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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

Résumé – Acides gras oméga-3 à longue chaîne et cognition chez les sujets âgés : interaction avec le génotype APOE. La recherche fondamentale et les études épidémiologiques suggèrent un effet protecteur des acides gras oméga3 à longue chaîne (AGPI-LC n-3) contre le déclin cognitif lié à l'âge. Cependant les études d'intervention avec des suppléments d'AGPI-LC n-3 ont donné des résultats décevants sur la cognition. Une raison pourrait en être un ciblage inadéquat des bénéficiaires potentiels d'une supplémentation en raison notamment de leur génotype pour le gène de l'Apolipoprotéine E (*APOE*). L'objectif de cet article était d'explorer l'effet potentiellement modificateur du génotype de l'*APOE* sur le métabolisme des AGPI-LC n-3 et sa relation avec le déclin cognitif chez le sujet âgé. Au moins cinq études épidémiologiques et trois études d'intervention ont mis en évidence une interaction entre les AGPI-LC n-3 et le génotype de l'*APOE* sur la cognition des personnes âgées. Cependant la direction de l'effet est inconstant entre les études, certaines montrent un impact des AGPI-LC n-3 uniquement chez les porteurs de l'allèle epsilon4 (*APOE4*), principal facteur de risque génétique de maladie d'Alzheimer, et d'autres inversement un effet chez les non-porteurs de l'*APOE4*. Ces résultats discordants peuvent s'expliquer par des différences d'âge, de statut cognitif, de domaine de la cognition mesuré, ou de quantités de DHA entre études. Les études expérimentales suggèrent que le génotype de l'*APOE* modifie le métabolisme du DHA. Les études épidémiologiques et d'intervention avec des AGPI-LC n-3 devraient systématiquement rechercher l'existence d'une interaction éventuelle avec l'*APOE*. La recherche doit se poursuivre pour comprendre les mécanismes sous-jacents à cette interaction gène X nutrition.

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-amyloide (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 *APOE* 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 *APOE* 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: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$. The risk of late-onset AD is strongly increased in individuals carrying the $\epsilon 4$ 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 $\epsilon 4$ allele, with some variability between populations.

The *APOE* gene encodes for apoliprotein 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

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

Reference	Exposure	Outcome	*APOE4* carriers	*APOE4* non-carriers
			Measure of association (95% CI) or *P* value	Measure of association (95% CI) or *P* value
(Huang *et al.*, 2005)	Fatty fish: 2 to 4 servings per week	8-yr incidence of dementia	HR = 0.91 (0.48 to 1.71)	HR = 0.60 (0.40 to 0.89)
(Barberger-Gateau *et al.*, 2007)	Fish at least once a week	4-yr incidence of dementia	HR = 1.28 (0.58 to 2.83)	HR = 0.60 (0.41 to 0.89)
(Beydoun *et al.*, 2007)	EPA + DHA in plasma cholesteryl esters	Cognitive decline on Word Fluency Test	OR = 0.80 (0.45 to 1.63) for 1 SD	OR = 0.61 (0.43 to 0.87) for 1 SD
(Whalley *et al.*, 2008)	Total LC n-3 PUFA in erythrocyte membranes	Cognitive performance on a score derived by PCA	$r = 0.02$ NS	$r = 0.35$ $P < 0.01$
(Samieri *et al.*, 2011)	EPA and DHA in total plasma fatty acids (for 1 SD)	Cognitive decline on Benton Visual Retention Test	DHA: $\beta = 0.061$, $P = 0.01$ EPA: $\beta = 0.077$, $P = 0.003$ in subjects with low depressive symptoms $\beta = 0.172$, $P < 0.001$ in subjects with high depressive symptoms	DHA: NS EPA: NS except in subjects with high depressive symptoms

HR = hazard ratio, OR = odds ratio, CI = confidence interval, SD = standard deviation, PCA = principal component analysis, NS = not significant.

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, in *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.

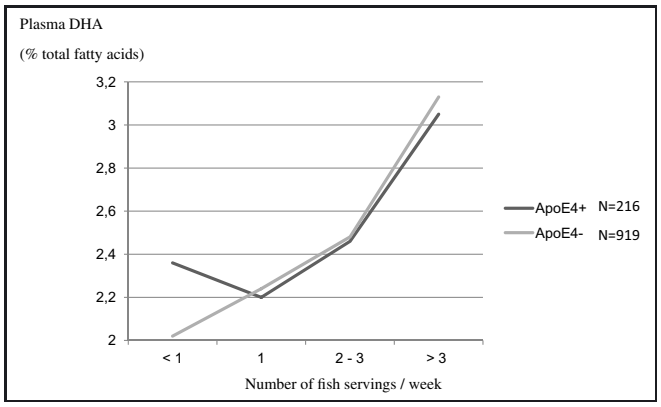

Fig. 1. Relationship between frequency of fish intake and plasma DHA according to *APOE4* genotype. The Three-City study Bordeaux.

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 ([^{13}C]-DHA) (Chouinard-Watkins *et al.*, 2013). In *APOE4* carriers, [^{13}C]-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 [^{13}C]-DHA which could explain their lower plasma [^{13}C]-DHA. There was no difference between *APOE4* carriers and non-carriers for apparent retroconversion of [^{13}C]-DHA into [^{13}C]-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 [^{13}C]-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 [^{13}C]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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