Brief report

Effect of plasma lipids and APOE genotype on cognitive decline

Fumihiko Yasuno, MD, PhD; Takashi Asada, MD, PhD

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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Keywords: *cognitive decline; APOE genotype; apolipoprotein E; high-density lipoprotein; low-density lipoprotein; triglyceride; total cholesterol*

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.[1-3] Additionally, APOE4 carriers have been reported to have higher rates of cognitive decline than noncarriers before the diagnosis of mild cognitive impairment.[4]

Apolipoprotein E (apoE) plays a significant role in cholesterol delivery to neurons and AD pathogenesis associated with amyloid beta (A β).[5-7] The plasma level of apoE has been shown to depend upon the APOE genotype.[8,9] 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.[8,9]

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

Author affiliations: Department of Neuropsychiatry, Institute of Clinical Medicine, University of Tsukuba, Japan (Fumihiko Yasuno, Takashi Asada); Department of Neuropsychiatry, Nara Medical University, Nara, Japan (Fumihiko Yasuno)

Address for correspondence: Takashi Asada, MD, PhD, Department of Neuropsychiatry, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan
(e-mail: tasada@md.tsukuba.ac.jp)

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.[10] 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,[11] memory ability using the Category Cued Recall test,[12] and language ability with a category fluency test.[13] Abstract reasoning ability was evaluated with the Similarities subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[14] The assessment procedures have been described elsewhere.[8,9] 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 ε2/ε3 [n=52], ε3/ε3 [n=457]) and E4+ (n=113) (genotypes [ε2/ε4 n=6], ε3/ε4 [n=99] and ε4/ε4 [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 I*. 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.[15]

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(η^2=0.04 for 2002, η^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(η^2=0.04 for 2002, η^2=0.03 for 2005 in the E4-,and η^2=0.12 for 2002, η^2=0.07 for 2005 in the E4+).

Brief report

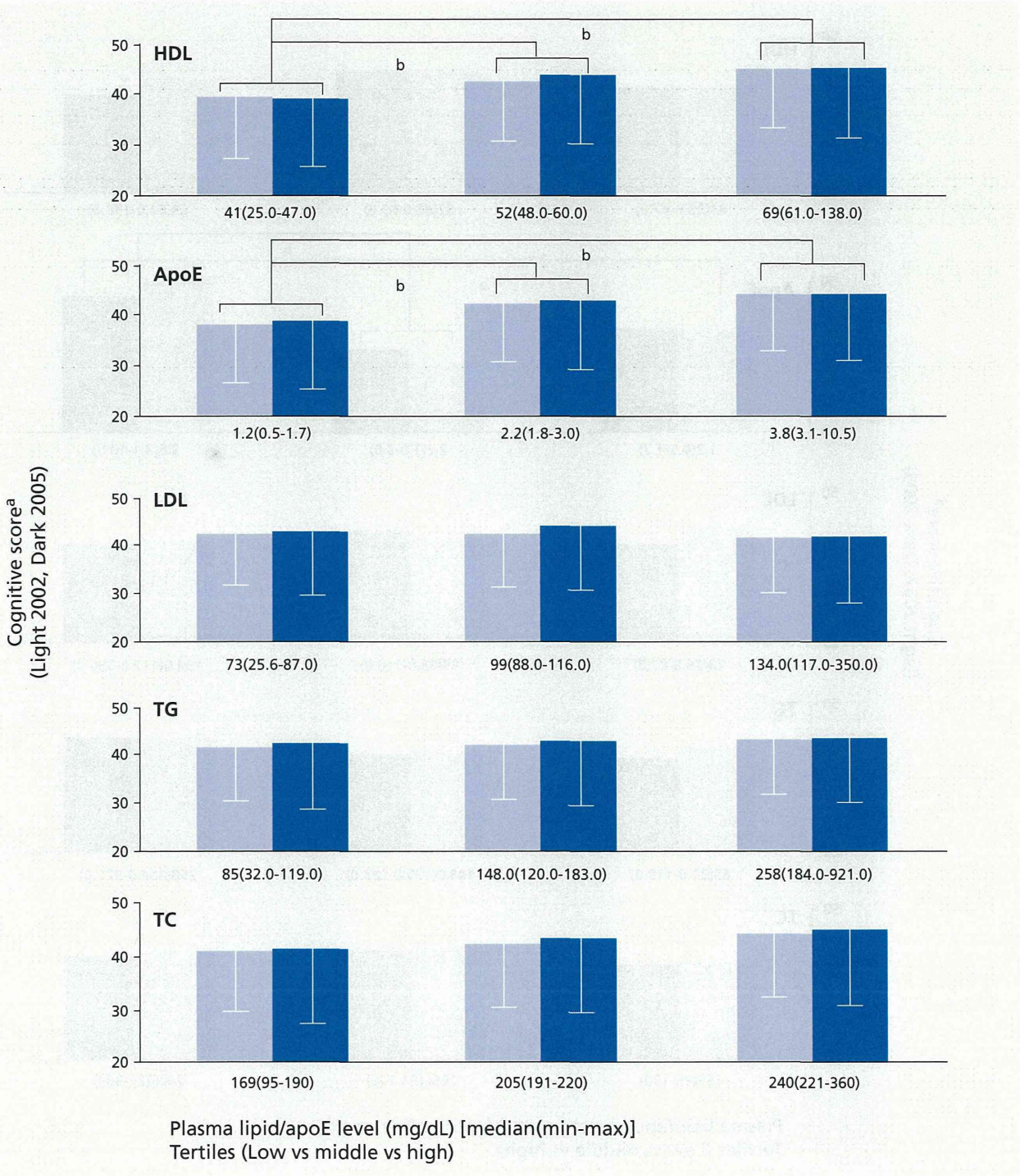

Figure 1. Mean cognitive test score of each tertile groups of lipid levels in the ApoE4- group. [a], data are mean after adjustment for age, sex, years of education, Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; [b], 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

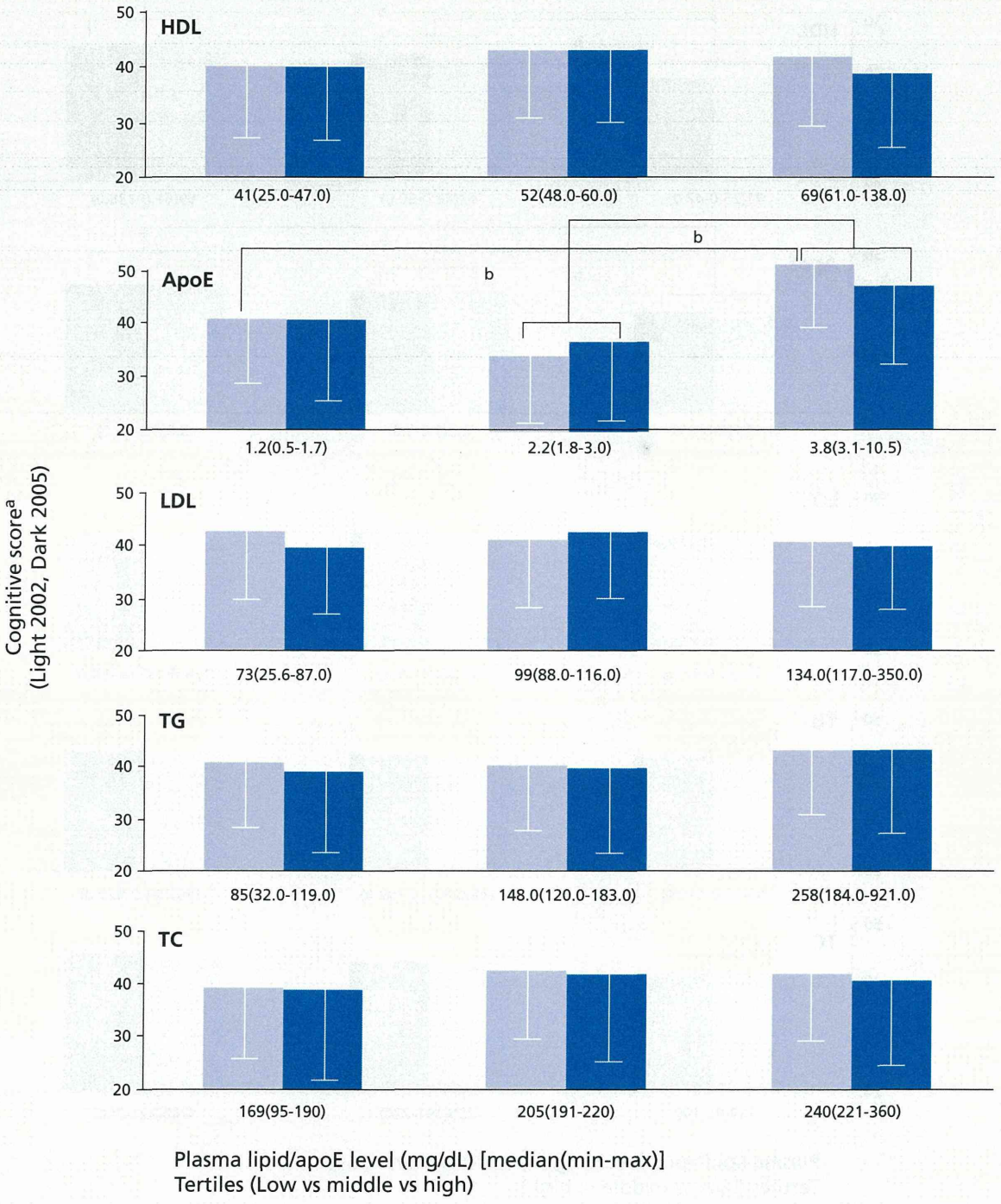

Figure 2. Mean cognitive test score of each tertile groups of lipid levels in ApoE4+ group. [a], data are mean after adjustment for age, sex, years of education; Geriatric Depression Scale score, cigarette smoking, and medical history of cardiovascular disease, diabetes mellitus, and hypertension; [b], 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

Brief report

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

Table I. Demographic characteristics in the analysis of the effect of lipids/lipoproteins. [a] *P* value was calculated by unpaired two-tailed t test. [b] *P* value was calculated by Pearson χ^2 two-tailed test. [c] *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.[16] An antioxidant role of apoE in promoting the regression of atherosclerosis has also been reported.[17] It is possible that a lower plasma apoE level impairs these normal physiological functions.[18] 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 Aβ and promote its clearance and degradation, such that a lower apoE level may reduce the efficiency of Aβ clearance, and contribute to AD pathogenesis.[19]

The expression of apoE is transcriptionally regulated by the ligand-activated nuclear receptors, peroxisome proliferator-activated receptor gamma (PPARγ) and liver X receptors (LXRs), which form obligate heterodimers with retinoid X receptors (RXRs).[20] 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 Aβ, and diminish behavioral abnormalities , in mice genetically engineered to express a mutant form of the APP gene.[21] They observed rapid clearance of soluble Aβ 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.[21,22] 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,[23,24] and it has been reported that HDL might prevent aggregation and polymerization of amyloid in the human brain.[25,26] Anti-inflammatory properties of HDL could prevent inflammation from neurodegenerative processes.[27]

Recent studies have presented evidence for the involvement of internalized triglyceride-rich lipoprotein (TRL)-derived apoE in the regulation of HDL metabolism.[28] The greater portion of TRL-derived apoE remains in peripheral recycling endosomes. This pool of apoE is then mobilized by HDL to be rec ycled 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 rec ycling of TRL-derived apoE4 is relatively inefficient.[29] 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 apoliproteína 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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RESEARCH ARTICLE

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ApoE4 is not associated with depression when mild cognitive impairment is considered

Mayumi Nose[1], Chiine Kodama[1], Chiaki Ikejima[1], Katsuyoshi Mizukami[2], Asaki Matsuzaki[3], Shiro Tanaka[4], Atsuko Yoshimura[5], Fumihiko Yasuno[6] and Takashi Asada[2]

[1]Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba City, Japan
[2]Department of Neuropsychiatry, University of Tsukuba, Tsukuba City, Japan
[3]National Center Hospital, National Center of Neurology and Psychiatry, Kodaira City, Japan
[4]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, Kyoto City, Japan
[5]Graduate School of Human Life and Health Science, Open University of Japan, Chiba City, Japan
[6]Department of Neuropsychiatry, National Cerebral and Cardiovascular Center, Suita City, Japan
Correspondence to: Takashi Asada, E-mail: tasada@md.tsukuba.ac.jp

Objective: The aim of the study was to examine the relationship between apolipoprotein E4 allele (ApoE4) and depression among an older Japanese population. Mild cognitive impairment (MCI) was taken into consideration.

Methods: This is a community-based cross-sectional study. We assessed the mood and cognitive function of Japanese community-dwelling individuals aged 65 years or older. In the first phase of the study, we evaluated the mood and cognitive function. In the second phase, face-to-face structured interviews were conducted. Individuals with dementia and other mental diseases were excluded on the basis of a consensus meeting of psychiatrists and neuropsychologists; 738 subjects with full data were included in the analyses. We subdivided depression into major depressive episode (MDE) and depressive symptoms cases (DSCs). DSC was defined as a score of 6 or more on the Geriatric Depression Scale but not having a diagnosis of MDE. The relationship between depression (MDE and DSC) and ApoE4 was examined by multivariate logistic regression.

Results: The adjusted odds ratio (OR) of ApoE4 on DSC was not significant (OR = 0.82, 95%CI = 0.48–1.39, $p < 0.46$). Sex (OR = 2.53, 95%CI = 1.33–4.79, $p < 0.01$), MCI (1.95, 1.21–3.14, $p < 0.01$), years of education (0.87, 0.79–0.95, $p < 0.01$), and Nishimura's activities of daily living scores (0.75, 0.63–0.89, $p < 0.01$) significantly correlated with prevalence of DSC. There were no significant risk factors for MDE.

Conclusion: Apolipoprotein E4 allele contributed to neither DSC nor MDE. The association of MCI with ApoE4 and DSC suggested that MCI is a confounder for the association between ApoE4 and DSC.

Key words: apolipoprotein E4 allele; depression; mild cognitive impairment; older people
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Introduction

The most challenging issues in the field of geriatric psychiatry include depression and various forms of dementia, such as Alzheimer's disease (AD). Several risk factors for depressive symptoms and depressive disorders in the older people have been pointed out by previous studies: number of chronic diseases (Bisschop *et al.*, 2004; Braam *et al.*, 2005; Schoevers *et al.*, 2005), poor health status (Copeland *et al.*, 1999; Gazmararian *et al.*, 2000), functional limitation (Blumstein *et al.*, 2004; Horowitz *et al.*, 2005; Jorm *et al.*, 2005), stressful life events (Kraaij and de Wilde, 2001; Oldehinkel *et al.*, 2003), and lower education (Beekman *et al.*, 2001; Jang *et al.*, 2002; Azar *et al.*, 2005).

Apolipoprotein E4 allele (ApoE4) is known as one of the most influential risk factors for AD. Additionally, a number of researchers have reported that ApoE4 is also a risk factor for depression (Krishnan *et al.*, 1996; Rigaud *et al.*, 2001; Yen *et al.*, 2007). However, among the older people, the role of ApoE4 has been controversial for more than a decade.

Using clinic-based data, Krishnan *et al.* (1996) studied 42 older people with depression and found that the proportion of ApoE3/4 carriers was significantly higher for late-onset depression compared with early-onset depression. Another study examining 140 patients with depression revealed that the presence of ApoE4 was significantly associated with late-onset depression (Rigaud *et al.*, 2001).

On the other hand, a clinic-based study by Ohara *et al.* (1999) included 134 clinic patients with depression; they found no association between early-onset or late-onset depressive disorders and ApoE4.

As for community-based studies, Bonger *et al.* (2009) investigated the association between a subtype of depression and impaired cognitive performance with ApoE4. They used data from 305 older subjects with depression who were seen in primary care offices in the Baltimore area; however, they failed to confirm an association. Harwood *et al.* (1999) used the Hamilton Depression Rating Scale to investigate a possible association between depressive symptoms and ApoE4 among 506 community-residing older subjects who were screened for cognitive impairment, but they failed to find an association. In a large retrospective study, Surtees *et al.* (2009) used data from 17 507 subjects but found no association between ApoE genotypes and a recent (within the past year) or chronic major depressive disorder.

Among community-based studies, only Yen *et al.* (2007) found that ApoE4 significantly enhanced the risk of depression. However, they assessed depressive symptoms by using a questionnaire, and the details of clinical data for depression were not included.

Although such previous studies provided much informative knowledge, the number of the subjects was generally small except for the study by Surtees *et al.* (2009) (Krishnan *et al.*, 1996; Ohara *et al.*, 1999; Rigaud *et al.*, 2001; Bonger *et al.*, 2009). Some of the studies dealt with major depression (Krishnan *et al.*, 1996; Ohara *et al.*, 1999; Rigaud *et al.*, 2001; Surtees *et al.*, 2009), whereas others focused on depressive symptoms (Harwood *et al.*, 1999; Yen *et al.*, 2007; Bonger *et al.*, 2009). Additionally, interviews to confirm the psychiatric diagnosis by psychiatrists were not performed in the community-based studies (Harwood *et al.*, 1999; Yen *et al.*, 2007; Bonger *et al.*, 2009; Surtees *et al.*, 2009).

During the last decade, a number of attempts have been made to detect a distinct state of abnormal cognition that does not amount to dementia but is distinguishable from normal cognitive decline associated with aging. We use the term "mild cognitive impairment" (MCI) to describe such a transitional status. Petersen *et al.* (1999) has provided the most frequently used definition of MCI. However, thus far, few epidemiological studies have used the parameters of MCI when looking at depression. In previous studies, overlooking MCI might have affected the results. In fact, Harwood *et al.* (1999) reported that mood disturbances were not associated with ApoE4 but more with memory complaints. We examined methods of cognitive assessment and presence or absence of MCI diagnosis from the previous studies described earlier (Table 1). Although the previous studies excluded those who had a diagnosis of dementia from the analysis, many of the studies used only screening tests such as the Mini-mental State Examination, and none of them made MCI diagnosis based on its recent definition.

We have conducted a community-based investigation of depression and dementia since 2001 in Tone Town, Ibaraki, Japan. As a part of this study, we examined the relationship between ApoE4 and depression. We took MCI into consideration and limitations of previous studies as described earlier.

Methods

The present cross-sectional study was conducted in Tone Town, Ibaraki, Japan. This town is located approximately 40 km northeast of central Tokyo and consists of 22 districts. On 1 May 2001, Tone Town had 3083 residents aged 65 years and older. These 3083 inhabitants were considered as potential subjects. The composition of Tone Town was similar to that of Japan's total population in 2001.

The prevalence of depression was estimated using a two-phase design. Seven psychiatrists and eight psychologists, who were trained for this study by the authors, and public health nurses conducted the first phase (screening and clinical evaluation) and the second phase (structured interview and cognitive assessment).

Ethical considerations

The protocol of this study was approved by the ethics committee of the University of Tsukuba (Miyamoto *et al.*, 2009; Sasaki *et al.*, 2009). Eligible subjects gave written informed consent to participate in the study

Table 1 Comparison of the association between ApoE4 and depression

Authors	Year	Country	Setting	Age range, years	*n*	Definition of depression	Cognitive function scale	Diagnosis of MCI (+/−)	Association with ApoE4
Krishnam *et al.*	1996	USA	Clinic	≥58	42	Major depression (DSM-IIIR)	MMSE ≥23	−	Late-onset depression ($p < 0.05$)
Ohara *et al.*	1999	Japan	Clinic		239	Depressive disorder (ICD-10)	MMSE >23	−	No association between ApoE4 and early-onset/late-onset depressive disorder
Harwood *et al.*	1999	USA	Community	≥60	506	Depressive symptoms (HAM-D)	MMSE 27.7 ± 1.9	−	No association between ApoE4 and depressive symptoms
Rigaud *et al.*	2001	France	Clinic		140	Major depression (DSM-IV)	MMSE 29.1 ± 1.0	−	Late-onset depression($p < 0.05$)
Yen *et al.*	2007	Taiwan	Community	65–74	283	Depressive symptoms (TDQ)	SPMSQ (normal, mild, moderate, severe)	−	Severe depression($p < 0.05$)
Bonger *et al.*	2009	USA	Clinic	≥65	305	Depressive symptoms (CES-D, CIDI)	MMSE 27.0 ± 2.8, FAS, HVLT, BTA	−	No association between ApoE4 and depressive symptoms
Surtees *et al.*	2009	UK	Community	41–80	17 507	Past-year or lifetime major depression (HLEQ, DSM-IV)	None/no description	−	No association between ApoE4 and major depression

Values are mean ± SD. MCI, mild cognitive impairment; ApoE4, apolipoprotein E4 allele; MMSE, Mini-mental State Examination; HAM-D, Hamilton Depression Rating Scale; TDQ, Taiwanese Depression Questionnaire; SPMSQ, Short Portable Mental State Questionnaire; CES-D, Center for Epidemiological Studies Depression Scale; CIDI, Composite International Diagnostic Interview; FAS, Controlled Oral Word Association Test; HVLT, Hopkins Verbal Learning Test; BTA, Brief Test of Attention; HLEQ, Health and Life Experiences Questionnaire.

and underwent a screening interview. Participants were assured that all data were confidential, and anonymity was preserved by assigning random numbers to the data sets.

First phase

This study was conducted between December 2001 and April 2002. Before the baseline examination, we sent an invitation letter explaining the objectives of the project to all potential subjects. We also asked local welfare commissioners (persons who are vested with promoting social welfare in each local area) to recommend individual residents for participation in the research. We excluded individuals with whom a local welfare commissioner could not meet and individuals whom we could not contact despite three telephone calls during the week prior to the initial examination (unreachable individuals).

We visited each of the 22 districts once per week and conducted two group screenings in the morning and afternoon. In addition to the group screenings in the 22 districts, we visited 44 individuals who were institutionalized in a long-term care facility and used the same methods described in the succeeding text.

Assessment procedures

Demographics and medical and psychiatric issues.

The interview consisted of a structured questionnaire assessing age, sex, education, and medical and psychiatric conditions. Subjects were also asked to provide blood samples for routine testing and genotyping of ApoE (Corder *et al.*, 1993).

Mood status.

The interview was followed by the 15-item short version of the Geriatric Depression Scale (GDS) for mood assessment. Those with a score of 6 or higher were considered to have depressive symptoms (Brink *et al.*, 1982).

Perceived memory difficulty.

Participants were asked whether they had memory difficulties in general, as well as difficulties in specific areas according to the 19 items of the Détérioration Cognitive Observée (DECO), which was originally developed as an objective assessment for memory difficulty (Ritchie and Fuhrer, 1992). DECO is a Likert scale dealing with changes in behavior (activity level, memory for places, events, procedures and persons, and learning of new skills). The maximum score on the scale is 38, and the minimum score is 0 (with lower scores indicating