms of methodological heterogeneity, we plan to report on length of follow-up, underlying study type (eg, cross-sectional and cohort) and AMSTAR 2 rating.

We do not plan to re-evaluate the data reported in the included systematic reviews but rather report the findings of the reviews. However, if significant flaws are identified or if there is enough available information to complete a missing analysis (eg, conduct a GRADE assessment), we will do so.

Patient and public involvement

Given the nature of secondary data capture and analysis, patients and the public will not be involved in the design or interpretation of this study. However, we will recruit at least one person living with cognitive impairment to collaborate on writing the plain language summary for the review.

Ethics and dissemination

No participant-identifying information will be used in this review. No ethics approval was required due to our study methodology. Our findings will be presented at national and international conferences and disseminated via social media and press releases.

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Contributors JZG, TJW, RDB, RSW, KAMG, NKV, WWW, KMR, RJU, RBP and MS-M were involved in the conception and design of the project. JZG, TJW and RSW were involved in the writing and registration of the protocol on PROSPERO. JZG, TJW, RSW, KAMG, KMR and MS-M were involved in the preparation of this manuscript for publication. All authors (JZG, TJW, RDB, RSW, KAMG, NKV, WWW, KMR, RJU, RBP and MS-M) reviewed and approved the final version of this manuscript. JZG and MS-M are the guarantors of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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