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 **Foresight**

**Mental Capital and Wellbeing:  
Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-E18  
Nutrition and Cognitive Health**

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## Summary

The number of elderly people is increasing worldwide. A side-effect of this increased survival and longevity is a dramatic increase in cognitive impairment and age-related disabilities. Therefore, there is heightened interest in achieving better knowledge of the factors associated with cognitive decline and functional disability and how to prevent them, in order to improve the quality of life of older people. Many environmental factors may influence healthy ageing and specifically cognitive health. Among them, adequate nutrition may play a pivotal role. However, the impact of poor nutritional status on functional and cognitive declines is not well known in the elderly. Similarly, our knowledge of the impact of nutrition in human brain development is limited.

In this review, we examine current knowledge regarding the associations between specific nutrients and cognitive development and decline. Given space limitations, we focus on those for which most evidence is available, namely dietary fats, antioxidants, and B vitamins.

### 1. Dietary fat intake

Studies aimed at assessing the potential effects of dietary fat intake on cognitive function have focused on n-3 polyunsaturated fatty acids (PUFA). The most compelling reason for this interest comes from the fact that docosahexaenoic acid [22:6(n-3)] (DHA) is the most abundant n-3 PUFA in the mammalian brain. In addition, other mechanisms have been postulated to support a role for n-3 PUFA as an intervention tool for preventing age-related cognitive decline and dementia. These include its anti-atherogenic, anti-inflammatory, anti-oxidant, anti-amyloid and neuroprotective properties (Wainwright et al., 2006).

DHA levels in brain membrane lipids are altered by the type and amount of fatty acids in the diet. DHA can be obtained by direct consumption or from the metabolism of precursors such as  $\alpha$ -linolenic acid [ALA, 18:3(n-3)] and eicosapentaenoic acid [EPA, 20:5(n-3)].

Most of the research linking n-3 PUFA with cognitive functions has focused on early development and on ageing-related decline. Current knowledge will be presented separately on brain development and cognition in early life and on those studies focusing on late cognitive decline.

#### 1.1. *N-3 PUFA and early development*

Eilander et al. (2007) have evaluated published, randomised controlled trials (RCT) assessing the efficacy of n-3 PUFA supplementation during pregnancy, lactation, infancy and childhood on cognitive (and visual) development. With the exception of studies in term infants, the total number of RCT on this topic is still very limited, especially for supplementation in older children. It is difficult to directly compare studies, as they assessed cognitive development by many different outcome measures, and also had multiple differences in design that could influence the outcomes and interpretation. Thus, there is a large heterogeneity among studies. Based on the available information, the authors conclude the following:

- i. For pregnant and/or lactating women, there is suggestive evidence for a beneficial effect of DHA supplementation during pregnancy and lactation (or lactation only) on mental development and on longer-term cognition.
- ii. For pre-term infants, DHA and AA supplementation appears to have a beneficial effect early in life on cognitive development at >12 months of age.

- iii. For term infants, supplementing with long chain (LC) PUFA in high doses (100 mg DHA and 200 mg AA per day) provides hardly any evidence for beneficial effects on cognitive development.
- iv. For healthy children older than two, there is no evidence for beneficial effects on cognitive performance following DHA supplementation.

Taken together, the evidence for the potential benefits of n-3 PUFA supplementation is promising, but as yet inconclusive. Whereas there may be several methodological reasons for the observed inconsistencies, it is important to highlight that better knowledge of the genetic factors involved in dietary response could be used to resolve the current discrepancies and to generate practical and relevant tools to provide more personalised recommendations. Along these lines, the work by Caspi et al. (2007) provides proof-of-concept supporting this notion. It has been shown that breastfed children attain higher IQ scores than those not fed breast milk, presumably because of the fatty acids uniquely available in breast milk. Most interestingly, these authors show that the association between breastfeeding and IQ is moderated by a genetic variant in *FADS2*, a gene involved in the control of fatty acid pathways. This higher IQ could work through multiple biological and social factors to modulate the age-related cognitive decline observed decades later in life.

## 1.2. n-3 in the middle-aged and elderly

Support for the notion that higher fatty fish or marine n-3 PUFA consumption is associated with a reduced risk of impaired cognitive performance or dementia in middle-aged and elderly populations comes from a series of cross-sectional, observational and epidemiological studies (van Gelder et al., 2007; Kalmijn et al., 2004; Barberger-Gateau et al., 2002; Huang et al., 2005; Morris et al., 2003a; Morris et al., 2003b; Morris et al., 2005b). Several population-based studies that examined fatty acid composition of erythrocyte membranes or plasma n-3 PUFA levels also reported inverse associations between cognitive decline with age or Alzheimers' Disease (AD) risk and n-3 PUFA (Tully et al., 2003; Conquer et al., 2000; Kyle et al., 1999; Heude et al., 2003; Beydoun et al., 2007a; Beydoun et al., 2007b).

However, the evidence supporting an inverse relationship between n-3 PUFA intake and risk of dementia is not consistent, even within the same study population (Kalmijn et al., 1997; Engelhart et al., 2002b). Several other studies, using dietary information (Manzato et al., 2003; Solfrizzi et al., 2006) or plasma fatty acid measures (Laurin et al., 2003) failed to find significant associations between n-3 PUFA and cognition-related traits. This inconsistency may arise because the relation is present only in the absence of the apolipoprotein E  $\epsilon$ 4 (APOE  $\epsilon$ 4) allele as shown by Whalley and colleagues (2008). These investigators followed up 120 volunteers, born in 1936, at approximate ages of 64, 66, and 68 years. Moreover, their intelligence quotient at 11 years of age was available. At first follow-up, the researchers determined APOE genotype and measured the PUFA composition of erythrocyte membranes. Six cognitive tests were administered at all follow-ups. They related cognitive performance at 64 years and cognitive changes from 64 to 68 years to erythrocyte n-3 PUFA composition on recruitment and to APOE  $\epsilon$ 4 allele status. Cognitive benefits were associated with higher erythrocyte n-3 PUFA content but were significant only in the absence of the APOE  $\epsilon$ 4 allele. These data are evidence of a gene/environment interaction for cognitive ageing. They are relevant to the analysis of trials of n-3 PUFA supplements in cognitive ageing and dementia prevention, and they support heterogeneity in cognitive ageing and, possibly, in Alzheimer's disease. However, it is important to keep in mind the small study size and the fact that these investigators did not control for several other factors known to modulate interactions with the APOE locus, such as smoking, drinking, other dietary components, obesity and physical activity.

Interventional studies of n-3 PUFA in dementia are limited, tend to be small in numbers and of short follow-up duration (Terano, 1999; Yehuda, 1996). A Cochrane review (Lim et al., 2006) examined the evidence that n-3 PUFA supplementation prevents cognitive impairment and dementia in cognitively intact elderly persons and found no randomised trials that met the selection criteria. However, a more recent study (Freund-Levi et al., 2006) demonstrated that administering n-3 PUFA to patients with mild to moderate AD did not delay the rate of cognitive decline according to the Mini Mental State Examination (MMSE) or the cognitive portion of the AD Assessment Scale.

The current evidence suggests a protective effect of n-3 PUFA against dementia. However, until more data from randomised trials become available for analysis, there is no good evidence to support the use of dietary or supplemental n-3 PUFA for the prevention of cognitive impairment or dementia.

## **2. Antioxidants**

Brain ageing has been associated with a progressive imbalance between antioxidant defences and intracellular concentrations of reactive oxygen species, as exemplified by increases in products of lipid peroxidation, protein oxidation, and DNA oxidation (Dröge and Schipper, 2007). Therefore, dietary antioxidants may have beneficial effects by boosting antioxidant defences and preventing or delaying the ageing of the brain. Some observational data supports this hypothesis.

The dietary antioxidant that has received most attention has been vitamin E which functions as an antioxidant, scavenging toxic free radicals. Evidence that free radicals may contribute to the pathological processes of cognitive impairment including AD has led to interest in the use of vitamin E in the treatment of AD and Mild Cognitive Impairment (MCI). Moreover, epidemiological data lends some support to the association between higher intake of vitamin E from food and reduced risk of AD (Morris et al., 2005a, Morris et al., 2002, Engelhart et al., 2002a). However, other studies have found weak – or no – evidence of a protective effect of previous vitamin E intake on cognitive function (Dunn et al., 2007; Kang et al., 2008).

The evidence regarding the efficacy of vitamin E in the treatment of AD and prevention of progression of MCI to AD based on RCT has been reviewed by Isaac et al. (2000). Only two studies met their inclusion criteria (Petersen et al., 2005; Sano et al., 1997) and these showed no evidence of efficacy of Vitamin E in the prevention or treatment of people with AD or MCI. This is consistent with epidemiological data supporting an association with vitamin E from food rather than from supplements. In this regard, Morris et al. (2005a) suggest that various tocopherol forms rather than alpha-tocopherol alone may be important in vitamin E's protective association with AD. Likewise, the results of the cognitive sub-study of the Women's Health Study, a randomised, double-blind, placebo-controlled trial of vitamin E supplementation (Kang et al., 2006) reported that long-term use of vitamin E supplements did not provide cognitive benefits among generally healthy, older women.

McNeill et al. (2007) examined the effect of daily supplementation with 11 vitamins and five minerals on cognitive function in older adults in North East Scotland in order to assess the possibility that this could help to prevent cognitive decline. The results of this RCT provided no evidence for a beneficial effect of multivitamin and multimineral supplements on cognitive function. In the Canadian Study of Health and Aging, a population-based, prospective five-year investigation of the epidemiology of dementia (Maxwell, 2005), subjects reporting a combined use of vitamin E and C supplements and/or multivitamin consumption at baseline were less likely to experience significant cognitive decline during follow-up. Subjects reporting any antioxidant vitamin use at baseline also showed a significantly lower risk for incident vascular cognitive impairment. However, a reduced risk for incident dementia or AD was not observed.

### 3. B vitamins

Vitamin deficiencies could influence memory function and might contribute to age-associated cognitive impairment and dementia. In this section, we focus on the association between the B vitamins, namely vitamins B6, B12 and folate, and cognitive-related traits.

Vitamin B6 is involved in the regulation of mental function and mood. Vitamin B6 deficiency is associated with increase in blood homocysteine levels. Homocysteine is a risk factor for cerebrovascular disease and may also have directly toxic effects on neurons of the central nervous system. Hyperhomocysteinaemia has been suggested as a cause or mechanism in the development AD and other forms of dementia. Supplementation with B vitamins including vitamin B6 has been shown to reduce blood homocysteine levels.

Vitamin B12 is a water-soluble vitamin. It has been suggested that deficiency of this vitamin might contribute to age-associated cognitive impairment. Low serum vitamin B12 concentrations are found in more than 10% of older people, and a high prevalence of low serum vitamin B12 levels, along with other indicators of vitamin B12 deficiency, have been reported among people with AD.

Folates are essential components of the human diet. They are particularly important during the early development of the brain and, in later life, are involved in the methylation processes essential for maintaining normal brain function. Folate deficiency leads to an increase of homocysteine. High intraneuronal levels of homocysteine could disturb brain metabolism and cause cognitive impairment (La Rue et al., 1997).

Despite their important role in cognitive function, the value of B vitamins supplementation is unknown. Several systematic reviews of the effect of vitamin B6, vitamin B12 and folic acid supplementation on cognitive function have been performed and their conclusions are listed below.

Malouf et al. (2003a) reviewed the evidence from RCT that examined the efficacy of vitamin B6 supplementation in reducing the risk of older healthy people developing cognitive impairment, or in improving cognitive functioning of people with cognitive decline and dementia. The two trials included (Bryan et al., 2002; Deijen et al., 1992) found no evidence for short-term benefit from vitamin B6 in improving mood or cognitive functions.

Another review by Malouf et al. (2003b) examined the effect of B12 supplementation on cognitive function of demented and elderly healthy people in terms of preventing the onset or progression of cognitive impairment or dementia. This review included three RCT (De La Fourniere et al., 1997; Hvas et al., 2004; Seal et al., 2002) that showed no statistically significant evidence of a treatment effect of vitamin B12 supplementation on cognitive function. Therefore, the evidence for any efficacy of vitamin B12 in improving the cognitive function of people with dementia and low serum B12 levels is insufficient.

The same group (Malouf et al., 2003c) examined the effects of folic acid supplementation, with or without vitamin B12, on elderly healthy and demented people, in preventing cognitive impairment or retarding its progress. Four randomised, controlled trials (Bryan et al., 2002; Fioravanti et al., 1997; Sommer et al., 2003; Clarke et al., 2003) fulfilled the inclusion criteria for this review. Analysis of these trials found no benefit from folic acid with or without vitamin B12, in comparison with placebo, on any measures of cognition or mood for healthy or cognitively impaired or demented people. Folic acid plus vitamin B12 was effective in reducing serum homocysteine concentrations. The available studies are limited in size and scope but provide no evidence that folic acid, with or without vitamin B12, has a beneficial effect on cognitive function or mood, either of healthy or cognitively-impaired older people.

Two other, recent reviews related to B vitamins and cognition have been published (Balk et al., 2007; Raman et al., 2007). The first of these focused on RCTs (Balk et al., 2007) of vitamins B6 and/or B12 and/or folic acid supplementation with cognitive function outcomes, whereas the second (Raman et al., 2007) included longitudinal cohort and case-control studies of B vitamins and analyses of cognitive tests or AD. The evidence from the 14 trials included in this review does not yet provide adequate evidence of an effect of vitamin B6 or B12 or folic acid supplementation, alone or in combination, on cognitive function testing in people with either normal or impaired cognitive function, in agreement with the conclusion reached by Malouf et al. (2003c).

The systematic review of population studies carried out by Raman et al. (2007) aimed to evaluate the association between vitamin B6, vitamin B12, folate and cognitive function in the elderly. Considerable heterogeneity was found among B-vitamin-level thresholds, comparisons, and data analyses. These studies did not reveal an association of vitamins B6 and B12 blood concentrations with cognitive test performance or AD, nor was B-vitamin dietary intake associated with cognitive function. Higher plasma homocysteine concentrations were associated with poorer cognitive function. Although the majority of studies indicated that low blood folate concentrations predicted poorer cognitive function, data supporting this association were limited because of the heterogeneity in cognition assessment methodology, and scarcity of good quality studies and standardised threshold levels for categorising low B-vitamin status.

More recent population studies have added little to resolve the current ambiguities regarding the association of serum vitamin B12 and folate concentrations with cognition in old subjects. Tettamanti et al. (2006) measured serum vitamin B12 and folate concentrations and carried out cognitive and functional evaluations in 80-plus-year-old subjects. The findings of this Italian population-based study suggest that subclinical folate deficiency may represent a risk factor for the cognitive decline associated with ageing, that could contribute to the development of AD as well as other dementias.

Some support for those concerned with folic acid supplementation of the entire food supply comes from the work by Morris et al. (2007) that examined the relationship between serum folate and vitamin B12 status and anaemia, macrocytosis, and cognitive impairment in senior participants in the 1999-2002 US National Health and Nutrition Examination Survey. In seniors with low vitamin B12 status, high serum folate was associated with anaemia and cognitive impairment. However, when vitamin B12 status was normal, high serum folate was associated with protection against cognitive impairment.

The most recent RCT (Durga et al., 2007) is part of the FACIT trial in the Netherlands, designed to assess the effect of folic acid on markers of atherosclerosis and cognitive performance in subjects aged 50-70 years with raised plasma total homocysteine and normal serum vitamin B12 at screening. These investigators assigned 818 participants to 800 micrograms daily oral folic acid or placebo for three years. Folate concentrations increased by 576% and homocysteine concentrations decreased by 26% in participants taking folic acid compared with those taking placebo. The three-year change in cognition variables were significantly better in the folic acid group than in the placebo group. Therefore, in this study, folic acid supplementation significantly improved cognitive functions that decline with age.

#### **4. Dietary patterns and cognitive function**

The emerging picture is that observational studies tend to show significant association between specific nutrients (i.e. n-3 PUFA, folic acid, vitamin E) and cognitive function. However, when these nutrients are individually tested using RCTs, there is no support for a positive effect for any of them. One potential reason is that a nutrient needs to be consumed in the food matrix or within the synergy of a healthy dietary pattern. This is supported by cross-sectional studies showing that higher intake of most 'healthy' food categories, including those consumed as part of a Mediterranean diet, are associated with better

cognition (Scarmeas et al., 2006; Solfrizzi et al., 2007; Morris et al., 2006). Conversely, for some food categories (i.e. refined sugars, high cholesterol and trans fats) higher intake results in lower cognitive scores (Engelhart et al., 2002b).

## 5. Conclusions and future advances

The epidemiological evidence linking specific nutrients such as n-3 PUFA, B vitamins and antioxidants to cognitive health is enticing but inconclusive

1. Most of the randomised clinical trials conducted so far to test the effectiveness of dietary supplementation on cognition-related parameters are small and carried out over relatively short periods of time. Moreover, most of them did not support a benefit from supplementation. Therefore, future randomised clinical trials should consider the following:

- a. Selection of study populations with low intakes or status for the nutrient (where an effect might be possible) as distinct from volunteers with adequate intakes/status for the nutrient.
- b. Studies designed with:
  - i. sufficient power to detect an effect if one existed;
  - ii. appropriate dose and form of the nutrient and administration for a sufficiently long period;
  - iii. outcome measures sufficiently sensitive to detect effects of such interventions;
- c. To examine whole foods and dietary patterns over individual nutrients.

2. Many different instruments are used to test cognitive function and health. This complicates the comparison across studies and the use of meta-analysis. Therefore, standardisation and understanding of these instruments are needed in future studies.

3. The concept of individual response to diet (gene-diet interactions) needs to be incorporated as part of epidemiological and randomised clinical trials. This also includes consideration of more complex interactions involving genes, diet and gender.

4. In addition to genomics, other '-omics', namely, metabolomics, transcriptomics and proteomics need to be part of future studies. This will provide a much richer phenotype and the ability to identify mechanisms of action. These technologies should be able to inform about environmental factors (e.g. diet) and their physiological effects. Moreover, they will provide better tools for classifying individuals according their cognitive/disease status and better definition and specificity of the changes over time or induced by dietary or pharmacologic intervention.

5. Given the increase in prevalence of obesity and of the metabolic syndrome, it will be important to investigate to what extent obesity-related cognitive problems will outweigh the effects of specific nutrients.

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