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Nutrition, Aging and Cognitive Function

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The aging population is growing and the risk for malnutrition and impaired cognitive functioning increases with advancing age. In the past few decades, it has become clear that many constituents of the diet, from macronutrients to micronutrients, influence brain function. Such influence on brain function in turn has an effect on mental health and performance, and subsequently on behaviour, social activities, and independence, especially in elderly people. Thus, a vicious cycle with more nutritional deficiencies and more cognitive problems is likely to develop. Cognitive decline and impaired mental well-being are strong predictors for dementia and depression, respectively. Since no curative approaches for these diseases in old age are currently available there is a need for early interventions in order to prevent these conditions from developing. Typically, preventive strategies focus on modifiable factors, including the diet. So far most of the available evidence comes from epidemiological studies. For example, cross-sectional studies have shown that low blood levels of certain nutrients such as folate, cobalamin and omega-3 fatty acids are associated with impaired cognitive functioning in elderly persons[1-4]. Moreover, prospective studies reveal that persons with suboptimal nutritional status might be at a higher risk for development of cognitive impairment[5-7]. To confirm causality, these findings need to be invesiged in clinical trials.

According to a recent systemic review[8] of available clinical trials, nutritional supplements may indeed improve the cognitive function of elderly persons. However, additional well designed trials are needed to identify what components of the diet are critical for cognitive function. Although a variety of dietary factors are believed to be vital in the maintenance of mental health, this review focuses on dietary factors which have been the focus of recent research: namely the B-vitamins, Omega -3 fatty acids and multivitamin/mineral supplements.

B-vitamins

Cobalamin (vitamin B12) deficiency is common in elderly people and results from either the inability to release cobalamin from food proteins (food malabsorption) or intestinal malabsorption, or inadequate intake[9-11]. Cobalamin is involved in the one-carbon metabolism where it plays a role in the transfer of methyl groups and methylation reactions that are important for the synthesis and metabolism of neurotransmitters and phospholipids in the central nervous system[12]. Moreover, cobalamin is also required for nucleic acid synthesis and haematopoiesis[11], and the metabolism of fatty acids and amino acids in the mitochondrial citric acid cycle[13]. In addition to causing anaemia, cobalamin deficiency has been linked with a variety of neuropsychiatric symptoms, such as neuropathy, myelopathy, dementia, depression, memory impairment, and cerebrovascular diseases[14,15]. While prolonged cobalamin deficiency may eventually result in irreversible neurological damage and cognitive impairment[16,17], early stages of cobalamin deficiency-detected by increased concentrations of plasma total homocysteine (tHcy) and methylmalonic acid (MMA)[15] and decreased concentrations of holotranscobalamin (holoTC)[18] - may result in milder forms of cognitive impairment in the absence of anaemia[19,20].

Several cross-sectional and prospective studies in both healthy and cognitively impaired elderly people have reported associations between impaired cobalamin status and cognitive performance[3,21,22]. So far, several intervention studies of cobalamin supplementation and cognitive performance have been performed[17,23-33], of which only three were randomized placebo controlled [30-32]. According to a recent review of published trials, evidence of efficacy of cobalamin in improving the cognitive function of people with dementia and low serum B12 levels is inconclusive[22]. The main reasons for this conclusion are; the short duration of these studies, different inclusion criteria with respect to cognitive status and cobalamin status, different doses and administration routes of cobalamin supplements, and use of global instead of sensitive neuropsychological tests to assess cognitive function. Recent trials so far lead to similar conclusions[32] for cobalamin supplementation or for cobalamin and folic acid[34] supplementation. Unfortunately none of these studies goes beyond duration of six months, hence, not addressing the potential for beneficial effects of longer term supplementation.

With cobalamin, folate is also one of the factors involved in methylation processes that are essential for the maintenance of normal brain function. Folate acts as a donor of methyl groups in a reaction catalysed by the enzyme methionine synthase to produce methylcobalamin needed for methylation of homocysteine to methionine. Folate deficiency therefore leads to an increase in blood and intracellular levels of homocysteine. Previous studies have reported an inverse association between plasma total homocysteine levels and simultaneously assessed cognitive function[2,35-38]. Noteworthy are findings from a prospective study including 1,092 subjects without dementia. After a median follow-up of 8 years an increased plasma homocysteine level turned out to be a strong, independent risk factor for the development of dementia and Alzheimer's disease[39]. Of particular interest are also findings from the Rotterdam Scan Study, which demonstrated an association between homocysteine levels, the risk of silent brain infarcts[40] and cognitive decline[41]. Though a Cochrane review of all available clinical trials suggests that folate supplementation has no effect on cognitive function in later life[42], a recent Dutch trial including 818 individuals aged 50-70 years old, is the first to demonstrate that folic acid may slow down cognitive decline (manuscript submitted for publication and Presented at the International Conference on the Prevention of Dementia, Alzheimer Association, Washington DC, 2005). This study underpins the importance of the longer study duration, as subjects complied for a period of three years to the use of an additional 800 micrograms of folic acid per day.

Omega-3 Fatty Acids

The idea that long-chain omega-3 fatty acids play a role in human health has been investigated for several years. The prominence of n-3 fatty acids in the central nervous system is suggestive for their role in mental health and brain function. The dry weight of the brain constitutes of 56% lipids, and a large portion of these lipids consist of polyunsaturated fatty acids, in particular docosahexaenoic acid (DHA). DHA is a major structural component of neuronal membrane phospholipids, whereas there is only a small amount of eicosapentaenoic acid (EPA) in neural tissue, which plays an important role in nerve and signal transmission. It is therefore to be expected that they are qualitatively and quantitatively very important in brain function. Moreover, the brain fatty acid profile appears to be sensitive to dietary modifications. If omega-3 fatty acids in the diet affect the fatty acid composition of the human brain, it is possible that this consequently influences brain function.

Dietary sources for Omega-3 fatty acids are vegetable oils (containing α-linolenic acid [ALA]) and foods from marine origin, in particular fatty fish (containing EPA and DHA). EPA and DHA may also be synthesized through elongation and desaturation of ALA from vegetable sources, but the efficiency of this conversion is limited in humans. It is estimated that only 5-15 % of ALA is ultimately converted to DHA[43]. Evidence for a role of EPA-DHA in mental processes in older ages is mostly emerging from observational[44,45] and epidemiological studies[46-49]. A population-based study showed that a decreased level of EPA-DHA in cell membranes appeared to be associated with cognitive decline in elderly people[50]. Furthermore, an inverse relationship between fish consumption and the risk of dementia was observed in both the Rotterdam

and the Zutphen Elderly studies[51] and in the Rotterdam Study plasma fatty acid composition was related to depression, not secondary to inflammation, atherosclerosis or other confounders[52]. Taken together the current evidence strongly suggests that EPA-DHA is beneficial for mental health, but again there is a need for well designed intervention studies. No such studies have been found so far in view of a scheduled Cochrane review entitled 'Omega 3 fatty acid for the prevention of dementia'[53]. However, it is envisaged that within the next few years, several studies will be concluded.

Multivitamin/mineral Supplements

Undernutrition is a continuing source of concern among the elderly (Manders et al, submitted). Several systematic reviews in older people[54-56] suggest that nutritional supplementation has beneficial effects on nutritional and mortality outcomes. None of these reviews could reveal an effect of nutritional supplementation on functional outcomes. This has mostly been ascribed to methodological defects in the reviewed studies. A recent meta-analysis suggests that any beneficial effect would be limited to hospitalized and institutionalized elderly patients[57]. Providing supplements to well nourished subjects would not be beneficial. So far most studies in institutionalized elderly could not show an effect of multivitamin/mineral supplementation on physical functioning probably due to a variety of reasons: e.g. the period of intervention might have been too short [58-60] or to the small number of participants in these studies[61,62]. However, two Dutch trials in institutionalized elderly people who received a nutrient dense drink did show a statistically significant and clinically relevant effect on cognitive performance in particular elderly people with low BMI[63]. Therefore, complete supplements may offer more to undernourished elderly people than just improvement of their nutritional status.

Conclusion

The evidence from epidemiological studies is strongly suggestive of a link between diet and cognitive function in older people. Some proof of the effectiveness of supplementation is emerging. So far the evidence is limited due to methodological challenges in establishing a causal effect between diet and cognitive performance. These limitations include; the study population characteristics, nutrients and doses tested, duration of the study, and the assessment tools of cognitive performance.

Future trials should probably be conducted in patients with (less than) mild cognitive impairment, because the window of opportunity for effective intervention may be as short as 1 year from the onset of medical symptoms, as Martin and colleagues[8] suggested. In addition, the duration of administration of the nutrient should be long enough to counteract reversible damage processes to the brain. In designing a trial, researchers should keep in mind which possible nutritional mechanism underlies their study. With respect to the outcome measures, the most ideal situation would be that researchers in the field could use one standard neuropsychological battery of sensitive tests. Comparing studies would thus become easier and more accurate.

The Whitehall-Robins Report is a Wyeth Consumer Healthcare Inc. publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.

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