

Nutritional Interventions for the Prevention of Cognitive Decline in Patients with Mild Cognitive Impairment and Alzheimer's Disease: Protocol for A Network Meta-Analysis of Randomized Control Trials

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Nutritional Interventions for the Prevention of Cognitive Decline in Patients with Mild Cognitive Impairment and Alzheimer's Disease: Protocol for A Network Meta-Analysis of Randomized Control Trials

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Abstract

Background: Mild cognitive impairment (MCI) is the status between cognitive decline by physiological ageing and the severity of the decline, particularly neurodegenerative disorders like Alzheimer's disease (AD). AD is one of the most popular neurodegenerative disorders characterised by cognition impairment. People with MCI are at a higher risk of developing AD. Even though MCI and AD are incurable, nutritional interventions might be one of the possible solutions to delay or prevent them. As a result, effective interventions used to decelerate or alleviate the progress of cognitive impairment in elders have become a great issue in geriatric care. Given the synergistic effects of nutrition on health, assessing whether nutritional supplements or dietary composition effectively prevent MCI/AD cognitive impairment is essential for developing an interventional strategy.

Objective: The aim is to estimate the effectiveness of various nutritional interventions on cognitive function in patients with MCI or AD by performing a network meta-analysis and systematic review and pairwise meta-analysis of clinical trials or randomised controlled trials.

Methods: This review will follow the Population, Exposure, Comparison, Outcome (PI(E)CO) model and adheres to the PRISMA-P guidelines. Two investigators will conduct an electronic database search using the PubMed database independently. Data extraction from the studies will be chosen by applying the inclusion criteria, and those data will assess their risk of bias by the revised tool. We will also assess the evidence quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. The outcomes of interest are assessing the cognitive function in patients with MCI or AD; the acceptability of nutritional interventions will also be included in the secondary outcome. Pairwise and network meta-analyses (random-effects model) will be used to assess the pooled effect of each intervention.

Results: To date, we included 39 randomized control trials in our study. We are still working on data extraction and cleaning. We plan to perform the network meta-analysis analysis in the following six months. We are going to publish the paper at the end of this year.

Conclusions: The goal of this study is to determine whether nutritional interventions are useful for the prevention of cognitive decline and which intervention is the most effective for delaying cognitive decline in patients with MCI and AD Clinical Trial: PROSPERO registration number CRD42022331173.

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Original Manuscript

Nutritional Interventions for the Prevention of Cognitive Decline in Patients with Mild Cognitive Impairment and Alzheimer's Disease: Protocol for A Network Meta-Analysis of Randomized Control Trials

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Abstract

Background

Mild cognitive impairment (MCI) is the status between cognitive decline by physiological ageing and the severity of the decline, particularly neurodegenerative disorders like Alzheimer's disease (AD). AD is one of the most popular neurodegenerative disorders characterised by cognition impairment. People with MCI are at a higher risk of developing AD. Even though MCI and AD are incurable, nutritional interventions might be one of the possible solutions to delay or prevent them. As a result, effective interventions used to decelerate or alleviate the progress of cognitive impairment in elders have become a great issue in geriatric care. Given the synergistic effects of nutrition on health, assessing whether nutritional supplements or dietary composition effectively prevent MCI/AD cognitive impairment is essential for developing an interventional strategy.

Objectives

The objective of our study is to assess the effectiveness of diverse nutritional interventions, including special dietary types, dietary patterns, specific foods, nutritional intake, and nutritional supplements, in preventing cognitive decline among patients diagnosed with MCI or AD. To achieve this, we will employ a comprehensive approach involving network meta-analysis, pairwise meta-analysis, and systematic review of randomized controlled trials (RCTs).

Methods

This review will follow the Population, Exposure, Comparison, Outcome (PI(E)CO) model and adheres to the PRISMA-P guidelines. Two investigators will conduct an electronic database search using the PubMed database independently. Data extraction from the studies will be chosen by applying the inclusion criteria, and those data will assess their risk of bias by the revised tool. We will also assess the evidence quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. The outcomes of interest are assessing the cognitive outcomes in patients with MCI or AD. A systematic literature search, identifying relevant RCTs that investigates the impact of these nutritional interventions on cognitive decline in individuals with MCI and AD. Next, a network meta-analyses (random-effects model) and pairwise meta-analyses will be used to estimate the relative effectiveness of different nutritional interventions.

Results

51 studies, which had been published between 1999 and 2023 (27 studies for AD and 24 studies for MCI) and involved 8,420 participants, will be included in our study.

Conclusions

Our study holds significant clinical relevance due to the rising prevalence and incidence of AD and the potential influence of nutritional interventions on cognitive function in individuals with MCI and AD. By

investigating this relationship, our research aims to provide valuable insights that can inform evidence-based decision-making in the development of prevention strategies for MCI and AD. Furthermore, the outcomes of our study are anticipated to contribute to the establishment of reliable recommendations for the management of MCI and AD, thereby offering substantial support in the field.

Registration

PROSPERO registration number CRD42022331173.

Keywords: Network meta-analysis; cognitive impairment; Alzheimer's disease

Introduction

Cognitive decline, particularly associated with mild cognitive impairment (MCI) and Alzheimer's disease (AD), represents a significant and growing public health concern worldwide [1]. As the aging population continues to increase, the prevalence of MCI and AD is also on the rise, leading to substantial personal, societal, and economic burdens [2]. One study indicated that the occurrence of MCI was higher than 22.5 per 1,000 person-years among elders aged over 75 years [3]. Patients with MCI are also at a high risk of developing into AD [4,5]. Therefore, identifying effective interventions to prevent or delay cognitive decline in individuals with MCI and AD is of utmost importance.

Currently, MCI and AD are incurable, however delay and prevention of MCI or AD are possible [6]. Modifiable factors such as metabolic (diabetes), vascular (hypertension), mental health (depression), social (isolation), and lifestyle (nutritional intake [7], dietary type [8], and physical inactivity) have been frequently linked with the risk of MCI and AD [9]. As such, it is critical to understand how modulating health and lifestyle factors may prevent cognitive decline. In recent decades, nutritional interventions have gained attention as potential strategies for cognitive decline prevention [10,11]. Various nutrients, dietary patterns, and dietary supplements have been investigated for their potential benefits in cognitive function and neuroprotection. Multiple types of intervention have been applied to these populations to reduce the decline of cognitive function, such as the Mediterranean diet and ketogenic diet, as well as the regulation of fatty acids, antioxidants, vitamins, and micronutrients [12–15]. Andrews et al. conducted a systematic review and meta-analysis of RCTs to evaluate the effect of dietary pattern, food, and nutritional supplement on cognitive function in individuals with MCI. The findings from this review demonstrated few nutritional interventions were found to convincingly improve cognition of individuals with MCI [16]. George et al. conducted a systematic review and found folate, vitamin E, omega-3 fatty acids, and certain multi-nutrient formulations have shown some preliminary promising results [17]. However, the evidence regarding the effectiveness of different nutritional interventions remains inconclusive, with conflicting findings reported across individual RCTs.

To address the limitations of traditional pairwise meta-analyses and provide a comprehensive synthesis of the available evidence, we propose conducting a network meta-analysis (NMA). A NMA is a type of meta-analysis that extends beyond regular meta-analysis [18,19]. By employing this approach, we aim to provide more precise and robust estimates of the effects of different nutritional interventions on cognitive decline in patients with MCI and AD. In this protocol, we outline the methodology for conducting a network meta-analysis of RCTs on nutritional interventions for the prevention of cognitive decline in patients with MCI and AD.

Methods

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist [20]. This protocol has been registered in the

International Prospective Register of Systematic Reviews (PROSPERO), study protocol registration CRD42022331173.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of studies will be conducted according to the principle of the Population-Intervention-Comparator-Outcomes-Study design (PICOS). The inclusion and exclusion criteria have been presented briefly in Table 1.



Table 1. Inclusion criteria for studies in the current meta-analysis

	Inclusion criteria	Exclusion criteria
Study design	RCTs reported as comparing one nutritional intervention with another or a placebo	Non-RCTs
Participants	Participants with MCI or AD older than 50 years	Participants with vascular dementia; Parkinson’s disease-related dementia; delirium; depression and other mental illnesses; congenital brain function hypoplasia, such as Down syndrome; or subarachnoid haemorrhage
Diagnosis of MCI or AD	Diagnosis according to NINCDS-ADRDA DSM or assessed by MMSE with score between 10 to 26	
Nutritional intervention assessment	Any type of nutritional intervention, such as special dietary type, dietary pattern, food, nutritional intake and nutritional supplements at all doses or ingested amounts with a duration of more than 12 weeks.	No definitive preventative impact evaluated, or the effects were evaluated for shorter than 12 weeks.
Outcome measurement	The primary outcome will be assessed by the MMSE. The secondary outcomes will assess with other scales like the ADAS-Cog, and/or the CDR, and/or the WAIS-R scores.	

Inclusion criteria

Type of study

All RCTs reported as comparing one nutritional intervention with another or a placebo in the prevention of cognitive decline in MCI or AD patients will be included.

Participants

Participants with MCI or AD older than 50 years, regardless of gender, ethnicity/race, geography, dwelling, or chronic diseases, will be included in the analysis.

Inclusion of patients with different degrees of MCI and/or AD

- 1) Participants will be considered as AD patients by fulfilling the requirement of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) [21-22].
- 2) Participants will have been evaluated as MCI by Mini-Mental State Examination (MMSE) [23].

Nutritional interventions assessment

Experimental interventions included any type of nutritional intervention, such as special dietary type, dietary pattern, food, nutritional intake and nutritional supplements at all doses or ingested amounts. Interventions were of a duration of more than 12 weeks and were with or without medication as cointervention. The control group received a placebo intervention.

Outcome measurement

Both the primary outcome and secondary outcome are the assessment of the cognitive function. The primary outcome will be assessed by the MMSE. The secondary outcomes will assess with other scales like the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog), and/or the Clinical Dementia Rating Scale (CDR), and/or the Wechsler Adult Intelligence Scale Revised (WAIS-R) scores. The standard mean difference (SMD, Cohen's d)

will evaluate the effect sizes of the continuous variable. A small-sample ($n < 20$) correction would be applied to SMD, which leads to an effect size called Hedges' g .

Exclusion criteria

- 1) The studies were non-RCT or in the form of a letter, editorial, commentary, or case report, among other formats.
- 2) There was no definitive preventative impact evaluated, or the effects were evaluated for shorter than 12 weeks.
- 3) Participants with vascular dementia; Parkinson's disease-related dementia; delirium; depression and other mental illnesses; congenital brain function hypoplasia, such as Down syndrome; or subarachnoid haemorrhage would be excluded from the study.

Search Strategy

Two investigators (H.Q. and W.C.H.) will perform the search strategy independently and disagreements will be decided by discussion or by a third investigator (Z.J.Y.). We will search for all the relevant citations published from the date of the respective database onset until 3 May 2022 in three English databases (PubMed, Embase, and Cochrane Library). We will establish search strategies that combine keywords and indexed terms indicative of MCI or AD, nutritional intervention and RCTs. Furthermore, the reference lists of the listed papers will be manually examined to seek for new studies that are related. Any controversies will be resolved through dialogue. Supplement 1 contained the search techniques.

Data Extraction

Two investigators (H.Q. and W.C.H.) will extract the data from all eligible studies published in English using standardised spreadsheets which are predefined independently. Any discrepancies will be resolved to consensus by the discussion of the two investigators or arbitrated by a third investigator (Z.J.Y.). The following information will be extracted from every study: first author, publication year, detailed trial information (randomisation, sequence concealment, blinding, nutritional intervention protocols, numbers of treatment arms, dose and frequency of interventions), criteria of diagnose, characteristics of patient (including age,

gender, race, and baseline MMSE scores), sample size, follow-up MMSE scores, number of completed interventions, and the duration of intervention as well as follow-up. We will contact the authors via email to obtain the raw data when the data on outcomes were incomplete in the original article, otherwise, we won't include these studies lacking such data. At last, two investigators will cross-check all retrieved data to verify the accuracy.

Quality Assessment

The quality of the included studies will be evaluated by the Cochrane collaboration using the criteria of the Risk of Bias assessment tool. [24]. Various bias like selection bias (randomised sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (dealing with incomplete outcome data); reporting bias (selective reporting); and overall biases will be assessed in our study. The trials will be categorized into three types, which are low risk of bias, unclear risk of bias and high risk of bias. Assessment of bias of the trials will be conducted by two investigators (H.Q. and W.C.H.), and disagreements will be resolved through discussion with a third investigator (Z.J.Y.). Moreover, we will contact the authors asking for the detailed allocation concealment and other characteristics when these cannot be available in the study.

Statistical Synthesis

Characteristics of included studies and information flow in the network

For the eligible trials included in our analysis, we will generate descriptive statistics to provide a comprehensive overview of the population characteristics and key variables across all trials. These descriptive statistics will encompass factors such as age, disease subtype, and other relevant risk factors that may impact the outcomes of interest. To visually represent the network of evidence, we will construct a network diagram. The edges connecting different interventions will be depicted with widths proportional to the inverse of the variance of the summary impact for each direct treatment comparison. The size of the nodes in the diagram will correspond to the quantity of evidence accumulated for each treatment, represented by the total number of studies contributing to that node. In addition, we will utilize a contribution

matrix to explore the direct comparisons that have a substantial influence on the relative effects within the network [21,22]. This matrix will help identify the specific comparisons that contribute significantly to the overall findings.

Assessment of the transitivity assumption

The transitivity assumption will be assessed by evaluating the distribution of modifiable variables, such as age and mean baseline cognitive function, between treatment and the control group [23].

Pairwise meta-analyses and network meta-analyses

By conducting the pairwise meta-analysis, we can quantitatively assess the effectiveness of interventions that have direct evidence. This analysis allows for a comparison of the treatment effects within individual studies, providing valuable insights into the efficacy of each intervention. To ensure transparency and facilitate interpretation, we will present the results of the pairwise meta-analysis using forest plots.

The network meta-analysis (NMA) will be conducted using a Bayesian framework, pooling data from all included studies [24]. To provide a visual representation of the network of evidence, we will generate network plots, which summarize the geometry of the network. These plots will help illustrate the connections between different interventions and highlight the available evidence for each comparison. For the estimation of effect sizes, we will utilize contrast-based methods within the NMA framework. The distribution of ranking probabilities and surface under the cumulative ranking curve (SUCRA) will be used to estimate the relative rank of the different nutritional interventions [25].

All data will be analyzed using the R 4.0.3 software, specifically utilizing the gemtc package. Estimates will be reported as standardized mean differences (SMDs) and 95% credible interval (95% CrI). We will use three Markov-chains with 100,000 iterations after an initial thinning of 10,000 and a thinning of 10. The convergence of model will be estimated by checking trace plots and the Brooks-Gelman-Rubin statistical value.

A systematic review will be considered in situations where there is a scarcity of studies, typically involving less than two available studies. Additionally, if the heterogeneity observed

among the included studies is exceptionally high, typically exceeding 95%, a systematic review approach will be adopted.

Assessment of inconsistency for network meta-analysis

Consistency is called the statistical manifestation of transitivity while a lack thereof is known as inconsistency [26]. Inconsistency suggests a disagreement between these estimates and indicates potential issues with the consistency of evidence across the network of studies. We will use node-splitting method to assess inconsistency [27-28]. The presence of inconsistency between different estimates using direct and indirect evidence can be evaluated by assessing the P value. Inconsistency in the network is indicated by a P value below 0.05.

Assessment of heterogeneity and sensitivity analyses

To quantify between-study heterogeneity, we will calculate the I^2 -statistic with 95% credible intervals (95% CrI) and τ^2 to convey the heterogeneity. The τ^2 represents the variability in intervention effects across studies, while I^2 quantifies the proportion of total variability that is due to heterogeneity rather than chance. $I^2 > 50\%$ will be considered as moderate to substantial heterogeneity, then the effect sizes will be estimated with a random-effect model [29]. Moreover, we will estimate the outlier and influential study when the $I^2 > 50\%$, then we will perform the NWM or pairwise meta-analysis again excluding the outliers and influential studies. Study-specific estimates and 95% CrIs, will be presented by forest plots. Subgroup meta-analyses and meta-regression analysis would be performed to estimate the source of heterogeneity. Subgroup analyses by different groups allow us to test specific hypotheses and describe why some type of study produces lower or higher effects than others. Performing subgroup analysis would help with estimating if the interventional effects for the primary outcomes are robust. Meta-regression analysis could help with quantify the effects by including covariates into the network meta-analysis models if suitable. Then we will run subgroup and meta-regression with the following criteria: cognitive dysfunction severity at baseline, study year, sample size, risk of bias, duration of intervention, and number of recruiting centres (single-centre or multicentric studies).

Sensitivity analyses will be conducted to assess the robustness of the primary outcome results in the meta-analysis. These analyses will involve examining the impact of outliers, influential

studies, risk of bias, and sample size by using the leave-one-out method. Specifically, each study will be systematically removed from the meta-analysis, and the pooled effect will be re-evaluated both in pairwise meta-analysis and network meta-analysis (NMA) for each iteration. Studies with changes in the effect size exceeding 10% will be noted.

Assessment of publication bias

The comparison-adjusted [26] and contour-enhanced funnel plots [30] will be used to find out whether the results in imprecise trials differ from more precise trials. In addition, network meta-regression models and Egger's test will be performed to detect the effects between study size and effect size, and to assess the asymmetry of the funnel plot respectively.

Results

The initial search yielded 30,269 citations, out of which 248 articles were identified as potentially eligible and will undergo evaluation for eligibility. Among these, a total of 197 articles will be excluded for various reasons. This exclusion consists of three duplicates, 39 articles without full text availability, 45 articles lacking an assessment of cognitive function, 40 articles not meeting the criteria of being RCTs, 28 articles not in English, and 42 articles unrelated to the study objective. Ultimately, 51 studies meeting the inclusion criteria will be included in our NMA. These studies, published between 1999 and 2023, consist of 27 studies focusing on AD and 24 studies focusing on MCI. In total, these studies involve 8,420 participants.

Discussion

The global phenomenon of population aging has led to a significant increase in the prevalence of cognitive impairment, particularly AD and MCI [31]. This demographic shift has garnered substantial attention from healthcare providers, researchers, and policymakers due to the immense personal, societal, and economic implications [32]. As the current treatments for MCI and AD are limited and primarily focused on symptom management, identifying effective preventive strategies is of paramount importance [15]. The potential benefits of nutritional interventions for cognitive health have been a subject of considerable interest [2].

Various nutrients, dietary patterns, and dietary supplements have been investigated for their potential neuroprotective effects and cognitive function improvement. Therefore, through this study, we aim to consolidate the available evidence and provide a rigorous and comprehensive synthesis using the network meta-analysis approach. Moreover, identifying the most effective interventions will help guide future research efforts and resource allocation towards the most promising strategies.

It is important to acknowledge the limitation of this study. While NMA provides a robust statistical framework for synthesizing evidence, it is reliant on the quality and availability of data from included RCTs. Potential sources of bias and heterogeneity among the studies may affect the robustness of the results.

In conclusion, the findings of this study will have significant implications for clinical practices, as well as for informing public health strategies and policy-making.

List of abbreviations

AD: Alzheimer's disease

ADAS-Cog: Alzheimer's Disease Assessment Scale cognitive subscale

CDR: Clinical Dementia Rating Scale

CrIs: Credible intervals

DSM: Diagnostic and Statistical Manual of Mental Disorders

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

MCMC: Markov Chain Monte Carlo

MMSE: Mini-Mental State Examination

MCI: Mild cognitive impairment

NMA: network meta-analysis

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

PICOS: Population-Intervention-Comparator-Outcomes-Study design

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RCT: Randomized Control Trials

SUCRA: surface under the cumulative ranking curve

SMD: standard mean difference

WAIS-R: Wechsler Adult Intelligence Scale Revised scores

Declarations

Ethics approval and consent to participate

Ethical approval is not required in the meta-analysis. Our study is merely based on the published literatures which have passed the ethical approval. In order to disseminate the evidence obtained, we will publish our results in an international peer-reviewed journal to improve preventive applications with scientific evidence.

Consent for publication

Not applicable.

Availability of data and materials

No additional data are available.

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Authors' contribution

Q.H. and C.H.W. participated in the study design, data collection, analysed the data and wrote the paper. A.N.B. participated in the discussion of the study design, data analysis, and edited the manuscript. J.Y.Z participated in the independent quality checking of all data included in the analysis. K.H.C. conceived the study, designed, coordinated the study, and revised the manuscript.

Competing interests

The authors declare that they have no competing interests.

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