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REVIEW ARTICLE

The role of nutrients in the prevention and treatment of Alzheimer's disease: methodology for a systematic review

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There is a large body of existing data on nutrition in Alzheimer's disease (AD). We are conducting a systematic review of published scientific literature to determine the role of specific nutrients, both individually and in combination, in the prevention and treatment of AD. This will contribute towards a structured evidence base to help inform the clinical management of AD. The objective of the systematic review is to evaluate the strength of evidence from both observational cohort studies and randomized controlled trials on the role of fats, vitamins, antioxidants and other nutrients in the prevention and treatment of AD. We present here the methodology of our systematic review.

Introduction

Just over 100 years ago Alois Alzheimer gave a lecture at a congress in Tübingen, Germany, on the first case of a disease that his employer, Emil Kraepelin later named Alzheimer's disease (AD) in his definitive psychiatry textbook [1]. Alzheimer described the case of Auguste D., a 51-year-old German housewife who had experienced a precipitous decline into dementia, and who upon autopsy, was shown to have the pathological features – plaques and tangles – that we today regard as the hallmark of AD. Dr Alzheimer questioned whether these symptoms and pathology represented a distinct disease process, or whether they simply represented accelerated brain ageing, or pre-senile dementia. Today, the exact aetiology of AD and whether its progression can be modified is still unknown. There is also no consensus within the scientific community on the role of amyloid in the neuronal death observed in AD [2].

The majority of current research in AD focuses on developing interventions predicated on the amyloid cascade hypothesis. However, most physicians and investigators believe that AD is not a singular condition defined exclusively by plaques and tangles [3] and many believe that the Alzheimer's diseases are rather an overlapping set of biological processes that constitute forms of severe brain ageing [4]. Terms like mild cognitive impairment (MCI), a kind of pre-demented state without impairment of function, are increasingly controversial and demonstrate the existence of a continuum of cognitive changes with age. Indeed, there is growing belief that the ecology of brain ageing throughout the life-course should be taken into consideration with a renewed focus on prevention and human care [4].

In addition to the well established risk factors for AD such as age and the APOE lipoprotein ϵ4 (APOE-ϵ4) genotype [5,6], there are multiple environmental and behavioural factors that might interact over the life-course to influence brain ageing. These include bio-psycho-social factors such as depression, stress, environmental exposures, physical and mental activity, head injury, and nutrition.

The evidence for the potential role of nutrition in the maintenance of cognitive function and the prevention of dementia comes from a variety of study designs including cross-sectional surveys, cohort studies and a few large randomized controlled trials (RCT). Several candidate nutrients have been identified as potentially important, but the most recent comprehensive review published in 2004 concluded that the current evidence was insufficient to make any definitive conclusions or recommendations regarding diet and AD [7].

Since the publication of this review, the results of several important cohort studies and RCT have been reported. We have, therefore, recently conducted a wide-ranging systematic review of the available published scientific literature to determine the role of specific nutrients, either singly or in combination, for the prevention of cognitive decline, dementia and AD and the treatment of individuals with AD. The current paper presents the methodology of our review.

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Systematic review – definition

A systematic review uses explicitly defined, *a priori*, methods to identify, select, appraise and analyse relevant data aimed at reducing the risk of bias. They provide a more objective summary of the available evidence compared with traditional literature reviews [8–10], which improves the reliability and accuracy of conclusions. Systematic reviews provide a good evidence base to inform practice, policy-making and research.

Methods

The main objective of this systematic review is to evaluate the effect of specific nutrients, either singly or in combination, on the prevention of cognitive decline, dementia and AD, and the treatment of AD. The review was planned, conducted and will be reported according to published guidelines, including those issued by the Cochrane Collaboration [11] and the QUORUM guidelines [12].

Identification and retrieval of studies

Electronic databases: PubMed, EMBASE and Cochrane Collaboration (accessed July 2007) were searched to identify potentially relevant studies. The search terms used included both Medical Subject Headings and free text terms. Neurocognitive search terms included 'Alzheimer's disease', 'dementia', 'cognitive decline' and 'cognitive impairment'. Nutrient search terms included the common and chemical names for the dietary factor of interest. The following nutrients were included in the searches : dietary fats, fatty acids, omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, Mediterranean diet, B vitamins (including B1, 2, 3, 5, 6, 7, 9, 12), vitamin C, vitamin D, vitamin E, choline, lecithin, phosphatidylcholine, ubiquinone, selenium, carotene, flavonoids, lycopene, coenzyme Q10, zinc, magnesium, and manganese. The neurocognitive and nutrient search terms were combined with a search strategy for identifying both randomized and non-randomized controlled studies and prospective cohort studies. Bibliographies of identified trials and previously published Cochrane and other systematic review articles were hand-searched for further relevant references.

Study selection criteria, data extraction and outcome measures

Studies were included based on rigorous inclusion and exclusion criteria (see Table 1). Human studies (double-blind, placebo-controlled randomized and non-randomized trials and prospective cohort studies) were

Table 1 Criteria for inclusion of studies into the systematic review

Selection criteria	Inclusion criteria	Exclusion criteria
Population	All human studies All age groups Nutritional status (well-nourished or malnourished) Cognitive status (normal or evidence of decline) Documented clinically accepted method of diagnosis of (probable) AD, dementia or MCI	Animal data
Treatment and prevention	All studies that focused on specific nutrients (single or in combination) Route of administration – oral or enteral	
Study type	Prospective cohort Randomized clinical trial Non-randomized clinical trial	Case–control study Case study/report Cross-sectional study Open-label study
Outcome measures	Cognitive function (e.g. improvement in MMSE, ADAS-cog etc.) Behaviour (e.g. reduced aggression, depression, anxiety etc.) Activities of daily living (ADLs) Quality of life (e.g. improvement in well being, mood etc.) Biochemical parameters (e.g. serum vitamin status etc.) Development/diagnosis of AD/MCI	

MCI, mild cognitive impairment; AD, Alzheimer's disease; ADL, Activities of daily living; MMSE, mini-mental state examination; ADAS-cog, Alzheimer's Disease Assessment Scale Cognitive subscale.

included that focused on the role of both single and combination nutrient interventions in the prevention of cognitive decline and the treatment and prevention of AD. Cross-sectional, case–control and open-label studies, case reports and data from animal studies were excluded. No other restrictions were placed on studies with regard to year of publication, publication format, language (providing an English abstract was available) and source.

Subjects eligible for inclusion included participants which were healthy older people, people with cognitive impairment/decline or people with any type of dementia (including vascular dementia) or AD, regardless of nutritional status. Where controlled trials enrolled patients with dementia or AD, the criteria used to confirm a diagnosis of AD was recorded. These diagnostic criteria included those of the International Classification of Diseases (ICD-10), the Diagnostic and Statistical Manual of Mental Disorders [13] and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) [14]. The diagnosis of MCI was by the clinical criteria of Petersen *et al*., 1999 [15].

Following the identification of potentially relevant studies based on title and abstract, full articles were obtained and independently evaluated by two researchers. Disputes regarding eligibility were referred to the author panel. A pre-determined data extraction table was designed to capture data about the study-design, number and characteristics of the patients and the outcomes of interest. For prospective cohort studies, the duration of follow-up, the number of incident cases of dementia or AD and the confounding factors adjusted for in any analysis were extracted. For RCT and non-randomized trials, details of the dietary intervention, such as the dose, frequency, route of administration and duration of therapy, adverse events and length of follow-up were recorded. The data required for outcomes reported as continuous data such as scores for quality of life (QoL) or cognitive function measurement scales were the mean change from baseline, the SD and the number of patients for each treatment group at each assessment.

The main outcome measures included in the analysis were measures of cognitive function, behavioural disturbance, activities of daily living (ADL), QoL, development/diagnosis of AD and MCI and biochemical parameters.

Quality assessment

The methodological quality of individual studies was assessed according to the guidelines set out by the Cochrane Collaboration [11]. Considering controlled trials; randomization (method of generation and concealment of allocation), blinding of observers/participants to treatment allocation and loss to follow-up (areas that have some association with biased estimates of treatment effects) were graded as adequate, inadequate or unclear to combine relevant 'high-quality' studies in the meta-analysis. The quality of cohort studies was assessed through assessment of potential selection bias of participants, the confounding variables that were controlled for, the completeness of follow-up and whether any blinding was reported.

Data analyses

Meta-analyses were undertaken to estimate overall treatment effects for trials considered to be similar enough to combine. Separate meta-analyses were undertaken for each treatment comparison and for each outcome with sufficient data. For continuous data (e.g. psychometric test scores and QoL scales), results were summarized across studies using weighted mean

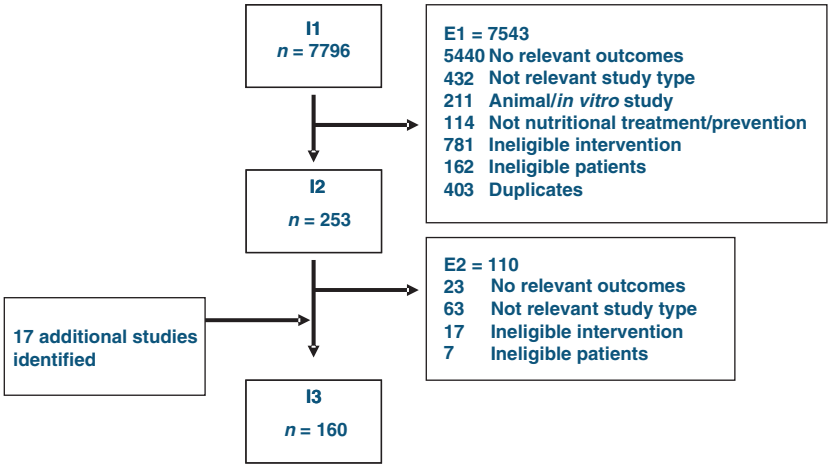

Figure 1 Results from the search strategy. The initial search strategy generated 7796 studies (I1) which were refined to 253 (I2) studies based on exclusion criteria found in the title/abstract of the manuscript. These studies were hand searched in full and a further 110 studies (E2) were excluded. An additional 17 studies were identified in the hand search resulting in 160 studies (I3) that met our inclusion criteria.

differences with 95% confidence intervals. For outcomes reported in different studies using different measurement scales, pooling of studies was conducted using the standardized mean difference if the same clinical phenomenon was measured. For dichotomous outcomes, results were expressed as risk ratios or risk differences and pooled using the Mantel-Haenszel fixed-effects method. A number of cohort studies reported dietary intake or serum concentrations of nutrients according to distribution properties, e.g. quartiles or quintiles. In order to facilitate the combination of such studies in a meta-analysis, the highest versus lowest category values were used from each study.

Testing for heterogeneity between trial results was conducted using the chi squared test. If significant heterogeneity was detected ($P < 0.1$) and the rationale for producing a pooled effect was sound, random effects estimates were calculated using DerSimonian and Laird methods. The I^2 statistic was also calculated to describe the proportion of variability in effect estimates because of heterogeneity rather than chance. A value of $> 50\%$, suggesting substantial heterogeneity, was further explored. If heterogeneity was detected, pre-specified sensitivity and sub-group analyses were performed to explore reasons for the heterogeneity (if sufficient studies were available).

Search results

The search strategy identified approximately 8000 studies. These were refined to 160 that met inclusion criteria; of these, 91 were RCT and 69 were prospective cohort studies (Fig. 1). Preliminary results of the review were presented at the ADI symposium in Caracas. Full results of the systematic review evaluating the strength of the totality of the evidence linking nutrition to cognitive decline, dementia and AD are expected to be published in 2009.

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Conflicts of interest

DRG has acted as a paid consultant and speaker for Nutricia; JR is an employee of Litmus MME who have been appointed by Nutricia to assist in the development of this manuscript; LS has acted as a paid consultant to Abacus and received funding for carrying out this work; BV has received funding and/or consultancy from Chiesi, Neurochem, Nutricia, Wyeth and Nestlé; PJW has acted as a paid consultant and speaker for Nutricia; ADD declares no conflicts of interest.

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