

Can nutrition support healthy cognitive ageing and reduce dementia risk?

Amy Jennings and colleagues describe the evidence and potential for food and food bioactive components to reduce the population prevalence of dementia

Around 50 million people worldwide have dementia, the main form of which is Alzheimer's disease. Dementia is a major cause of disability and dependency in older adults and, owing to expanding and ageing populations, its prevalence is expected to almost triple by 2050. This increase is being partly offset by decreasing age standardised dementia rates in some high income countries, attributed to more years of education and improved cardiovascular health.¹ In England and Wales, dementia is the first and second leading cause of death in women and men, respectively, responsible for 16.3% and 8.7% of total mortality in 2017 (www.ons.gov.uk). Almost two thirds of cases of dementia are in women. The cause of this difference between the sexes is poorly understood.²

Interventions to improve cognition and reduce dementia risk

No licensed drugs are available that prevent or reverse dementia. For Alzheimer's disease four drugs are used to treat symp-

oms temporarily (donepezil, rivastigmine, galantamine, and memantine). Therefore, behaviour which prevents or delays progression of neuropathology and brain vascular dysfunction could help to reduce the individual risk and population burden of the disease. The 2014 report, "The trajectory of dementia in the UK—making a difference," estimated that a two or five year delay in the onset of dementia would reduce the number of people with the disease in the UK by 19% and 33%, respectively, by 2050.³ In a US based analysis, Brookmeyer and colleagues predicted that interventions associated with a five year delay would almost halve cases of dementia over 50 years.⁴

It is estimated that about one third of cases of Alzheimer's disease worldwide are attributable to modifiable risk factors,⁵ many of which are nutrition and lifestyle dependent (depression, mid-life obesity, mid-life hypertension, and type 2 diabetes). Cardiometabolic health is a major determinant of age related cognition function and risk of dementia. Research into the role of nutrition in age related cognitive decline is in its relative infancy compared with other chronic conditions, such as cardiovascular diseases, type 2 diabetes mellitus, osteoporosis, and gastrointestinal disorders.

Although the results are not fully consistent,⁶ a growing body of prospective cohort evidence shows that bioactive components of food are associated with a reduced risk of dementia.^{7,8} Much of the research has considered dementia as a composite, despite the recognition that owing to differences in pathology, dementia subtypes (eg, Alzheimer's disease, vascular dementia, dementia with Lewy bodies) are probably influenced by differing dietary factors. Furthermore, a large retrospective cohort study⁹ has shown that behaviour, including a healthy diet, partly mitigates the penetrance of a high dementia genetic risk score. Model systems have provided insight into the potential underlying molecular and physiological mechanisms for the associations observed, including

improved cardiometabolic health and brain perfusion, and direct effects within the brain on neuronal function, energy metabolism, and β amyloid processing.

The randomised controlled trial evidence is more limited and less convincing,^{7,10} with cognition and brain volume (as assessed by MRI) as the main study endpoints, and few primary prevention randomised controlled trials with incident dementia as an outcome measure.

Nutrition and cognition

Some evidence suggests that individual food bioactive components protect cognitive health (for review see Scarmeas et al⁸), including B vitamins, antioxidant vitamins, selenium, vitamin D, medium chain triglycerides, and long chain omega-3 fatty acids (see supplementary table on bmj.com). This evidence is not conclusive, however. Any effects of intervention with such individual components are most likely to appear after long term exposure, and in those with a low baseline habitual intake. Evidence that nutrition has a beneficial effect on brain function is stronger for healthy dietary patterns, probably because the synergistic effect of several bioactive components affects many physiological processes and signalling pathways underlying cognitive function and decline. Intuitively, one would predict that the effect of nutrition would be more evident in people who are still cognitively healthy or prodromal, rather than in those with diagnosed dementia, where significant neuronal loss has already occurred, but this has not been rigorously tested.

Here we focus on fish/the omega-3 fatty acid docosahexaenoic acids (DHAs), ketogenic interventions, and a plant based dietary pattern (eg, Mediterranean diet) as approaches to nutrition with a strong potential to mitigate age related cognitive decline. The state of advancement of knowledge and inconsistencies in these areas provide insight into the research approaches used and the challenges encountered in confirming nutrition-cognition causal relations, especially during ageing.

KEY MESSAGES

- Global prevalence of dementia is predicted to almost triple by 2050 and no current treatments are effective
- Improved eating behaviour could reduce the risk and population prevalence of dementia
- Owing to dementia's multifactorial aetiology, multiple dietary components that target several physiological pathways and risk factors simultaneously are needed
- Changes to dietary patterns and foods (rather than single dietary components) therefore hold most promise to meaningfully improve cognition
- Randomised controlled trials with robust validated cognitive outcomes are needed to support the prospective cohort evidence, establish efficacy and effect size, and inform public health policy

Omega-3 fatty acids and improved brain function

Oily fish, which includes salmon, mackerel, herring, fresh tuna, and sardines, are the almost exclusive dietary source of the long chain n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid (DHA). Algal oil capsules provide a vegan source of DHA. The brain is highly enriched in DHA, which constitutes 15% of brain lipids compared with less than 5% in most other tissues.¹¹ The role of DHA in the developing fetal and infant brain is widely accepted. In prospective cohort studies, high fish and DHA intake has been consistently associated with improved cognitive health in older age, with a 10-30% reduced risk of Alzheimer's disease and death, brain atrophy, and cognitive decline, and effect sizes equivalent to two to four years of ageing¹²⁻¹⁶; there is some indication of greater effects in women.¹⁵ In a meta-analysis of 21 cohort studies, a 100 mg increment of dietary DHA was associated with lower risks of dementia (relative risk 0.86, 95% confidence interval 0.76 to 0.96) and Alzheimer's disease (0.63, 0.51 to 0.76).¹⁴ Fish is also a source of multiple nutrients needed by the brain, including vitamin B₁₂, selenium, and vitamin D, which may contribute to the observed cognitive benefits. Thus, where possible, fish itself rather than fish oil supplements is recommended as a source of DHA.

For a dietary component such as DHA/fish, which could be considered a signature of an overall healthy diet (such as a Mediterranean-style diet discussed below) and healthy behaviour, the possibility of residual confounding should be considered, as some of the cognitive benefits associated with DHA seen in prospective cohorts could be due to a yet unknown factor associated with intake,¹⁷ and the benefits associated with eating fish and DHA could be biased.¹⁸

A number of randomised controlled trials have reported mixed findings with DHA supplementation over periods of up to three years (see supplementary data). DHA is one of the bioactive ingredients in Souvenaid (Fortasyn Connect) medicinal food, designed to support cognitive ageing. In the LipiDiDiet trial, Souvenaid had no effect on the primary outcome measure, but was associated with an improved clinical dementia rating score and reduced hippocampal (a main brain region affected in Alzheimer's disease) atrophy.¹⁹

Response to DHA interventions is heterogeneous and may partly depend on DHA and cognitive status at baseline.

Cognitive benefits are reported for healthy younger adults²⁰ and in mild cognitive impairment,²¹ in contrast to those with more advanced disease.²² Early indications are that *APOE4* carriers (25% of white populations), and particularly older women with the *APOE4* variant, may have lower brain DHA uptake and status, and would benefit from higher dose DHA supplementation.^{2,23,24} For DHA and other dietary components, several variables need to be considered, including delivery to the brain and time taken to reach a steady state, and whether the cognitive benefits are direct effects on brain structure, perfusion, or metabolism, or an indirect effect attributable to, for example, cardiometabolic health. Brain DHA half life is estimated to be 2.5 years,²⁵ and thus supplementation periods of at least a year are probably needed to detect the cognitive benefits associated with DHA enrichment of neuronal cells, and effects on β -amyloid and tau protein metabolism and synaptic plasticity.^{2,26}

Brain glucose use, ketones, and cognitive health

One of the challenges facing the ageing brain is a chronic deficit in brain glucose uptake. Cognitively healthy older adults have about 7-8% lower brain glucose uptake than younger adults, a decline accentuated in mild cognitive impairment (the prodromal phase of Alzheimer's disease) and even more so in Alzheimer's disease itself.²⁷ Although low brain glucose could be a consequence of the disease process, two facets of the declining glucose uptake, brain cell loss, cognitive decline continuum suggest that this interpretation should be reconsidered. Firstly, brain glucose uptake is already lower in those at risk of Alzheimer's disease (that is, older age but still cognitively normal, carriers of the presenilin mutation or *APOE4*, or type 2 diabetes) but *before* their cognition declines.²⁸

Secondly, studies with positron emission tomography imaging and a ketone tracer (¹¹C-acetoacetate) show that, unlike glucose, brain ketone uptake is normal during ageing, mild cognitive impairment, and Alzheimer's disease.²⁹⁻³¹ Ketones are the brain's second most important fuel and, as for glucose, brain ketone uptake is an active, transporter mediated process. Hence, many of the brain cells in which glucose metabolism is deteriorating owing to age or Alzheimer's disease are not apoptotic (or dead) because they can still metabolise ketones. Rather, they are

gradually becoming energy (glucose) starved, but perhaps their function could be revived or maintained by ketones, an emerging therapeutic concept called "brain energy rescue".³²

Under normal circumstances, glucose supplies about 95% of the brain's fuel. It is, however, effectively replaced by ketones (β -hydroxybutyrate and acetoacetate) when dietary carbohydrate or total dietary energy is limited. Furthermore, when a ketogenic supplement is included in the diet, the brain of someone with mild cognitive impairment or Alzheimer's disease uses ketones in direct proportion to the increased ketones provided by the circulation, thereby sparing brain glucose use.^{33,34}

Recent experimental clinical studies have shown that brain energy rescue with ketones is associated with improved cognitive outcomes in both mild cognitive impairment and Alzheimer's disease. These studies used either a very low carbohydrate (ketogenic) diet³⁵⁻³⁷ or 20-30 g/day of ketogenic medium chain triglyceride supplement.^{34,38,39} With ketone positron emission tomography imaging, two of these studies showed that not only did ketones access the brain of someone with mild cognitive impairment³⁷ but that improvement on several cognitive tests was directly proportional to the rise in plasma ketones,³⁴ implying a direct mechanistic link between restoration of brain energy levels by ketones and the improved cognitive performance. Ketogenic interventions may also be disease modifying because preclinical and clinical reports show that the neuropathological process involving accumulation of the dementia associated proteins, amyloid β and phosphorylated tau, can be partially blocked by ketogenic supplements.^{37,40,41} These results are encouraging but compliance is low with ketogenic diets, and ketogenic medium chain triglycerides can cause gastrointestinal discomfort. Thus more work is needed to optimise ketogenic interventions (dose, duration, formulation) and test them in larger randomised controlled trials in order to convincingly assess their efficacy in improving cognitive outcomes in people with mild cognitive impairment or Alzheimer's disease. Ketogenic interventions may indirectly affect cognitive outcomes, in part, by improving insulin sensitivity or stimulating weight loss; they would also be predicted to be more efficient in slowing down Alzheimer's disease if combined with exercise.⁴² Given the emerging evidence

for the cardiometabolic safety of the ketogenic diet and the growing interest in its use to treat type 2 diabetes,⁴³ a long term controlled intervention assessing its effect on cognitive outcomes and risk of Alzheimer's disease is warranted.

Dietary patterns and cognitive health

Recent research has moved away from the reductionist approach to nutrition, health, and chronic disease,¹⁷ and focused on the effect of dietary patterns, such as the Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension) diet, and the hybrid MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet. Additionally, the World Health Organization and Public Health England have advocated whole diet approaches to delay or prevent cognitive decline.^{7 44} A Mediterranean diet is high in fruits, vegetables, olive oil, whole grains, unsaturated fatty acids, and fish, with restrictions of red meat, and moderate but regular drinking of alcohol. A meta-analysis of 34 168 participants showed that higher adherence to a Mediterranean diet was associated with a 21% reduced risk of developing cognitive disorders and a 40% reduced risk of Alzheimer's disease.⁴⁵ In a recent analysis of the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk cohort, the global cognitive benefit of high versus low adherence to a Mediterranean diet was equivalent to 1.7 fewer years of cognitive ageing.⁴⁶

Numerous foods in modern Western-style diets are not traditionally included in a Mediterranean diet, such as high fat dairy products, processed meats, carbonated drinks, sweets, and pastries. The PREDIMED, MIND, and DASH diets are Mediterranean-style diets and all three improved cognitive outcomes,^{47 48} with respectively a 53%, 54%, and 39% lower incidence of Alzheimer's disease after 4.5 years.⁴⁹ A multidomain lifestyle intervention trial (FINGER), which included modified eating behaviour as one of four concurrent interventions, improved cognitive outcomes. After two years, a 25% improvement in global cognition (as assessed by the neuropsychological test battery), and higher executive function (150%) and processing speed (89%) was evident in the intervention versus control group.^{50 51} These findings indicate that whole diet approaches that encourage Mediterranean-style elements and discourage energy dense foods typical of a Western-style diet are beneficial for cognitive health. Although

the PREDIMED study reported a lower prevalence of mild cognitive impairment after a Mediterranean diet,⁵² longitudinal randomised controlled trials, with incident mild cognitive impairment/Alzheimer's disease as the primary end point, are still lacking.

The totality of evidence supports the protective effect of adherence to diets rich in whole foods for dementia and cognitive function, but there are inconsistencies within and between diets.⁴⁵ Contradictory findings may be due to the geographical region, with a recent systematic review reporting that 80% of cohort studies conducted in Mediterranean regions showed significant associations with cognitive health, compared with only 50% in non-Mediterranean regions.⁵³ Possible reasons for this geographical disparity are firstly, diet adherence scores may reflect different food patterns in Mediterranean versus non-Mediterranean countries—for example, olive oil, fish, and legumes are more commonly eaten in Mediterranean regions; secondly, adherence scores do not consider foods reflective of Western-style diets in non-Mediterranean regions; or, thirdly, in Mediterranean regions the Mediterranean diet score is “capturing” a lifestyle with characteristics protective of cognitive decline, including increased social interactions when eating, and physical activity.^{54 55}

Heterogeneity in dietary response could also be due to individual differences in nutrient metabolism. Beneficial changes in the gut microbiome, together with taxonomic shifts in microbiota composition, have been seen in those following plant based diets.⁵⁶ A higher intake of plant based foods is associated with lower trimethylamine oxide levels and increased faecal short chain fatty acids, fibre degrading microbiota, and gut microbial diversity.^{57 58} These gut microbial changes are linked to the gut-brain axis. Thus short chain fatty acids—in particular, butyrate, enhance brain derived neurotrophic factor expression, and trimethylamine oxide is linked to reduced expression of synaptic plasticity related proteins, including N-methyl-D-aspartate-receptors, both important factors for learning and memory.^{59 60} If the microbiome can affect the gut-brain axis then diet induced changes in the gut microbiota, through plant based or Mediterranean diets associated with higher consumption of fibre, polyphenols, and probiotics could affect development of cognitive impairment. Equally, microbiome

speciation and metabolism could influence the cognitive response to dietary change and may emerge as a tractable target for interventions.

In addition to the nutrients needed for brain function, the reduced content of refined sugars in Mediterranean-type diets may also help to improve glucose tolerance. This would help the ageing brain meet its energy needs (both glucose and ketones) by reducing creeping insulin resistance during ageing, thereby improving the chance of maintaining optimal cognition.

Conclusions

Prospective cohort evidence suggests that a change in eating behaviour may delay the onset of dementia, possibly by several years. The trial evidence to date is reliant on cognitive or other surrogate markers of dementia risk with often, uncertain prognostic value, and lacking sensitivity and specificity to dementia subtypes. Longitudinal randomised controlled trials with robust cognitive outcomes are still needed, ideally, with incident disease (either dementia or mild cognitive impairment) as the primary outcome. Metabolic and preclinical studies will help to provide insights into mechanisms so as to collectively provide the evidence needed to make causal inferences, fully establish efficacy, and inform policy.¹⁷ Randomised controlled trials are often expensive and long term. They should be supported by validated imaging and biochemical biomarkers of disease, both to select at risk and responsive subgroups, and to screen potentially effective interventions.

Are we yet in a position to provide dietary guidelines specifically to promote cognitive health and reduce the risk of dementia in later life? Global and national dietary macronutrient (particularly fat and carbohydrate) and food guidelines (eg, eating fruit and vegetables and reducing salt) are, in large part, based on the management of cardiometabolic risk (obesity, cardiovascular diseases, and type 2 diabetes mellitus). Given the established importance of cardiometabolic health on cognitive function (especially in mid-life), greater adherence to existing dietary recommendations is likely to reduce the incidence of dementia. To develop dietary guidelines specifically focused on prevention of dementia or improving mild cognitive decline, further research is needed to gain insight into which dietary strategies most effectively improve neuronal function and reduce neuropathology.

Box 1: Controversies and research gaps

- Strong associations between dietary patterns and food bioactive components in prospective cohort studies and experimental preclinical studies are often not replicated in human randomised controlled trials
- Randomised controlled trial design should assess whether the intervention indirectly affects systemic processes, such as cardiometabolic function or inflammation, or whether it directly affects neuronal function, brain energy metabolism, or the “hallmarks” of dementia, such as amyloid β and tau protein metabolism. The time and dose needed to produce meaningful increases in brain function must be considered in the trial design to preclude the risk of a type 2 error (false positive findings)
- Longitudinal follow-up randomised controlled trials are needed, ideally with incident disease as the primary outcome measure
- It is unclear when to intervene in the cognitive course from health to diagnosed dementia, and which interventions are best suited to dementia subtype and disease progression
- Little is known about the overall effect of neuropathology on the brain uptake and metabolism of dietary components
- Identification is needed of targeted approaches to nutrition for at risk subgroups, such as women with the *APOE4* gene or insulin resistant individuals

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