A recent large intervention study has shown no effect of dietary doses of n3 fatty acids (FA) on global cognitive decline in coronary heart disease patients [1]. N3-FA, which include α-linoleic acid, eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) (Figure 1), have been subject of intense investigation in the recent years for expected benefits in delaying cognitive decline. Previous epidemiological and experimental animal studies suggested that deficiency in n3-FA, in particular DHA that is one of the most represented fatty acid in the brain, accelerates cognitive decline and increases the risk of developing AD [2-7]. With the Geleijnse’s trial, is it enough to suggest stopping investigation on n3-FA in the context of cognitive decline in man?

The disappointing results of the work of Geleijnse et al. [1] come after other clinical trials of EPA-DHA intake and cognitive function. Terano et al. [8] showed that 720 mg/d of DHA reduced the rate of cognitive decline over 3 and 6 months, but not over one year of follow up in 20 Japanese elderly patients who suffered a thrombotic stroke. In a 6-month trial, in 174 Alzheimer’s disease patients, no effect of EPA-DHA (2300 mg/d) on cognitive performance was found, except in a small subgroup with mild cognitive impairment [9]. Rogers et al. [10] found no effect of EPA-DHA (1500 mg/d) on cognitive function in 190 depressed U.K. adults after 12 weeks of treatment. In a 6-month trial, in 302 healthy Dutch subjects aged 65 years, EPA-DHA doses of either 400 mg/d or 1800 mg/d did not affect any of the cognitive domains studied [11]. Dangour et al. [12] assigned 867 subjects aged 70 to 79 years and without cognitive impairment to 700 mg of EPA-DHA (ratio of 2:5) or olive oil for 2 years. A large number of cognitive tests were applied, none of which was significantly influenced by treatment [12]. A recent well-conducted trial, enrolling 402 patients and designed to determine if treatment with DHA improved the symptoms and course of patients with mild to moderate Alzheimer disease, did not find treatment group differences on any of the primary or secondary outcomes despite elevations of plasma phospholipids and cerebrospinal fluid DHA [13]. It has also to consider that no relationship between serum n3-PUFA and AD or other forms of dementia was found in the Canadian Study of Aging and Dementia [14].

Taken together, these data should restrain the emphasis on beneficial effects of n3 fatty acids and help to shift towards little studied fatty acids. The intense investigation conducted with n3-FA contrasts with the paucity of studies concerning the effects of other FA in neurodegeneration and ageing, including the essential fatty acid linoleic acid (LA), which belongs to the n6 class of FA (Figure 1). The interest in n3-FA can be found in the seminal studies on anti-inflammatory actions opposed to n6-FA, which are thought of in a negative context because n6-FA are putative delivers of bioactive inflammatory eicosanoids, leading to a hugely popular theory of balance between proinflammatory n6-PUFA and anti-inflammatory n3-FA. In this context, the potential harmful effects of n3-FA associated with their sheer oxidizability, leading to the formation of bioactive docosanoids and neuroketals [15,16], has not usually been a matter of concern.

In spite of the popular, yet unproven, theory of “nonbeneficial” n6-FA, a recent clinical trial of linoleic acid supplementation in man showed that high-dose n6-FA intake did not cause any sign of inflammation or oxidative stress [17]. It is worthy to mention that linoleic acid has several beneficial effects - including lowering of blood pressure and blood cholesterol, and inhibition of platelet aggregation - implicated in the reduced risk of lacunar infarction and protection against ischemic stroke [18]. A neuroprotective effect of n6-FA [19] and
a linear, inverse association between the risk of Alzheimer disease and intake of n6-FA have been reported [20]. Interestingly, a recent study reported that linoleic acid, dose dependently, acts as anticonvulsant in a seizure rat model [21].

Studies focusing on dietary supplementation with arachidonic acid, a downstream product of linoleic acid, showed improvement of membrane fluidity, synaptic plasticity, and spatial cognition in aged rats [22,23]. Arachidonic acid was also reported to be a survival molecule for glial cells [24], and to be decreased in postmortem brain tissue from Alzheimer disease and schizophrenic patients [25-28]. Studies in other clinical settings further support a potential useful role of n6-FA. A diet high in vegetable n6-FA decreased abdominal fat and ameliorated insulin resistance compared to saturated fat [29]. In addition, linoleic acid has been inversely related to alamine aminotransferases in blood [30].

Nutritional strategies may be relevant tools to counteract cognitive decline, for which there is no substantial treatment to date, and among them lipids are striking candidates. However, theory needs experimental support to effectively translate into medicine. There is enough data to redirect research on fatty acids and cognitive decline by shifting towards a little explored class of fatty acids, the n6-FA.

References