Long-chain omega3 polyunsaturated fatty acids and cognition in older people: interaction with APOE genotype

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Abstract – Basic research and epidemiological studies suggest a protective effect of long-chain omega3 polyunsaturated fatty acids (LC n-3 PUFA) against age-related cognitive decline. However, most randomized controlled trials with LC n-3 PUFA supplements have yielded disappointing results on cognitive outcomes in older persons. One explanation for this discrepancy may be an inadequate targeting of potential beneficiaries of LC n-3 PUFA according to their Apolipoprotein E (APOE) genotype. The aim of this paper was to examine the potential modifying effect of APOE genotype on LC n-3 PUFA metabolism and its relation to cognitive decline in older persons. At least five epidemiological studies and three intervention studies with LC n-3 PUFA supplements have found an interaction between LC n-3 PUFA and APOE genotype on cognition. However, the direction of the effect is inconsistent across studies: the impact of LC n-3 PUFA on cognition is stronger in APOE4 carriers (the main genetic risk factor for Alzheimer’s disease) in some studies, but conversely stronger in APOE4 non-carriers in other studies. These discordant results may be explained by different age groups, cognitive status, measures of cognition, or amounts of DHA intake across studies. Experimental studies suggest that the APOE4 genotype modifies the metabolism of DHA. The APOE genotype should be systematically taken into account and interactions tested in epidemiological and intervention studies with LC n-3 PUFA. Further research is needed to better understand the underlying mechanisms of this gene X diet interaction.

Keywords: Cognition / aging / omega3 fatty acids / Apolipoprotein E gene / DHA


Mots clés : Cognition / vieillissement / acides gras oméga3 / gène de l’Apolipoprotéine E / DHA

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1 Introduction

Alzheimer’s disease (AD) is the main cause of cognitive decline and dementia in older persons (Cummings, 2004). AD is characterized by the progressive accumulation of beta-amyloid (Abeta) peptide in senile plaques and hyperphosphorylated tau protein in neurofibrillary tangles. These neurodegenerative lesions are accompanied by increased oxidative stress, inflammation, and neuronal death leading to brain atrophy and cognitive decline (Querfurth and LaFerla, 2010).

AD results from a complex interplay between non-modifiable risk factors, such as age and genetics, especially the epsilon 4 allele of the Apolipoprotein E gene (APOE4), and modifiable protective or detrimental factors (Barberger-Gateau, Lambert, et al., 2013). In particular, high blood cholesterol at midlife has been associated with increased risk of late-life cognitive decline and dementia (Solomon et al., 2009). High blood cholesterol is a well known vascular risk factor but it may also impair the brain-blood barrier (Shobab et al., 2005). In the brain, cholesterol is an important component of neuron membranes and regulates the scission of the amyloid precursor protein (APP) to Abeta (Shobab et al., 2005).

Among protective factors, nutrition is one of the most promising avenues for the prevention of AD (Barberger Gateau, Lambert, et al., 2013). In particular, basic research as well as epidemiological studies suggest a protective effect of long-chain omega3 polyunsaturated fatty acids (LC n-3 PUFA) against pathological brain aging and cognitive decline (Barberger Gateau, Feart, et al., 2011; Barberger Gateau, Samieri, et al., 2013; Cunnane et al., 2009). However, most randomized controlled trials (RCT) with LC n-3 PUFA supplements have been disappointing regarding cognitive outcomes in older persons (Jiao et al., 2014). One explanation for this discrepancy may be an inadequate targeting of potential beneficiaries of LC n-3 PUFA according to their APOE genotype (Barberger Gateau, Samieri, et al., 2013).

Indeed, the APOE4 genotype might modify the impact of n-3 on cognition in AD (Barberger Gateau, Samieri, et al., 2011). The aim of this narrative review was to examine the potential modifying effect of APOE4 genotype on LC n-3 PUFA metabolism and its relation to AD and cognitive decline in older persons.

2 APOE gene and Apolipoprotein E

The APOE gene located on chromosome 19 has three different alleles: e2, e3 and e4. The risk of late-onset AD is strongly increased in individuals carrying the e4 allele (APOE4): this risk is increased by about 14 fold in homozygotes and by 3 fold in heterozygotes (Farrer et al., 1997; Genin et al., 2011). Conversely, the risk of AD is decreased in APOE2 carriers. This translates into a cumulative risk of AD at age 85 of about 50% in homozygotes, 25% in heterozygotes, vs. only 10% in non carriers of the APOE4. In European countries, about one in five individuals carries at least one e4 allele, with some variability between populations.

The APOE gene encodes for apolipoprotein E (ApoE). ApoE3 is the most common isoform. ApoE is a cholesterol transporter: the ApoE4 isoform binds preferably to LDL and VLDL cholesterol while ApoE2 and ApoE3 bind preferably to HDL cholesterol (Lane and Farlow, 2005). ApoE isoforms influence the composition of membrane lipid rafts and delivery of essential fatty acids such as DHA to neurons (Lane and Farlow, 2005). In particular, ApoE can coordinate the mobilization of cholesterol for maintenance and repair of neuron membranes (Poirier, 2003). In addition to its role in lipid metabolism, ApoE exerts multiple functions (Jofre-Monseny et al., 2008). Indeed, ApoE has antioxidant properties depending on its isoforms, with a protective effect of ApoE2 while ApoE4 is associated with increased oxidative stress. ApoE modulates inflammation in as isoform dependent manner, especially in the brain where ApoE is associated with increased microglial activation resulting in greater inflammation (Lane and Farlow, 2005). ApoE4 is also associated with decreased cerebral glucose metabolism (Lane and Farlow, 2005). Finally, ApoE binds to soluble Abeta in an isoform dependent pattern thus contributing to its clearance from both extra-cellular and intra-cellular compartments in the brain, ApoE4 being associated with less efficient clearance of Abeta at the blood-brain barrier (Lambert and Amouyel, 2011; Poirier, 2003). All these mechanisms explain why the ApoE4 isoform is associated with an increased risk of late-onset AD.

3 Interactions between LC n-3 PUFA and APOE4 on cognition

Several epidemiological and intervention studies, but not all, have found an interaction between LC n-3 PUFA intake or blood levels and APOE4 on cognition. Table 1 summarizes the few epidemiological studies that have tested and evidenced this interaction. The first two studies (Barberger-Gateau et al., 2007; Huang et al., 2005) have examined the association between fish consumption and incidence of dementia. Both have found that the risk of dementia was decreased by 40% by regular fish consumption only in APOE4 non-carriers while no association was observed in APOE4 carriers. The two following studies (Beydoun et al., 2007; Whalley et al., 2008) have considered the relationship between blood concentrations of EPA and DHA and cognitive decline. Similarly, both have observed a significantly lower decline with higher proportions of EPA and DHA only in APOE4 non-carriers.

The last study conducted in a sample of 1214 elderly community dwellers participating in the Three-City (3C) study in Bordeaux has also linked blood EPA and DHA to cognitive decline but has yielded conflicting results (Samieri et al., 2011). Indeed, in APOE4 non-carriers, there was no significant association between plasma DHA or EPA and cognitive decline over 7 years on Benton Visual Retention Test (BVRT), a test of working memory and attention, except a protective association with EPA in subjects with high depressive symptoms. Conversely, a protective association was observed for both EPA and DHA with performance on BVRT in APOE4 carriers. There was no association of plasma EPA or DHA with Isaac Set Test, Trail Making Test or Mini Mental Status Examination, a test of global cognitive functioning, whatever the APOE genotype.

Three intervention studies with EPA and/or DHA have also found an interaction with APOE4 genotype. In the first
study, healthy young adults consuming very little fish (less than 200 mg EPA plus DHA per week) were randomized to receive 1.16 g DHA per day or a placebo (Stonehouse et al., 2013). Analyses were stratified according to APOE genotype. Both APOE4 carriers and non-carriers who received DHA showed improvements in working memory but the effect was considerably greater in APOE4 carriers due to both improvements in the DHA group and a worsening of performance in the placebo group. There was no significant improvement of attention with DHA. However, APOE4 carriers who received DHA did not worsen as did those receiving the placebo hence the difference was significant. Thus this study seemed to show a higher impact of DHA in APOE4 carriers.

A large RCT comparing two different doses of EPA and DHA and a placebo in 302 cognitively healthy older individuals did not find any significant effect of the supplementation on cognition, except an improvement in the cognitive domain of attention in APOE4 carriers with both doses of supplementation compared to placebo (van de Rest et al., 2008). However, this finding might be due to chance because of multiple comparisons in that study.

The third study included 402 individuals who already had mild to moderate AD, consuming little fish (< 200 mg/d DHA) (Quinn et al., 2010). They were randomized to receive 2 g/d DHA or a placebo for 18 months. There was no impact of DHA on any of the cognitive outcomes or MRI biomarkers. However, in post-hoc analyses stratified according to APOE4 genotype, there was a significantly slower decline on ADAS Cog, assessing global cognitive functions, in APOE4 non-carriers receiving DHA, contrarily to what was observed in the other two intervention studies.

In summary, several studies have reported this APOE gene X diet interaction, with inconsistent results: the impact of LC n-3 PUFA on cognition is more important in APOE4 carriers in some studies, APOE4 non-carriers in other studies. One of the plausible biological explanations for this interaction might be that APOE genotype modifies the metabolism of long-chain n-3 PUFA.

### Table 1. Epidemiological studies showing an interaction between LC n-3 PUFA and APOE genotype on cognition.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Measure of association (95% CI or P value)</th>
<th>Measure of association (95% CI or P value)</th>
</tr>
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<tbody>
<tr>
<td>(Huang et al., 2005)</td>
<td>Fatty fish: 2 to 4 servings/wk</td>
<td>8-yr incidence of dementia</td>
<td>HR = 0.91 (0.48 to 1.71)</td>
<td>HR = 0.60 (0.40 to 0.89)</td>
</tr>
<tr>
<td>(Barberger-Gateau et al., 2007)</td>
<td>Fish at least once a week</td>
<td>4-yr incidence of dementia</td>
<td>HR = 1.28 (0.58 to 2.83)</td>
<td>HR = 0.60 (0.41 to 0.89)</td>
</tr>
<tr>
<td>(Beydoun et al., 2007)</td>
<td>EPA + DHA in plasma cholesteryl esters</td>
<td>Cognitive decline on Word Fluency Test</td>
<td>OR = 0.80 (0.45 to 1.63) for 1 SD</td>
<td>OR = 0.61 (0.43 to 0.87) for 1 SD</td>
</tr>
<tr>
<td>(Whalley et al., 2008)</td>
<td>Total LC n-3 PUFA in erythrocyte membranes</td>
<td>Cognitive performance on a score derived by PCA</td>
<td>r = 0.02</td>
<td>r = 0.35</td>
</tr>
<tr>
<td>(Samieri et al., 2011)</td>
<td>EPA and DHA in total plasma fatty acids (1 SD)</td>
<td>Cognitive decline on Benton Visual Retention Test</td>
<td>DHA: β = 0.061, P = 0.01</td>
<td>DHA: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EPA: β = 0.077, P = 0.003</td>
<td>EPA: NS except in subjects</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>β = 0.172, P &lt; 0.001</td>
<td>with high depressive symptoms</td>
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<td></td>
<td></td>
<td></td>
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<td>in subjects with high depressive symptoms</td>
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</tbody>
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HR = hazard ratio, OR = odds ratio, CI = confidence interval, SD = standard deviation, PCA = principal component analysis, NS = not significant.

**Fig. 1.** Relationship between frequency of fish intake and plasma DHA according to APOE4 genotype. The Three-City study Bordeaux.

4 APOE genotype and metabolism of LC n-3 PUFA

Very few studies have investigated this hypothesis. In the 3C study we examined the relationship between fish consumption and plasma DHA according to APOE4 genotype in elderly community dwellers and found a borderline significant interaction (P = 0.06) (Samieri et al., 2013). In individuals eating little fish, that is less than one serving per week, carriers of the APOE4 had higher mean plasma DHA than non-carriers (Fig. 1). There was no significant difference in plasma DHA between carriers and non-carriers for higher frequency of fish intake. Plasma DHA strongly increased with increasing fish
intake in both groups. There was no interaction with APOE genotype for plasma EPA.

The group of S.C. Cunnane has further investigated this issue in a series of experimental studies. The first study included 28 adult men who were given a supplement containing 3 g/d EPA+DHA for 6 weeks (Plourde et al., 2009). The proportion of fatty acids in each plasma fraction was measured before and after supplementation. At baseline, APOE4 carriers had higher EPA proportions in non-esterified fatty acids than non-carriers but this proportion did not increase during the supplementation (P for interaction 0.04). There was no significant difference between APOE4 carriers and non-carriers for EPA in triglycerides but the increase was slightly less pronounced in APOE4 carriers (borderline significant P = 0.07 for interaction). Regarding DHA, there was no significant difference between carriers and non-carriers for change in non-esterified fatty acids although the proportion of DHA was always slightly lower in APOE4 carriers. Conversely, the proportion of DHA in triglycerides was slightly higher at baseline but increased less in APOE4 carriers than non-carriers after supplementation. Thus APOE4 carriers appeared to be less responsive to supplementation with LC n-3 PUFA, suggesting an altered n-3 metabolism.

The second experiment involved 40 cognitively healthy older participants who received a single dose of 40 mg DHA labeled with carbon 13 ([13C]-DHA) (Chouinard-Watkins et al., 2013). In APOE4 carriers, [13C]-DHA in plasma total lipids from 1 h to 28 days post-dose was 31% lower compared with APOE4 non-carriers. APOE4 carriers also had higher cumulative beta-oxidation of [13C]-DHA which could explain their lower plasma [13C]-DHA. There was no difference between APOE4 carriers and non-carriers for apparent retroconversion of [13C]-DHA into [13C]-EPA (Chouinard-Watkins et al., 2013). This disturbance in DHA metabolism in APOE4 carriers might contribute to their greater vulnerability to cognitive decline.

In the last experiment, the [13C]-DHA tracer was administered again after a period of 5 months of supplementation with 3.2 g/d of EPA+DHA (Hennebelle et al., 2014). During the supplementation, beta-oxidation of [13C]DHA was lower in APOE4 carriers contrarily to what was observed before supplementation (Chouinard-Watkins and Plourde, 2014). Moreover, APOE4 carriers had an increased plasma response to the tracer after the supplementation, suggesting slower clearance of DHA to or use by tissues (Hennebelle et al., 2014).

5 Conclusion

At least five epidemiological studies and three intervention studies with LC n-3 PUFA supplements have found an interaction between LC n-3 PUFA and APOE genotype on cognition. However, the direction of the effect is inconsistent across studies: the impact of LC n-3 PUFA on cognition is stronger in APOE4 non-carriers in some studies, but conversely stronger in APOE4 carriers in other studies. These discordant results may be explained by different age groups (adults vs. older persons), cognitive status (healthy vs. mild Alzheimer’s disease), measures of cognition (working memory, attention, or global cognition) or amounts of DHA intake across studies. These inconsistent findings require that the APOE genotype should be systematically taken into account and interactions tested in epidemiological and intervention studies with LC n-3 PUFA.

Experimental studies reported in this paper suggest that the APOE4 genotype modifies the metabolism of DHA. Other studies have shown that APOE genotype may also affect the impact of LC n-3 PUFA on inflammation, triglycerides concentration or cholesterol level (Anil, 2007; Carvalho-Wells et al., 2010; Carvalho-Wells et al., 2012). Further research is needed to better understand the underlying mechanisms of this gene X diet interaction.

Conflicts of interest

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