

## *Effect of plasma lipids and APOE genotype on cognitive decline*

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*A central tenet of brain aging is that “what is good for the heart is good for the brain.” We examined the combined effect of plasma lipids and APOE genotype on cognitive function in elderly individuals. Plasma concentrations of high-density lipoprotein (HDL), low-density lipoprotein, triglyceride, total cholesterol, and apolipoprotein E (apoE) were evaluated in 622 community-dwelling individuals aged 65 years and older. We investigated the associations between plasma lipids and cognitive function in APOE4 carrier (E4+) and APOE4 noncarrier (E4-) groups using 3-year longitudinal data. At baseline and 3 years later, cognitive scores were correlated with plasma apoE levels in both E4- and E4+, and HDL level in E4-. Our findings suggest that an interaction between apoE and HDL is facilitated by APOE4, and is possibly linked with an enhancement of neuroplasticity and with resultant protective effects on cognitive function in later life. Preservation of higher plasma apoE and HDL from early life is proposed as a possible strategy for maintaining cognitive function in later life, especially for APOE4-positive individuals.*

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### Introduction

The presence of an apolipoprotein E4 allele (APOE4) increases the risk of, and reduces the age at onset of, Alzheimer’s disease (AD) in a dose-dependent manner.<sup>1-3</sup> Additionally, APOE4 carriers have been reported to have higher rates of cognitive decline than noncarriers before the diagnosis of mild cognitive impairment.<sup>4</sup>

Apolipoprotein E (apoE) plays a significant role in cholesterol delivery to neurons and AD pathogenesis associated with amyloid beta ( $A\beta$ ).<sup>5-7</sup> The plasma level of apoE has been shown to depend upon the APOE genotype.<sup>8,9</sup> In elderly individuals without dementia, the interactive effect of apoE and other plasma lipids on cognitive function has also been reported to vary, depending upon the APOE genotype.<sup>8,9</sup>

A complex synergism of APOE4 and cerebrovascular pathology in cognitive function of the elderly has been reported. The detrimental effect of APOE4 may be exacerbated by synergistic preventable risk factors such as plasma apoE/lipids. With stratification by APOE allele status, we examined the effect of plasma apoE/lipids on

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longitudinal change in the cognitive function of community-dwelling elderly using the data from a 3-year follow-up study.

### Three-year follow-up examinations of the effect of plasma apoE/lipids on cognitive function in the elderly

Participants were recruited in the present study from the "Tone Project" in Tone town, Ibaraki, Japan.<sup>10</sup> A total of 1395 volunteers participated in the first baseline study between December 2001 and April 2002. Three years later, 622 of them who had no history of stroke during follow-up were able to be evaluated again between December 2004 and April 2005, and we used the results from those subjects tested twice. At the initial examination, all of the eligible subjects provided written informed consent for their participation in the study. This study was approved by the ethics committee of Tsukuba University.

All participants underwent the same cognitive assessment at the baseline and 3-year examinations using a set of four tests to measure the following cognitive domains: attention, memory, language, and reasoning. We evaluated attention by using the Japanese version of a Set-dependent activity,<sup>11</sup> memory ability using the Category Cued Recall test,<sup>12</sup> and language ability with a category fluency test.<sup>13</sup> Abstract reasoning ability was evaluated with the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).<sup>14</sup> The assessment procedures have been described elsewhere.<sup>8,9</sup> A composite cognitive score was computed from the four scores using the first component of the scores of principal component analysis.

Blood samples were collected from the subjects at fasting visits at the initial examination. Plasma levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC) were measured using standard enzymatic methods on routine automated chemistry systems. Plasma apoE levels were determined by turbidimetric immunoassay. Genomic DNA was used for APOE typing. Subjects were divided into two APOE groups by E4 status with E4- (n=509) (genotypes  $\epsilon 2/\epsilon 3$  [n=52],  $\epsilon 3/\epsilon 3$  [n=457]) and E4+ (n=113) (genotypes [ $\epsilon 2/\epsilon 4$  n=6],  $\epsilon 3/\epsilon 4$  [n=99] and  $\epsilon 4/\epsilon 4$  [n=8]) to test for the influence of genotype on the association between lipids and cognitive function.

The subjects in each category were divided into three

strata according to the plasma concentrations of lipids. To examine the influence of plasma lipids on cognitive function, composite cognitive scores of the three strata of plasma concentrations were compared in E4- and E4+ groups separately by ANCOVA, with age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of diseases as covariates.

### Cognitive scores were associated with plasma apoE level in both E4- and E4+, and the HDL level in E4-

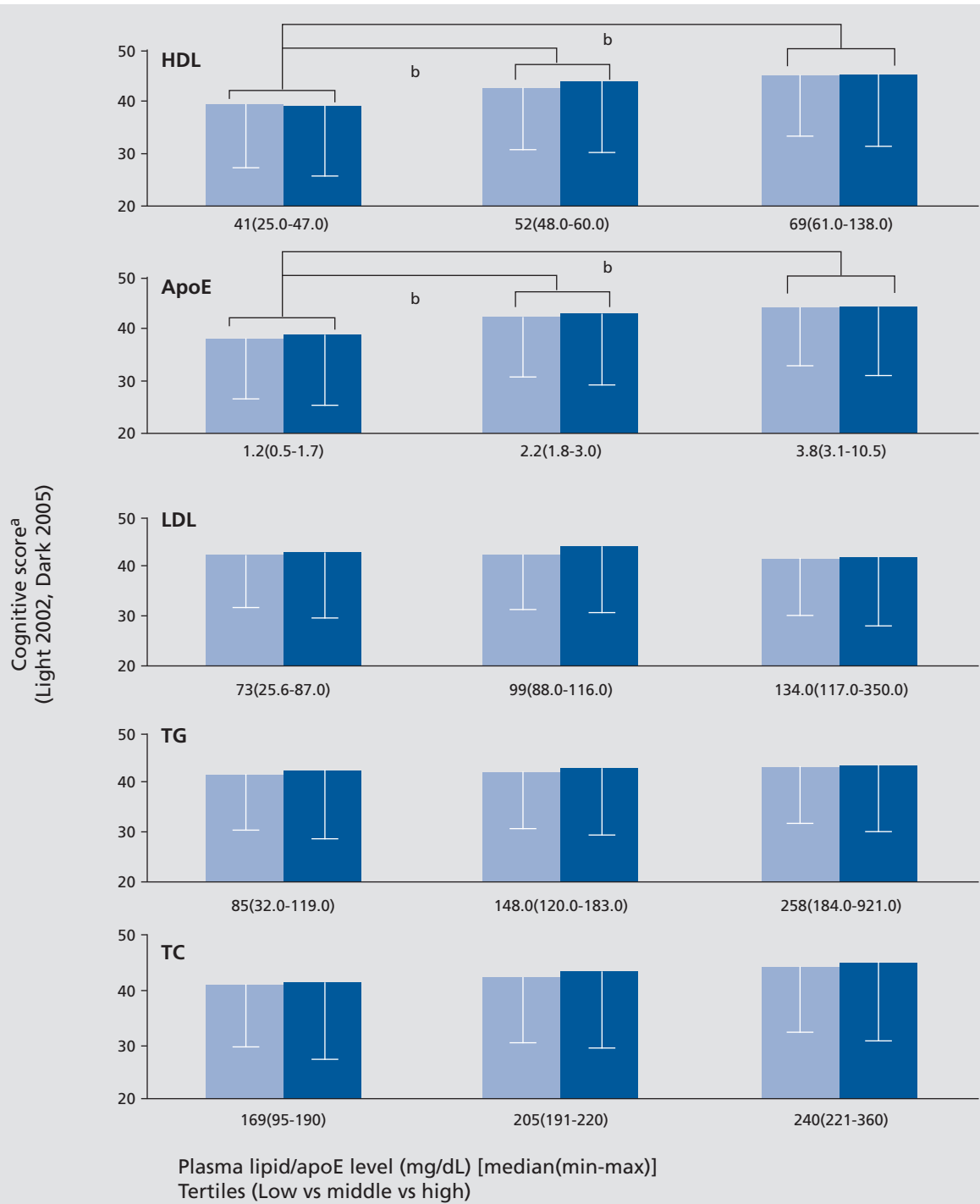
The demographic data for the E4- and E4+ groups in the analysis of the effect of lipids/apoE on cognitive function are shown in *Table 1*. There were no group differences in demographic characteristics, except for the cognitive score. Our finding of a higher cognitive score at 2002 and 2005 in the E4- group is consistent with previous studies.<sup>15</sup>

*Figures 1* and *2* show the median plasma concentrations of lipids for the three strata according to the tertiles of plasma levels of lipids/apoE, and the mean cognitive scores of the E4- and E4+ groups at 2002 and 2005 according to the three strata of plasma concentrations of lipids/apoE.

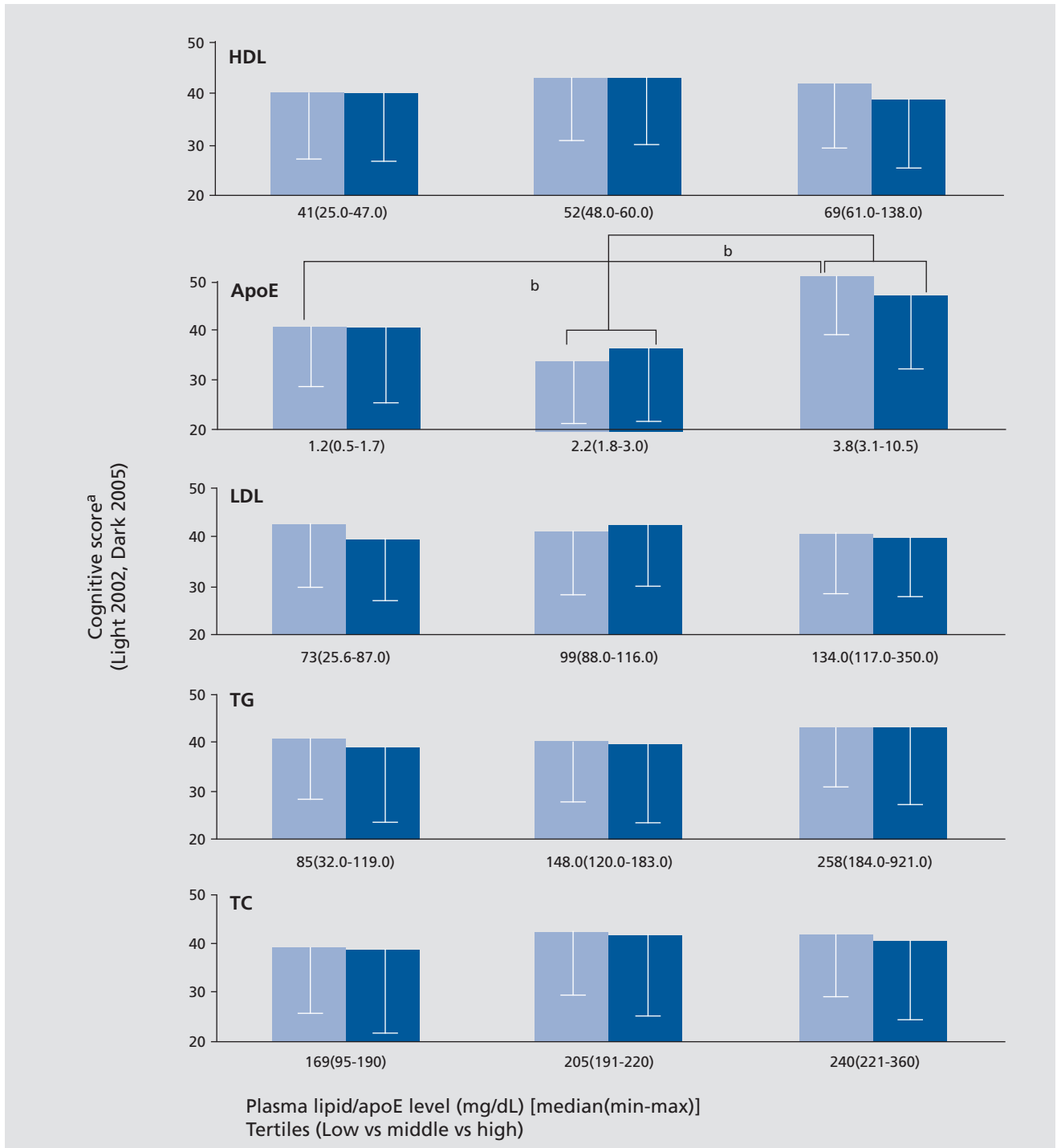
ANCOVA analysis evaluating the influence of lipids level on cognitive function showed a significant influence of the HDL level on composite cognitive scores at both 2002 and 2005 in the E4- group ( $F_{2,498}=9.3$ ,  $P<0.001$  for 2002,  $F_{2,498}=9.3$ ,  $P<0.001$  for 2005). Subjects with higher HDL concentrations had higher cognitive scores. The effect size of the influence of the plasma HDL level on cognitive score was more than 0.01 ( $\eta^2=0.04$  for 2002,  $\eta^2=0.04$  for 2005). No such significant association was observed in the E4+ group (*Figure 2*).

A significant main effect of the apoE level was found by ANCOVA on composite cognitive scores at 2002 and 2005 in both of the E4- and E4+ group ( $F_{2,498}=11.3$ ,  $P<0.001$  for 2002,  $F_{2,498}=7.3$ ,  $P=0.001$  for 2005 in the E4-, and  $F_{2,102}=7.0$ ,  $P=0.001$  for 2002,  $F_{2,102}=4.0$ ,  $P=0.02$  for 2005 in the E4+). Subjects with higher plasma apoE concentration had higher cognitive scores in both groups. The effect size of the association of the plasma apoE level on these cognitive scores was more than 0.01 ( $\eta^2=0.04$  for 2002,  $\eta^2=0.03$  for 2005 in the E4-, and  $\eta^2=0.12$  for 2002,  $\eta^2=0.07$  for 2005 in the E4+).

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**Figure 1.** Mean cognitive test score of each tertile groups of lipid levels in the ApoE4- group. <sup>a</sup>, data are mean after adjustment for age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; <sup>b</sup>, indicates significance at  $P < .05$  after Bonferroni adjustment for multiple comparisons. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; apoE, apolipoprotein E



**Figure 2.** Mean cognitive test score of each tertile groups of lipid levels in ApoE4+ group. <sup>a</sup>, data are mean after adjustment for age, sex, years of education; Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; <sup>b</sup>, indicates significance at  $P < .05$  after Bonferroni adjustment for multiple comparisons. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol; apoE, apolipoprotein E



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Characteristic	ApoE4- (n =509)	ApoE4+ (n = 113)	t, $\chi^2$ or F <sup>a-c</sup>	P <sup>a-c</sup>
Age, y <sup>a</sup>	73.0 ± 5.4	72.7 ± 4.8	t <sub>620</sub> =0.5	0.6
Male, No (%) <sup>b</sup>	226 (44%)	43 (38%)	$\chi^2_1$ =1.5	0.2
Years of education, y <sup>a</sup>	10.1 ± 2.6	10.3 ± 2.9	t <sub>620</sub> =0.3	0.5
GDS score <sup>a</sup>	2.6 ± 2.5	2.1 ± 2.2	t <sub>620</sub> =1.8	0.1
Cigarette smoking, No (%) <sup>b</sup>	188 (37%)	37 (33%)	$\chi^2_1$ =0.7	0.4
History of disease, No (%)				
Cardiovascular disease <sup>b</sup>	15 (2.9%)	2 (1.7%)	$\chi^2_1$ =0.5	0.5
Diabetes mellitus <sup>b</sup>	20 (3.9%)	7 (6.1%)	$\chi^2_1$ =1.1	0.3
Hyperlipidemia <sup>b</sup>	19 (3.7%)	7 (6.1%)	$\chi^2_1$ =1.4	0.2
Hypertension <sup>b</sup>	195 (38.3%)	44 (38.9%)	$\chi^2_1$ =0.02	0.9
Cognitive score in 2002 <sup>c</sup>	42.8±11.7	40.3±11.8	F <sub>1,611</sub> =4.1	0.04
Cognitive score in 2005 <sup>c</sup>	43.1±13.8	39.0±13.8	F <sub>1,611</sub> =8.3	0.004

**Table 1.** Demographic characteristics in the analysis of the effect of lipids/lipoproteins. <sup>a</sup> P value was calculated by unpaired two-tailed t test. <sup>b</sup> P value was calculated by Pearson  $\chi^2$  two-tailed test. <sup>c</sup> P value was calculated by analysis of covariance (ANCOVA) with age, sex, and years of education, Global Depression Scale (GDS) score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension as covariates. ApoE4, apolipoprotein E4. Data are mean±sd after adjustment for covariates.

## Why are cognitive scores associated with plasma apoE and HDL levels?

Each of the analyses using the data from the baseline and 3-year follow-up examinations revealed that cognitive scores were associated with the plasma apoE level in both E4- and E4+, and the HDL level in E4-. We will discuss these findings.

ApoE plays a significant role in response to neuronal injury by reducing inflammation, endothelial dysfunction, and lipid oxidation.<sup>16</sup> An antioxidant role of apoE in promoting the regression of atherosclerosis has also been reported.<sup>17</sup> It is possible that a lower plasma apoE level impairs these normal physiological functions.<sup>18</sup> If this is the case, a lower plasma apoE level may lead to cognitive decline and the exacerbation of cerebral degenerative changes. On the other hand, apoE is thought to bind A $\beta$  and promote its clearance and degradation, such that a lower apoE level may reduce the efficiency of A $\beta$  clearance, and contribute to AD pathogenesis.<sup>19</sup>

The expression of apoE is transcriptionally regulated by the ligand-activated nuclear receptors, peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and liver X receptors (LXRs), which form obligate heterodimers with retinoid X receptors (RXRs).<sup>20</sup> Expression of the ApoE gene is increased by agonist of these receptors. Recently, Cramer et al tested whether the RXR agonist bexarotene, which activates both the PPAR-RXR and LXR-RXR receptors, would rapidly alter the amount of

A $\beta$ , and diminish behavioral abnormalities, in mice genetically engineered to express a mutant form of the APP gene.<sup>21</sup> They observed rapid clearance of soluble A $\beta$  from the brain, reduction in neuritic plaque burden, and reversal of behavioral deficits. The effects of bexarotene were not observed when the drug was administered to mice lacking the APOE gene.<sup>21,22</sup> These observations support our finding of the significant protective effect of apoE on cognitive decline in later life, and that the strategies increasing apoE expression might prevent cognitive decline in old age.

Higher plasma levels of HDL were associated with better cognitive function in the E4- group. Low-level HDL is thought to be a risk factor for atherosclerotic diseases,<sup>23,24</sup> and it has been reported that HDL might prevent aggregation and polymerization of amyloid in the human brain.<sup>25,26</sup> Anti-inflammatory properties of HDL could prevent inflammation from neurodegenerative processes.<sup>27</sup>

Recent studies have presented evidence for the involvement of internalized triglyceride-rich lipoprotein (TRL)-derived apoE in the regulation of HDL metabolism.<sup>28</sup> The greater portion of TRL-derived apoE remains in peripheral recycling endosomes. This pool of apoE is then mobilized by HDL to be recycled back to the plasma membrane, followed by apoE resecretion and the subsequent formation of apoE-containing HDL. This recycling of apoE may prevent cognitive decline. We found no significant association between HDL and cognitive function in the E4+ group. A recent study has

shown that HDL-induced recycling of TRL-derived apoE4 is relatively inefficient.<sup>29</sup> Thus, in the E4+ group, the inefficiency might reduce the recycling of apoE and decrease the protective effect of HDL on cognitive decline.

### Conclusion

Our findings showed positive effect of plasma apoE and HDL on better cognitive function of elderly. They suggest a possible interaction between apoE and HDL may be linked to a protective effect on cognitive decline and

that the interaction is affected by APOE4 allele in later life. It is known that neuropathological cascades leading to cognitive impairment and AD start to develop before the manifestation of cognitive impairment. Therefore, ensuring higher plasma apoE and HDL from an earlier stage of life may be useful for the maintenance of cognitive function in later life, and especially for APOE4 carriers. □

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#### Efecto de los lípidos plasmáticos y el genotipo APOE en la declinación cognitiva

*Un postulado central del envejecimiento cerebral es que “lo que es bueno para el corazón es bueno para el cerebro”. Se examinó el efecto combinado de los lípidos plasmáticos y del genotipo APOE sobre la función cognitiva de sujetos de edad avanzada. Se evaluaron las concentraciones plasmáticas de lipoproteína de alta densidad (HDL), lipoproteína de baja densidad, triglicéridos, colesterol total y apolipoproteína E (apoE) en 622 individuos de 65 años y más que viven en la comunidad. Se investigaron las asociaciones entre lípidos plasmáticos y función cognitiva en grupos portadores de APOE4 (E4+) y no portadores de APOE4 (E4-) empleando información a lo largo de tres años. Al momento inicial y 3 años después las puntuaciones cognitivas se correlacionaron con los niveles plasmáticos de apoE tanto en el grupo E4- como en el E4+ y el nivel de HDL en el grupo E4-. Los resultados sugieren que una interacción entre apoE y HDL está facilitada por APOE4 y posiblemente relacionada con un aumento de neuroplasticidad y los consiguientes efectos protectores en la función cognitiva en la vejez. Una posible estrategia para el mantenimiento de la función cognitiva en la edad avanzada es la conservación de niveles plasmáticos más altos de apoE y HDL desde la juventud, especialmente en los sujetos APOE4-positivos.*

#### Effet des lipides plasmatiques et du génotype APOE sur le déclin cognitif

*Le principe central du vieillissement cérébral est que « ce qui est bon pour le cœur est bon pour le cerveau ». Nous avons donc examiné l'effet combiné des lipides plasmatiques et du génotype APOE sur la fonction cognitive chez les personnes âgées. Les concentrations plasmatiques des HDL (high-density lipoprotein), des LDL (low-density lipoprotein), des triglycérides, du cholestérol total et de l'apo E (apolipoprotéine E) ont été évaluées chez 622 résidents en institution âgés de 65 ans et plus. Nous avons analysé les associations entre les lipides plasmatiques et la fonction cognitive dans les groupes porteurs de l'APOE4 (E4+) et non porteurs de l'APOE4 (E4-) en utilisant des données longitudinales sur 3 ans. Initialement et 3 ans plus tard, les scores cognitifs étaient corrélés aux concentrations plasmatiques en apoE chez les E4- et les E4+ et les concentrations en HDL chez les E4-. Nos résultats suggèrent qu'une interaction entre apoE et HDL est facilitée par les APOE4 et probablement liée à une amélioration de la neuroplasticité et à des effets protecteurs sur la fonction cognitive dans la vie future. La préservation de concentrations de HDL et d'apoE plasmatiques plus élevées dès le plus jeune âge est proposée comme stratégie éventuelle pour maintenir la fonction cognitive ultérieure, en particulier pour les sujets qui sont APOE4-positifs.*

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