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Original Study

Nutritional Strategies in the Management of Alzheimer Disease: Systematic Review With Network Meta-Analysis

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A B S T R A C T

Background: Alzheimer disease (AD) is the major cause of dependency and disability in the elderly. Numerous studies have sought to achieve its prevention and/or management examining a role for modifiable risk factors, such as nutrition. This work aims to investigate the effects of food and/or nutrients in the management of AD at different stages.

Methods: Electronic databases were searched for clinical trials examining the effect of nutrient intervention in individuals with AD, compared with placebo, published up to 2014. The outcomes investigated were neuropsychological assessment scales, neuroimaging, and biomarkers. The Cochrane tool was employed to assess risk of bias. Pairwise meta-analyses were performed in a random-effect model by estimating the weighted mean differences with 95% confidence interval (CI) for each outcome measure. The Network meta-analysis was undertaken on cognitive outcome.

Results: Selected studies used antioxidants, B-vitamins, inositol, medium-chain triglyceride, omega-3, polymeric formulas, polypeptide, and vitamin D. AD outcome measurements were mainly restricted to cognitive state and functional abilities. Estimate treatment effects from pairwise meta-analyses showed large but nonsignificant effect in the supplementation with proline-rich polypeptide [weighted mean difference 6.93 (95% CI −3.04, 16.89); $P = .17$] and B-vitamins [weighted mean difference 0.52 (95% CI −0.05, 1.09); $P = .07$) on cognitive function measured by the Mini-Mental State Examination. The other nutrients supplementation did not show any significant effect on any outcome measures.

Conclusions: Isolated nutrient supplementations show no convincing evidence of providing a significant benefit on clinical manifestations or neuropathology of AD. During the initial stages of AD, nutrient supplementation did not show any effect when delivered individually, probably because of their synergistic function on brain, at different domains.

Dementias are caused by different brain modifications that disrupt multiple cortical functions, leading to intellectual and cognitive impairments; dementia constitutes one of the major causes of disabilities and dependence in aging.[1,2] Alzheimer disease (AD), the most common form of dementia, is characterized by progressive synaptic loss, dysfunction, and neuronal death, and vascular toxicity, triggered by the deposition of pathologic inducers of lesions in the brain tissue, amyloid β peptide (Aβ), and hyperphosphorylated tau protein.[2] The neuropathogenesis of AD has been associated with mitochondrial dysfunction, inflammation, abnormal accumulation of transition metals, and oxidative stress. The brain is susceptible to oxidative damage, which in turn increases Aβ production and deposition, promotes the phosphorylation of tau and the consequent neuropathology, creating a vicious cycle that boosts the beginning and progression of AD.[3,4] Therapies attempting to counteract these lesions have not achieved permanent successful results.[5] Thus, investigating strategies that may prevent or delay the progression of dementia is a matter of the utmost importance.[6]

Extensive research has indicated that nutritional adjustments have strong effects on health and might have a preventive effect in

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neurodegenerative diseases.[7] Some dietary components or patterns (folate, fish, antioxidants, coffee, Mediterranean diet, among others) have been identified as protective factors against the development of AD. In addition, some nutrition-related conditions (hyperhomocysteine, hypertension, frailty, and type 2 diabetes mellitus) increase the risk for AD, suggesting that effective dietary interventions may reduce the growing incidence of this disease.[8,9] The beneficial effects of nutrients in AD may imply a safe, cost-effective, easy to administer and socially acceptable approach.[10]

Herein, we hypothesize that clinical and neuropathologic manifestations of AD can be counteracted, at least partially, through the ingestion of specific nutrients, foods and/or dietary patterns. Many studies on the influence of nutrients in cognitive impairment have been reported over the last few years, demonstrating the need for the systemic discussion of these data.[11] Although some systematic reviews regarding specific nutrients related to AD exist in the literature, none of these evaluated simultaneously the effects of the ingestion of nutrients, foods, and dietary patterns. As such, this systematic review and meta-analysis aims to gather, organize, critically assess, and quantitatively measure the evidence examining the use of nutrients, foods, and/or dietary patterns, in the management of AD at different stages; we addressed whether nutrition interventions are capable of slowing down the progress or decreasing some symptoms of AD, and whether exists any therapeutic association between consumption of specific nutrients, food, or dietary patterns with the pathologic manifestations of AD in the elderly.

Methods

This study was performed in accordance with the Cochrane Handbook for the Systematic Review of Interventions[12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] Studies were organized into groups according to the type of nutrient.

Eligibility Criteria

Inclusion criteria for eligible studies are summarized in Table 1.

Sources and Search Strategy

Electronic databases (the Cochrane Controlled Trial Registered, EMBASE, PubMed, Virtual Health Library and Web of Science) were exhaustively searched for potentially relevant studies, up to December 2014. The search strategy was built by crossing key search terms with the Boolean operator "AND" for each component of the review question (clinical condition, type of intervention and type of study). Key search terms are shown in Supplementary Table 1.

Data Extraction and Quality Assessment

The first author screened and evaluated primary studies by title and abstract for inclusion. Studies that matched clinical condition, intervention, and study design of interest were selected and documented. Duplicate studies were identified simultaneously in the database searches. Afterward, a second author accessed the study records to evaluate them for inclusion. Final decisions on study inclusion were reached in a consensus meeting. The first author retrieved and perused the full texts of preliminary relevant reports identified in the preceding step for compliance with eligibility criteria and data extraction. Clinical trials were characterized according to the recommendations of the Cochrane Collaboration.[12] The quality of studies was independently evaluated by two authors using the Cochrane Risk of Bias Tool.[12] The assessment was categorized by domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias) specifying the source of bias and grading domains as "low," "unclear," or "high" risk. The final assessment of bias for the inclusion of studies was determined by the risk of the main domains for this study: selection bias, performance bias, and attrition bias. Disagreements were resolved by a second consensus meeting. Articles classified as high risk were excluded. The overall assessment was presented in a risk of bias summary figure using the RevMan software.[14] The quality of evidence and strength of recommendation was determined according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which is based on the risk of bias, inconsistency, indirectness, imprecision and publication bias of included studies. To assess imprecision, the optimal information size) calculated at http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html.[15]

Statistical Analysis

We run different pairwise meta-analyses of continuous variables for each outcome and nutrient intervention using the method of the inverse variance in a random effect model (DerSimonian and Laird method) to calculate the estimative of treatment effect, the weighted mean difference (WMD), and its 95% confidence interval (CI). All outcome measures were estimated based on the change from baseline to follow-up.[16] The heterogeneity was appraised with the I^2 statistic (low <40%; moderate 30%–60%; substantial 50%–90%; and considerable heterogeneity 75%–100%) and the χ^2 test with significance (P value) at the level of .10. Heterogeneity was explored and explained if significant (I^2 >30% and χ^2 $P < .10$). Statistical analyses were carried out using the software Review Manager (RevMan) v 5.3.[14] A Network Meta-analysis (NMA) was performed for cognitive outcome measure in a Bayesian framework using Markov Chain Monte Carlo method with a random effect model (mean difference with 95% credible interval) using ADDIS release 1.16.6[17] to analyze the consistency and

Table 1
Eligibility Criteria PICOS

	Inclusion Criteria	Exclusion Criteria
Participants	AD at any stage with or without chronic diseases; aged over 60 y old; both sexes; any race/ethnicity or geographic location.	Healthy participants; mild cognitive decline or other types of non-Alzheimer dementia; familial AD initiated before 50 y old or related to other genetic diseases (eg, trisomy of chromosome 21).
Interventions	Any type of nutrient, food, special diet, or dietary pattern at all doses or ingested amounts without restriction on the duration of intervention; with or without medication as cointervention.	Other different than nutrient or food interventions
Comparisons	Placebo or control	
Outcomes	Primary: neuropsychological scales and structural, functional, or other methods of neuroimaging. Secondary: biochemical biomarkers of AD and oxidative stress and/or inflammatory biomarkers in CSF or plasma.	Plasma nutrient levels, nutritional status, or food intake without any direct association with disease status or progression.
Study design	Blinded clinical trials completed and published from the beginning of the databases up to 2014	Nonhuman animal model studies, in vivo, or in vitro. Full-texts published in languages other than English, Portuguese, or Spanish.