education, presence of apolipoprotein E 4, MCI, and so on (Djernes, 2006). Chi-squared test, *t*-test, and ANOVA were used for continuous and categorical variables, respectively. For analyses in which the expected frequency was less than five, Fisher's exact probability test was used. Statistical analysis was conducted using SAS package version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

General findings

Diagnostic procedure of *depression* is illustrated in Figure 1. As shown, 385 of the 3083 inhabitants died, moved, or were not contacted, yielding 2698 baseline candidate for the study. Among them, 1035 residents refused to participate in the first phase, but 225 of them participated in the third phase. Consequently, 1888 individuals (1663 for the first phase and 225 for the third phase) (70.0%) of 2698 baseline candidates were enrolled. Table 1 shows the demographic and clinical data for the 1888 participants. Of the 1888 participants, all of the 44 institutionalized people were diagnosed as having dementia. A total of 738 participants participated in the second phase, and the remaining 881 individuals took part in the first phase but not in the second or underwent the second phase but lacked any data (hereafter the combined persons are termed "first (+)/second (−) participants"). Of the 225 individuals who participated in the third phase, 86 were missing at least one data point, so the data from the remaining 139 individuals contributed to the prevalence estimation.

Between the 877 subjects individually interviewed for depression diagnosis and the remaining 1011 subjects, significant differences were found in the following: GDS score and age were lower, and the score of the five tests excluding the clock drawing test were higher for the interviewed subjects. These results indicate that the subjects were functionally better than those who were not interviewed for suspected depression.

Table 1 Demographic and clinical data for all participants

$n = 1888$	Mean ± SD
Age (years)	73.8 ± 6.0
Women, *n* (%)	969 (58.3)
Education (years)	9.9 ± 2.7
GDS score	2.9 ± 2.6
NADL score	49.6 ± 1.7
IADL score	5.1 ± 1.6
BMI	22.8 ± 3.2

GDS, Geriatric Depression Scale; NADL, Nishimura's activities of daily living; IADL, instrumental activities of daily living; BMI, body mass index.

Prevalence and characteristics of depression

Among the 738 second-phase participants (147 with GDS scores of ≥6 and 591 with GDS scores of <6), 24 of the 147 subjects with GDS scores of ≥6 were diagnosed as having MDE, and the remaining 123 subjects had a diagnosis of DSC. Twelve of the 591 subjects with GDS scores <6 were diagnosed as having MDE. Thus, 36 participants were diagnosed with MDE. On the other hand, among the 139 third-phase participants with full data, 3 were found to have MDE, and 10 were found to have DSC. In this diagnostic process, neither MDE nor DSC was diagnosed for the individuals with dementia.

In total, among the 877 interviewed subjects, 39 and 133 individuals were diagnosed with MDE and DSC, respectively. The prevalence of MDE and DSC for the target population were estimated to be 4.5% (95% CI, 3.4–6.0) and 11.5% (4.2–28.0), respectively.

Table 2 shows the demographic and clinical data for the 877 subjects in terms of the *depression* and normal mood groups. The prevalence of MCI was higher for the *depression* group, whereas ADL was better and education year was longer for the normal mood group.

Prevalence of coexisting depression and mild cognitive impairment

Different from the prevalence estimation study for the *depression*, for the purposes of accuracy in prediction of the prevalence of coexisting depression and MCI, the subjects of this portion of the study were confined to those who underwent the face-to-face interview for depression diagnosis. Among the 877 participants with full data (738 second-phase and 139 third-phase participants), the prevalence of the coexistence of the *depression* and the four MCI subtypes were estimated (Table 3). Using cutoff values of 1.5 SD for the diagnosis of MCI, 171 of the 877 participants (19.5%) were indicated to have MCI. The proportion of all subtypes of MCI combined was higher ($p < 0.01$) for the *depression* group (26.2%) than the normal mood group (17.9%). In addition, the prevalence of *depression* was significantly higher ($p < 0.01$) for the MCI group (26.3%) than the normal cognition group (18.0%). Taken together, the individuals with MCI were more likely to develop depressive symptoms, and vice versa.

Table 2 Demographic and clinical data for interviewed subjects

Characteristic	Non-depression	Depression (DSC or MDE)	*p*
	n = 705	*n* = 172	
Age (years)	73.5 ± 5.6	73.4 ± 5.4	NS
Women, *n* (%)	414 (58.7)	91 (52.9)	NS
Education (years)	10.1 ± 2.7	9.6 ± 2.3	$p < 0.05$
NADL	49.6 ± 1.4	49.1 ± 2.7	$p < 0.01$
MCI, *n* (%)	138 (16.7)	45 (26.2)	$p < 0.01$
APOE4 carrier, *n* (%)	147 (20.9)	32 (18.6)	NS
Habitual alcohol drinking, *n* (%)	242 (34.3)	54 (31.4)	NS
Habitual smoking, *n* (%)	239 (33.9)	60 (34.9)	NS
Hypertension, *n* (%)	212 (30.0)	37 (21.5)	NS
Diabetes, *n* (%)	40 (5.7)	7 (4.1)	NS
Hyperlipidemia, *n* (%)	22 (3.1)	5 (2.9)	NS
Cerebral vascular disease, *n* (%)	24 (3.4)	7 (4.8)	NS

DSC, depressive symptoms case; MDE, major depressive episodes; NADL, Nishimura's activities of daily living; MCI, mild cognitive impairment; APOE4, apolipoprotein E type 4; NS, not significant.

Table 3 Coexistence of mild cognitive impairment and depression among the interviewed 877 subjects

Mood/cognition	Normal (80.5%)		Depressed pooled DSC + MDE (19.6%)		DSC (15.2%)		MDE (4.4%)	
	n = 705 (100%)		*n* = 172 (100%)		*n* = 133 (100%)		*n* = 39 (100%)	
Normal 706 (80.5%), NS	579	(82.1%)	127	(73.8%)	95	(71.4%)	32	(82.1%)
aMCIs 14 (1.6%), NS	10	(1.4%)	4	(2.3%)	4	(3.0%)	0	(0.0%)
aMCIm 25 (2.9%), NS	15	(2.1%)	10	(5.8%)	7	(5.3%)	3	(7.7%)
naMCIs 109 (12.4%), NS	89	(12.6%)	20	(11.6%)	18	(13.5%)	2	(5.1%)
naMCIm 23 (2.6%), NS	12	(1.7%)	11	(6.4%)	9	(6.8%)	2	(5.1%)
aMCIs + naMCIs 123 (14.0%), NS	99	(14.0%)	24	(13.9%)	22	(16.5%)	2	(5.1%)
aMCIm + naMCIm 48 (5.5%)*	27	(3.8%)	21	(12.2%)*	16	(12.0%)	5	(12.8%)

DSC, depressive symptom case; MDE, major depressive disorder; aMCIs, amnestic MCI single; aMCIm, amnestic MCI multiple; naMCIs, non-amnestic MCI single; naMCIm, non-amnestic MCI multiple; NS, not significant.
Statistical issues: comparison between normal mood group versus depressed pooled group.
*$p < 0.01$.

It was also examined whether the *depression* group exhibited a prototypical profile of cognitive dysfunction. Using the generalized linear model, the difference in the proportion for each type of MCI between the normal mood and *depression* groups was examined. No significant differences were present in the prevalence of each of the four MCI types between the two groups. However, not MCI single (aMCIs + naMCIs) but MCI multiple (aMCIm + naMCIm) was more prevalent in the *depression* group (12.2%) than the normal group (3.8%).

Discussion

Prevalence of depression

Beekman *et al.* (1999) reviewed studies that dealt with the prevalence of depression in later life. According to the severity of cases, the reported weighted average of the prevalence of major and minor depressions was 1.8% (from 0.4% to 10.2%) and 9.8% (from 2.4% to 14.3%), respectively. To our knowledge, eight previous studies (Blazer and Williams, 1980; Kay *et al.*, 1985; Weissman *et al.*, 1985; Bland *et al.*, 1988; Kivela *et al.*, 1988; Komahashi *et al.*, 1994; Lobo *et al.*, 1995; Pahkala *et al.*, 1995) determined the prevalence of major depression based on the *DSM-III* or *DSM-III-R* criteria. The prevalence ranged from 0.4% to 3.7%. Because of the previously described many risk factors for depression besides ethnicity (Djernes, 2006), it is extremely difficult to make comparisons between the prevalence of the present study and the previous ones after controlling for the factors. However, a 4.5% prevalence rate of the *DSM-III-R* MDE in the present study appears to be similar to the results of the previous studies. As a category of depressive status other than MDE, we did not use dysthymia as listed in

the *DSM-III-R* but used our original definition of the DSC. The prevalence of DSC was estimated to be 11.5%. Regarding this issue, Djernes (2006) examined the prevalence of cases with depressive symptoms other than depressive disorders according to the *DSM* and International Classification of Diseases diagnostic criteria. Their cases of depressive symptoms were clinically diagnosed based on the presence of some depressive symptoms detected by rating scales, including the GDS. They reported that the prevalence of the cases among community-living older people widely ranges from 1.6% to 49%. However, more than half (12/22) of the studies showed the prevalence between 10% and 20%. Again, the risk factors aside, the results appear to be similar to our DSC prevalence.

As shown in Table 2, besides more prevalence of MCI, shorter education year and worse ADL for the *depression* groups were found. Both of them have been known as the risk factor for depression (Djernes, 2006). Although some studies reported cerebrovascular disease as the risk factor (Valvanne *et al.*, 1996; Schoevers *et al.*, 2006), our study did not find such result. Alcohol use has generally been regarded as a risk factor (Wilkins *et al.*, 2009); however, alcohol use was not higher for the *depression* group. The relationship between apolipoprotein E type 4 and depression has been controversial (Rigaud *et al.*, 2001; Bonger *et al.*, 2009), and we could not find the relationship.

Prevalence of coexisting depression and mild cognitive impairment

The present study showed high coexistence rate for *depression* and MCI (all subtypes of MCI combined). Regarding the epidemiology of depression among MCI individuals, several population-based studies (Chan *et al.*, 2003; Solfrizzi *et al.*, 2007; Geda *et al.*, 2008; Muangspaisan *et al.*, 2008) focused on the coexistence of exclusively amnestic MCI, and their results varied widely (prevalence of depression from 11.0% to 63.3%). Different from these studies, the cardiovascular health study (Lyketsos *et al.*, 2002) that determined the coexistence rate taking other types of MCI showed 26% coexistence of MCI (MCI amnestic type plus MCI multiple cognitive deficit type) and depressive symptoms. This result seems a little lower than our 36% prevalence for aMCIs plus aMCIm. The difference might be attributable to the difference in the methods between the two studies and the smaller sample size of our study.

This is the first study to report the prevalence of the four types of MCI among community-dwelling older people with depression. The present study also found higher prevalence of MCI among the subjects with *depression*. It is particularly interesting to understand whether individuals with *depression* show a certain prototypical profile of cognitive impairment. It has been said that older individuals with depression are likely to be worse in memory, attention, and executive function (Lockwood *et al.*, 2000; Butters *et al.* 2004; Rapp *et al.*, 2005), whereas those with Alzheimer's disease are likely to develop more severe amnesia (O'Brien *et al.*, 1994). However, in comparison with the normal mood group in the present study, individuals with *depression* showed no particular association with any of the four MCIs. It is possible that the *depression* group, especially the DSC group, was too heterogeneous to share cognitive impairment patterns, and that the number of the subjects was too small to show statistical significance. However, the prevalence of MCIm (aMCIm + naMCIm) was significantly higher for the *depression* group (12.2%) than the normal mood group (3.8%). A possible explanation for the result is that *depression* is apt to develop additional cognitive impairment in individuals with MCIs. Another explanation is that depression-related impairment in attention could simultaneously affect other cognitive domains.

The strength of the present study was that unlike most previous studies, the final diagnosis of MDE was performed on the basis of a face-to-face structured interview, and detailed cognitive assessments for the accurate examination of the relationship between depression and MCI were conducted. In terms of limitations, less than half of the first-phase participants underwent the individual interview. The resulting second-phase participants were superior in functions and demographics to the first (+)/second (−) participants. Thus, the prevalence of *depression* and coexisting conditions could have been underestimated.

In addition to higher prevalence of *depression* among individuals with MCI, this study was the first to report higher prevalence of MCI among community-dwelling depressed older people. Several researchers (Li *et al.*, 2001; Mondrego and Ferradez, 2004) have reported that the presence of depression promoted the conversion from MCI to dementia. Therefore, the present study suggests that attention should be paid to the risk of developing dementia for the older people with depression in general and the depressed older people with MCI in particular.

Conclusion

The prevalence of *depression* in our subjects seems to be similar with that of the previous studies. MCI was more prevalent in subjects with depression than those with normal mood. Individuals with *depression*

Key points

- The prevalence of major depressive disorder and DSC of the present study were 4.5% and 11.5%, which are similar to that of previous studies.
- Older subjects with depression were more likely to show MCI than those with normal mood.
- Although the older subjects with depression showed no prototypical profile of cognitive dysfunction, they were likely to show MCI multiple.
- Older subjects with MCI were more likely to develop depression than those with normal cognitive function.
- The risk of developing dementia in the depressed older people in general and those with coexisting MCI in particular should be acknowledged.

showed no particular association with any of the four MCIs. Given that depression and MCI are often associated with each other and that MCI is a predictor for the development of dementia, the risk of developing dementia in the depressed older people, particularly in older people with coexisting MCI, should be acknowledged.

Author contributions

All of the authors contributed to the conception and design, and analysis and interpretation of data. Fumio Yamashita, Chiine Kodama, Chiaki Ikejima, Shin Hidaka, Megumi Sasaki, Satoshi Tanimukai, Katsuyoshi Mizukami, and Takashi Asada contributed to the collection of data. Toru Kinoshita, Shiro Tanaka, Hideto Takahashi, and Tatsuyuki Kakuma contributed to the statistical analysis. Shin Hidaka contributed to the drafting of the article, and Takashi Asada did the final approval of the version to be published.

Conflict of Interest

None declared.

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Association Between Cognitive Function and Plasma Lipids of the Elderly After Controlling for Apolipoprotein E Genotype

Fumihiko Yasuno, M.D., Ph.D., Satoshi Tanimukai, M.D., Ph.D., Megumi Sasaki, M.D., Ph.D., Shin Hidaka, M.D., Chiaki Ikejima, M.A., Fumio Yamashita, M.D., Chiine Kodama, M.A., Katsuyoshi Mizukami, M.D., Ph.D., Makoto Michikawa, M.D., Ph.D., Takashi Asada, M.D., Ph.D.

Objective: *Although the relationship between cognitive function and plasma lipids has attracted attention, previous studies have shown conflicting results. One possible confounding factor is due to the influence of gene-related modulator. We investigated the relationship between cognitive function and lipid plasma levels of old age after controlling for apolipoprotein E* (APOE) *genotype.* **Methods:** *One thousand three hundred ninety-five subjects without dementia age 65 and older participated in this study. They were divided into two groups, with and without APOE4 [E4 (+) and E4 (−)]. Plasma concentrations of high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), total cholesterol (TC) and apolipoprotein E (apoE) were measured. Associations between plasma concentrations of lipids and cognitive function were investigated for each group.* **Results:** *We found a positive association between cognitive scores and plasma apoE level in both E4 (−) and E4 (+) groups. A positive relationship was also observed between cognitive score and HDL level in the E4 (−) group, but not in the E4 (+) group. No substantial association between cognitive score and LDL, TG, and TC levels was found in either of the groups.* **Conclusions:** *Our findings suggest that plasma apoE have a positive influence on cognitive function in both E4 (−) and E4 (+) groups, whereas the positive influence of plasma HDL was shown only in E4 (−) group. The identification of the influences of* (APOE) *genotype and the intracellular linkage among apoE and HDL metabolism is hoped for new preventive and therapeutic strategies for cognitive change of elderly.* (Am J Geriatr Psychiatry 2012; 20:574–583)

Key Words: Apolipoprotein E, cognitive function, high-density lipoprotein, low-density lipoprotein, triglyceride, total cholesterol

Received July 3, 2010; revised January 5, 2011; accepted January 14, 2011. From the Department of Neuropsychiatry, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan (Fumihiko Y, ST, MS, SH, CI, FY, CK, KM, TA); Department of Neuropsychiatry, National Cerebral and Cardiovascular Center, Osaka, Japan (Fumihiko Y); Department of Neuropsychiatry, National Center of Neurology and Psychiatry, Tokyo, Japan (Fumio Y); Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Ehime, Japan (ST); Department of Alzheimer's Disease Research, National Center for Geriatrics and Gerontology, Aichi, Japan (MM). No disclosures to report.
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Send correspondence and reprint requests to Fumihiko Yasuno, M.D., Ph.D., Department of Neuropsychiatry, National Cerebral and Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. e-mail: yasunof@hsp.ncvc.go.jp

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OBJECTIVE

Despite the conflicting results of previous studies, a possible relationship between cognitive function and plasma lipids has been attracting increasing attention. In one study of aged persons, a low plasma concentration of high-density lipoprotein (HDL) was related to cognitive impairment and dementia, whereas no association was found between low-density lipoprotein (LDL), triglycerides (TG) and Mini-Mental State Examination (MMSE) scores.[1] On the contrary, a 4-year longitudinal study of postmenopausal women reported that high-LDL levels were associated with concurrent cognitive impairment, whereas HDL and TG levels were not associated with cognition.[2] In younger middle-aged groups, HDL and TG concentrations were unassociated with memory performance, whereas higher plasma concentration of LDL was associated with better memory performance.[3] In a study of Alzheimer disease (AD) patients, no concurrent associations were found between HDL, LDL, or TG and MMSE.[4] In a systematic review of prospective studies of relationships between total cholesterol (TC) and dementia or cognitive decline, an association between high midlife TC and cognitive impairment was found, but there was only weak evidence for an association between TC and cognitive decline.[5]

One possible explanation for these contradictory results may lie in the age of the subjects when cognitive function and plasma lipids were assessed. The influence of gene-related modulator might be another confounding factor. Apolipoprotein E (apoE) is a polymorphic protein arising from 3 alleles ($\varepsilon 2/\varepsilon 3/\varepsilon 4$) at a single gene locus. Its three major isoforms, apoE2, apoE3, and apoE4, differ from one another only by single amino acid substitutions, yet these changes have profound functional consequences both at cellular and molecular levels.[6] The apolipoprotein E (*APOE*) gene plays a central and pervasive role in lipid metabolism.[7] Previous study supported the association between *APOE* gene polymorphisms and the vulnerability of the aging brain.[8] Cross-sectional studies have reported the association of E4 inheritance with poor global cognitive function, episodic memory, and executive function.[9,10] Thus, failure to control for *APOE* genotype may influence the result observed between cognitive function and plasma lipids. In one previous study, the different association of cholesterol on cognitive functioning was shown in oldest old (> = 85 years old) with and without *APOE4* allele, and the necessity of further examination of the role of *APOE* genotype is suggested.[11] The current study examines the relationship between cognitive function and plasma levels of lipids including HDL, LDL, TG, TC, and apoE in the community-dwelling elderly (> = 65 years old) with stratification by *APOE4* allele status.

METHODS

Participants

We recruited the participants in the present study from the "Tone Project" in Tone town, Ibaraki, Japan.[12] This town is located about 40 miles northeast of central Tokyo, and consists of both of newly-developed residential and agricultural areas. On November 30th, 2001, the town had 2,698 inhabitants age 65 and older (14.0% of the town population). On the basis of data from the national census, the age distribution in Tone town was almost identical to that of the whole of Japan. They were asked to participate in the project, and 1,888 of them were finally enrolled in the Tone Project between December 2001 and April 2002.

After the assessment, a group of psychiatrists and neuropsychologists reviewed the data and reached a consensus regarding the presence or absence of psychiatric disease including dementia according to DSM-IV criteria. We excluded the data from those with psychiatric diseases (n = 123).

Two hundred eighty participants refused blood sampling because of fear or some other personal reason. Sixty-one participants had no blood sampling data because of error of blood sampling or of some measurement procedure. One hundred eighty-six participants did not complete the series of examinations of cognitive assessment because of fatigue, refusal, performance mistake, and so on. Among these participants, 157 participants had neither blood sampling nor cognitive assessment. After excluding data from those without blood data and/or incomplete data, we used the data from 1,395 subjects without dementia for the analysis.

At the initial examination, all of the eligible subjects provided their written informed consent to participate in the study. This study was approved by the ethics committee of Tsukuba University.

Plasma Parameters

Blood samples were collected from the subjects at fasting visits. Plasma levels of LDL, HDL, TG, and 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. The *APOE* gene was amplified by the primer and amplification conditions described by Wenham and colleagues.[13] After amplification, the PCR product was digested with the restriction enzyme *Hha* I, and subjected to electrophoresis in a 15% polyacrylamide gel.

Screening and Structured Interview

After blood sampling, all participants underwent a screening interview consisting of a structured questionnaire (questions on age, sex, education). This was followed by the 15-items short version of the Geriatric Depression Scale (GDS).[14] The participants were asked for their medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia and hypertension for which they had received medical care. During the interview, we estimated visual acuity, hearing and speech ability of each subject.

Cognitive Assessment

After completing the interview, all the participants underwent group cognitive assessment using a set of four tests to measure these cognitive domains: attention, memory, language, and reasoning. We evaluated attention by using the Japanese version of a set-dependent activity.[15] The test assesses alternating attention, which refers to the capacity for mental flexibility that allows individuals to shift their focus of attention between tasks with different cognitive requirements. To assess memory ability, we used the Category Cued Recall test.[16] We examined language ability with a category fluency test.[17] The subjects were asked to generate as many examples as possible in 2 minutes from the semantic category "animals." To assess abstract reasoning ability, we employed the similarities subset of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[18]

This cognitive assessment was conducted in a group setting (maximum 50 participants) by an examiner using a projector. Before each of the four tests, the participants were given instructions by an examiner. All the participants were asked to record their answers on the answer sheet. Each screening was supervised by members of our research team, and they prevented communications among participants. If the responders had questions, the members answered them right away. The mean length of the four-test examination was 35 minutes. For proving the validity of the group-setting method, we examined the agreement of four tests scores between group setting and face-to-face method among 15 participants. For this purpose, the participants first underwent group-setting tests, and 35 days later they underwent face-to-face tests. Between the two trials, Pearson's correlation coefficient was above 0.70, and significance was $p < 0.01$ for all of the four tests. For participants with difficulty understanding tasks or with impaired hearing or vision ($n = 261$), we conducted the assessment by using the individual versions of the four tests in a face-to-face setting.

For delineating the cognitive composite score, a simple average score of the four individual scores is not enough, because the contribution of the individual scores to the composite scores should be considered. Evaluation of the results of the four tests revealed that the score for the four cognitive domains showed normal distribution and significant mutual correlation. Therefore, we attempted to convert the four scores into a composite cognitive score using the first component of the scores of principal component analysis (Eigenvalue 2.85, proportion 71%, N = 1395, Composite cognitive score = 0.853* attention score + 0.809* memory score + 0.856* language score + 0.859* reasoning score.)

Statistical Analysis

Subjects were divided into the two groups of E4(−)(n = 1118) (genotypes $\varepsilon2/\varepsilon2$ [n = 4], $\varepsilon2/\varepsilon3$ [n = 107], $\varepsilon3/\varepsilon3$ [n = 1007]) and E4(+) (n = 277) (genotypes $\varepsilon2/\varepsilon4$ [n = 18], $\varepsilon3/\varepsilon4$ [n = 240] and $\varepsilon4/\varepsilon4$ [N = 19]) to test for the influence of genotype on the association between lipids and cognitive function.

Group differences in demographic characteristics were examined by unpaired *t*-test and Pearson χ^2 test. To examine the influence of group differences on cognitive function, cognitive scores were compared between groups by analysis of covariance (ANCOVA), with age, sex, years of education, GDS score, and medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension as covariates (Table 1). To examine group differences in the concentrations of lipids, ANCOVA was performed with age and sex as covariates (Table 2).

The subjects in each category were divided into three strata according to tertiles of the plasma concentrations of lipids. To examine the influence of plasma lipids and ApoE genotype on cognitive function, we performed ANCOVA with the three strata of the level of lipids and genotype as independent variables, the composite cognitive scores as dependent variables, and age, sex, years of education, GDS score, and the medical history of diseases as covariates (Tables 3–7).

Individual test scores and composite cognitive scores were compared in E4 (−) and E4 (+) groups separately among the three strata by ANCOVA, with age, sex, years of education, GDS score, and medical history of diseases as covariates. In addition, effect sizes were calculated using partial eta-squared (η^2) to estimate and compare the effect of the level of lipids on cognitive score between groups of different sample size η^2 0.01 was regarded as no substantial effect. Follow-up *t*-tests were performed to specify differences of cognitive score among the three strata according to the levels of lipids (Tables 3–7, Figure 1).

To examine whether the tertile of lipids/apoE level were related to composite cognitive scores in the E4 (−) and E4 (+) groups, we performed multiple regression analysis with composite cognitive score as dependent variable and the tertiles of lipids/apoE level as independent variables, after adjustment for other factors of age, sex, years of education, GDS score, and medical history of diseases.

Multiple comparisons were adjusted by Bonferroni correction. All statistical tests were two-tailed and reported at α <0.05. Statistical analysis of the data was performed using SPSS for Windows 16.0 (SPSS Japan, Inc., Tokyo, Japan).

RESULTS

The demographic data of the E4 (−) and E4 (+) groups are shown in Table 1. There were no group differences in demographic characteristics between the groups except the cognitive score. Our finding of a higher cognitive score of the E4(−) group is consistent with previous studies.[10] Table 2 shows the mean of the plasma concentrations of lipids for the E4 (−) and E4 (+) groups. There were group differences in the plasma concentrations of TC and apoE. The concentration of TC was lower and that of apoE was higher in the E4 (−) group.

Tables 3–7 show the median plasma concentrations of lipids for the three strata according to the tertiles of plasma levels of lipids and apoE. Individual test scores and composite cognitive scores of the E4 (−)

TABLE 1. Demographic Characteristics, Mean ± SD

Characteristic	ApoE4(−) (n = 1,118)	ApoE4(+) (n = 277)	df	*t*, χ^2 or *F*	p
Age, y[a]	73.6 ± 5.7	73.6 ± 5.8	1393	$t = 0.06$	0.95
Male, No (%)[b]	467 (42%)	108 (39%)	1	$\chi^2 = 0.71$	0.40
Education, y[a]	10.0 ± 2.6	10.0 ± 2.7	1393	$t = 0.20$	0.85
GDS score[a]	3.0 ± 2.7	2.7 ± 2.6	1393	$t = 1.63$	0.10
Cardiovascular disease, No (%)[b]	40 (3.6%)	11 (4.0%)	1	$\chi^2 = 0.10$	0.76
Diabetes mellitus, No (%)[b]	59 (5.3%)	13 (4.7%)	1	$\chi^2 = 0.16$	0.69
Hyperlipidemia, No (%)[b]	31 (2.8%)	13 (4.7%)	1	$\chi^2 = 2.68$	0.10
Hypertension, No (%)[b]	314 (28.4%)	70 (25.2%)	1	$\chi^2 = 0.88$	0.35
Composite cognitive score[c]	39.3 ± 12.0	37.1 ± 12.0	1, 1384	$F = 7.3$	0.005[d]

[a]The p value was calculated by unpaired two-tailed *t* test.

[b]The p value was calculated by Pearson χ^2 two-tailed test.

[c]The p value was calculated by analysis of covariance (ANCOVA) with age, sex, years of education, score of GDS and medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia and hypertension as covariates. Data are mean ± SD after adjustment for covariates.

[d]p <0.05.

TABLE 2. Concentrations of Lipid and ApoE in *APOE4*(−) and *APOE4*(+) Groups[a]

Concentration	*APOE4*(−) (n = 1,118)	*APOE4*(+) (n = 277)	ANCOVA (df = 1, 1,390) *F*	p
HDL (mmol/L)	1.44 ± 0.38	1.41 ± 0.38	1.33	0.25
LDL (mmol/L)	2.66 ± 0.83	2.73 ± 0.83	1.97	0.16
TG (mmol/L)	1.93 ± 1.17	1.97 ± 1.17	0.31	0.58
TC (mmol/L)	5.32 ± 0.92	5.48 ± 0.92	6.76	0.01[b]
apoE (mg/dL)	2.66 ± 1.44	2.28 ± 1.45	15.8	<0.001[c]

[a]Data are mean ± SD after adjustment for age and sex.
[b]p <0.05.
[c]p <0.001.

and E4 (+) groups according to the three strata of plasma concentrations of lipids/apoE are also shown in these tables.

ANCOVA analysis of the influence of HDL level and genotype on composite cognitive scores revealed interaction between HDL level and genotype (Table 3). In the E4 (−) group, subjects with higher HDL concentration had higher cognitive score. The effect size of the plasma HDL level on cognitive score showed a substantial influence of the HDL level on three individual test scores and composite cognitive scores. Follow-up *t*-tests showed differences of these cognitive scores among the three strata. In the E4 (+) group, such an association was not observed (Table 3, Figure 1). In multiple regression analysis, plasma HDL level positively related to composite cognitive score (β = 0.12, p <0.001, df = 1108) in the E4 (−) group.

A significant main effect of the apoE level was found by ANCOVA analysis of the influence of the apoE level and genotype on composite cognitive scores (Table 4). Subjects with higher apoE concentration had higher cognitive score in all individual and composite cognitive scores in the E4 (−) group, and one individual and composite cognitive scores in the E4 (+) group. The effect size of the plasma apoE level on these cognitive score showed a substantial influence of the apoE level on two individual and composite cognitive scores in the E4 (−) group, and one individual and composite cognitive scores in the E4 (+) group. Follow-up *t*-tests showed differences of these cognitive scores among the three strata. (Table 4, Figure 1). In multiple regression analysis, plasma ApoE level positively related to composite cognitive scorein the group of E4 (−) (β = 0.13, p <0.001, df = 1108) and E4(+) (β = 0.12, p = 0.009, df = 267).

TABLE 3. Mean Cognitive Score of Each Tertile of HDL Level by *APOE4*(−) and *APOE4*(+) Groups[a,b]

Concentrations, median (min–max)		HDL concentration (mmol/L), tertiles: Low 1.09 (0.57–1.24)	Middle 1.37 (1.27–1.58)	High 1.81 (1.60–3.57)	ANCOVA[c] *F*	p	η^2	Between groups[d]
E4(−)	Attention	15.0 ± 11.1	15.8 ± 11.1	16.8 ± 11.8	6.74	<0.001[f]	0.012[g]	B
	Memory	9.7 ± 7.3	10.3 ± 7.3	11.3 ± 7.7	12.4	<0.001[f]	0.022[g]	B, C
	Language ability	12.6 ± 6.6	13.2 ± 6.6	13.3 ± 7.0	3.15	0.043[e]	0.006	
	Reasoning	6.5 ± 6.1	7.2 ± 6.2	8.0 ± 6.5	17.5	<0.001[f]	0.031[g]	A, B, C
	Composite score	37.0 ± 20.1	39.2 ± 20.1	41.7 ± 21.3	14.2	<0.001[f]	0.025[g]	A, B, C
E4(+)	Attention	14.4 ± 10.6	15.7 ± 11.3	14.5 ± 11.6	1.06	0.35	0.008	
	Memory	9.5 ± 8.4	10.6 ± 8.9	9.8 ± 9.2	1.10	0.34	0.008	
	Language ability	12.9 ± 7.0	12.8 ± 7.4	12.5 ± 7.6	0.21	0.81	0.002	
	Reasoning	6.4 ± 5.7	7.2 ± 6.0	7.0 ± 6.2	1.30	0.28	0.010	
	Composite score	36.6 ± 21.3	39.0 ± 22.5	37.1 ± 23.2	0.97	0.38	0.007	

[a]Data are mean ± SD after adjustment for age, sex, years of education, GDS score, and medical history ofcardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension as covariates.
[b]With ANCOVA analysis of the effect of the level of HDL and genotype on composite cognitive scores,main effect of HDL level, $F_{[2,1381]}$ = 4.55. p = 0.01; main effect of genotype, $F_{[1,1381]}$ = 7.84. p = 0.005;HDL level-by-genotype interaction, $F_{[2,1381]}$ = 3.25. p = 0.04.
[c]df = 2,1107 for *APOE4*(−), 2, 266 for *APOE4*(+).
[d]Significance at p <0.016 (0.05/3) after Bonferroni adjustment for multiple comparisons: A, low to middle:B, low to high: C, middle to high concentration group comparison.
[e]p <0.05.
[f]p <0.001.
[g]η^2 >0.01

TABLE 4. Mean Cognitive Score of Each Tertile of apoE Level by *APOE4*(−) and *APOE4*(+) Groups[a,b]

		apoE concentration (mg/dL), tertiles			ANCOVA[c]			
Concentrations, median (min–max)		Low 1.3 (0.5–1.7)	Middle 2.3 (1.8–3.0)	High 4.0 (3.1–10.5)	F	p	η^2	Between groups[d]
E4(−)	Attention	14.3 ± 11.5	15.8 ± 11.1	17.2 ± 11.1	17.2	<0.001[f]	0.030[g]	A, B, C
	Memory	9.9 ± 7.7	10.5 ± 7.4	10.9 ± 7.4	4.90	0.008[e]	0.009	B
	Language ability	12.8 ± 6.9	12.8 ± 6.7	13.4 ± 6.6	3.61	0.027[e]	0.006	
	Reasoning	6.5 ± 6.5	7.2 ± 6.2	7.8 ± 6.2	11.9	<0.001[f]	0.021[g]	A, B
	Composite score	36.7 ± 21.0	39.0 ± 20.3	41.7 ± 20.3	15.7	<0.001[f]	0.028[g]	A, B, C
E4(+)	Attention	13.9 ± 10.0	15.3 ± 11.3	15.8 ± 12.4	2.24	0.11	0.017[g]	
	Memory	9.3 ± 7.9	10.3 ± 8.9	10.6 ± 9.8	1.68	0.19	0.012[g]	
	Language ability	12.3 ± 6.6	12.9 ± 7.4	13.2 ± 8.2	1.14	0.32	0.008	
	Reasoning	5.9 ± 5.3	7.5 ± 5.9	7.5 ± 6.5	7.72	<0.001[f]	0.055[g]	A, B
	Composite score	35.0 ± 19.9	38.9 ± 22.4	39.8 ± 24.7	3.91	0.021[e]	0.029[g]	B

[a]Data are mean ± SD after adjustment for age, sex, years of education, GDS score, and medical history ofcardiovascular disease, diabetes mellitus, hyperlipidemia and hypertension as covariates.

[b]With ANCOVA analysis of the effect of the level of apoE and genotype on composite cognitive scores,main effect of apoE level, $F_{[2,1381]} = 11.3$. p = 0.00001; main effect of genotype, $F_{[1,1381]} = 4.96$. p = 0.03; apoE level-by-genotype interaction, $F_{[2,1381]} = 0.45$. p = 0.64.

[c]df = 2, 1107 for *APOE4*(−), 2, 266 for *APOE4*(+).

[d]Significance at p <0.016 (0.05/3) after Bonferroni adjustment for multiple comparisons: A, low to middle:B, low to high: C, middle to high concentration group comparison.

[e]p <0.05.

[f]p <0.001.

[g]η^2 >0.01.

TABLE 5. Mean Cognitive Score of Each Tertile of LDL Level by *APOE4*(−) and *APOE4*(+) Groups[a,b]

		LDL concentration (mmol/L), tertiles			ANCOVA[c]			
Concentrations, median (min–max)		Low 1.89 (0.47–2.28)	Middle 2.59 (2.30–2.97)	High 3.44 (3.00–9.05)	*F*	p	η^2	Between groups[d]
E4(−)	Attention	16.3 ± 11.0	15.8 ± 11.4	15.2 ± 11.7	2.37	0.09	0.004	
	Memory	10.6 ± 7.3	10.7 ± 7.5	10.0 ± 7.7	3.12	0.05	0.006	
	Language ability	13.3 ± 6.5	13.2 ± 6.7	12.5 ± 6.9	5.00	0.007[e]	0.009	B, C
	Reasoning	7.2 ± 6.1	7.3 ± 6.4	7.0 ± 6.5	0.76	0.47	0.001	
	Composite score	40.0 ± 20.0	39.8 ± 20.7	37.7 ± 21.2	4.03	0.02[e]	0.007	B
E4(+)	Attention	15.0 ± 11.9	14.9 ± 11.1	14.7 ± 10.8	0.05	0.95	0.0004	
	Memory	10.0 ± 9.4	10.1 ± 8.7	9.8 ± 8.5	0.14	0.87	0.001	
	Language ability	13.1 ± 7.8	12.9 ± 7.2	12.3 ± 7.0	0.92	0.40	0.007	
	Reasoning	7.1 ± 6.3	7.0 ± 5.9	6.5 ± 5.8	0.78	0.46	0.006	
	Composite score	38.2 ± 23.7	37.9 ± 22.1	36.6 ± 21.5	0.44	0.65	0.003	

[a]Data are mean ± SD after adjustment for age, sex, years of education, GDS score and medical history ofcardiovascular disease, diabetes mellitus, hyperlipidemia and hypertension as covariates.

[b]With ANCOVA analysis of the effect of the level of LDL and genotype on composite cognitive scores,main effect of LDL level, $F_{[2,1381]} = 2.70$. p = 0.07; main effect of genotype, $F_{[1,1381]} = 6.89$. p = 0.009;LDL level-by-genotype interaction, $F_{[2,1381]} = 0.05$. p = 0.95

[c]df = 2, 1107 for *APOE4*(−), 2, 266 for *APOE4*(+).

[d]Significance at p<0.016 (0.05/3) after Bonferroni adjustment for multiple comparisons: A, low to middle:B, low to high: C, middle to high concentration group comparison.

[e]p <0.05.

We found no main effect of LDL and its interaction with genotype by ANCOVA analysis of the influence of LDL level and genotype on composite cognitive scores (Table 5). We found an association between cognitive scores and the plasma concentration of LDL in the E4 (−) group in two individual and composite cognitive score. In multiple regression analysis plasma LDL level positively related to composite cognitive score (β = −0.06, p <0.001, df = 1,108) in the E4 (−) group. However, the effect size of the plasma

TABLE 6. Mean Cognitive Score of Each Tertile of TG Level by *APOE4*(−) and *APOE4*(+) Groups[a,b]

Concentrations, median (min–max)		TG concentration (mmol/L), tertiles: Low 0.98 (0.34–1.31)	Middle 1.63 (1.32–2.03)	High 2.77 (2.04–10.4)	ANCOVA[c]: *F*	p	η^2	Between groups[d]
E4(−)	Attention	15.4 ± 11.0	15.7 ± 11.4	16.4 ± 11.5	2.17	0.12	0.004	
	Memory	10.4 ± 7.3	10.5 ± 7.5	10.4 ± 7.6	0.08	0.92	0.0002	
	Language ability	13.0 ± 6.5	12.9 ± 6.7	13.1 ± 6.8	0.25	0.78	0.0004	
	Reasoning	7.2 ± 6.1	7.0 ± 6.4	7.4 ± 6.4	0.96	0.38	0.002	
	Composite score	38.7 ± 20.1	39.0 ± 20.8	39.9 ± 21.0	0.95	0.39	0.002	
E4(+)	Attention	14.0 ± 11.5	15.0 ± 11.5	15.5 ± 10.4	1.37	0.26	0.009	
	Memory	9.7 ± 9.1	10.6 ± 9.1	9.6 ± 8.2	1.08	0.34	0.008	
	Language ability	12.3 ± 7.5	13.1 ± 7.5	12.9 ± 6.8	0.80	0.45	0.006	
	Reasoning	6.3 ± 6.1	6.9 ± 6.1	7.3 ± 5.5	2.13	0.12	0.016[e]	
	Composite score	35.6 ± 22.9	38.5 ± 22.9	38.3 ± 20.7	1.35	0.26	0.009	

[a]Data are mean ± SD after adjustment for age, sex, years of education, GDS score, and medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension as covariates.
[b]With ANCOVA analysis of the effect of the level of TG and genotype on composite cognitive scores, main effect of TG level, $F_{[2,1381]} = 1.58$. $p = 0.21$; main effect of genotype, $F_{[1,1381]} = 7.71$. $p = 0.006$; TG level-by-genotype interaction, $F_{[2,1381]} = 0.59$. $p = 0.56$.
[c]df = 2, 1107 for *APOE4*(−), 2, 266 for *APOE4*(+).
[d]Significance at $p < 0.016$ (0.05/3) after Bonferroni adjustment for multiple comparisons: A, low to middle: B, low to high: C, middle to high concentration group comparison.
[e]$\eta^2 > 0.01$.

TABLE 7. Mean Cognitive Score of Each Tertile of TC Levels by *APOE4*(−) and *APOE4*(+) Groups[a,b]

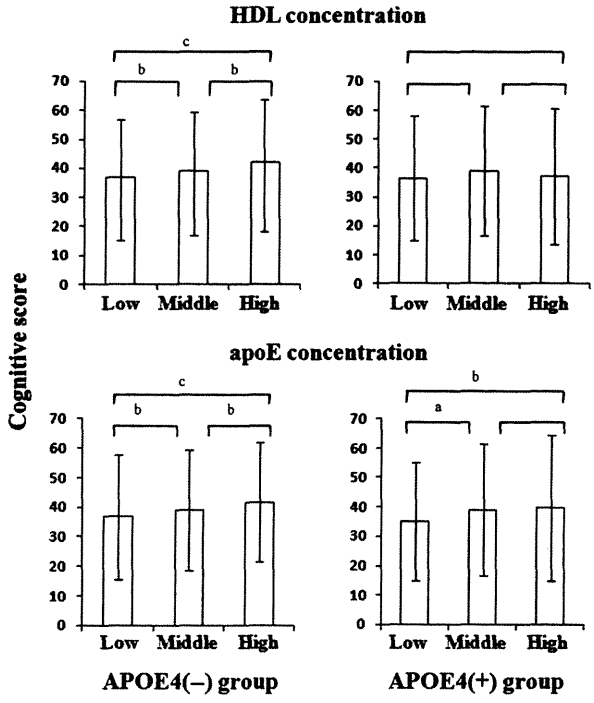
Concentrations, median (min–max)		TC concentration (mmol/L), tertiles: Low 4.34 (1.78–5.04)	Middle 5.33 (5.07–5.87)	High 6.28 (5.90–9.31)	ANCOVA[c]: *F*	p	η^2	Between Groups[d]
E4(−)	Attention	15.2 ± 10.6	16.2 ± 11.1	16.0 ± 13.2	2.53	0.08	0.005	
	Memory	10.2 ± 7.0	10.7 ± 7.4	10.4 ± 8.7	0.97	0.38	0.002	
	Language ability	12.9 ± 6.3	13.1 ± 6.2	13.0 ± 6.6	0.10	0.91	0.0001	
	Reasoning	6.8 ± 5.9	7.4 ± 6.2	7.5 ± 7.4	3.84	0.02[e]	0.007	B
	Composite score	38.2 ± 19.3	40.0 ± 20.3	39.7 ± 24.1	2.51	0.08	0.005	
E4(+)	Attention	13.9 ± 11.5	14.8 ± 11.3	15.8 ± 11.5	1.75	0.18	0.013[f]	
	Memory	9.6 ± 9.2	10.3 ± 9.0	9.9 ± 9.1	0.43	0.65	0.003	
	Language ability	12.2 ± 7.5	13.4 ± 7.3	12.6 ± 7.5	1.98	0.14	0.015[f]	
	Reasoning	6.3 ± 6.1	7.0 ± 6.0	7.3 ± 6.1	1.51	0.22	0.011[f]	
	Composite score	35 ± 23.0	38.5 ± 22.5	38.6 ± 22.9	1.44	0.24	0.009	

[a]Data are mean ± SD after adjustment for age, sex, years of education, GDS score and medical history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and hypertension as covariates.
[b]With ANCOVA analysis of the effect of the level of TG and genotype on composite cognitive scores, main effect of TC level, $F_{[2,1381]} = 2.95$. $p = 0.06$; main effect of genotype, $F_{[1,1381]} = 7.99$. $p = 0.005$; TC level-by-genotype interaction, $F_{[2,1381]} = 0.033$. $p = 0.97$
[c]df = 2,1107 for *APOE4*(−), 2, 266 for *APOE4*(+).
[d]Significance at $p < 0.016$ (0.05/3) after Bonferroni adjustment for multiple comparisons: A, low to middle: B, low to high: C, middle to high concentration group comparison.
[e]$p < 0.05$.
[f]$\eta^2 > 0.01$.

LDL level on these cognitive scores was small and less than 0.01, and we could not regard this influence of the LDL level as a substantially meaningful one on cognitive scores. In the E4 (+) group, significant association was not observed (Table 5).

By ANCOVA analysis of the influence of TG or TC level and genotype on composite cognitive scores, we found no main effect of TG/TC and their interaction with genotype (Tables 6 and 7). We found no association between cognitive scores and the concentrations

FIGURE 1. Mean cognitive scores of each of the tertiles of lipid measures by E4 (−) and E4 (+) groups



Two-sample *t*-tests were performed to specify differences in cognitive score among the three strata according to the levels of HDL and apoE. P values after Bonferroni adjustment for multiple comparisons are shown.
[a]p <0.033 (0.10/3), [b]p <0.016 (0.05/3), [c]p <0.00033 (0.001/3).

of TG in either of the groups (Table 6). Subjects with higher TC concentration had one higher individual cognitive score in the E4 (−) group, but the effect size was small and less than 0.01. In the E4 (+) group, significant association was not observed (Table 7). In multiple regression analysis, there was no relationship of TG or TC level to composite cognitive score in either of the groups.

CONCLUSIONS

This is the first study to examine the relationship between cognitive function and the plasma levels of lipids including LDL, HDL, TG, TC, and apoE of elderly adults from the general population under consideration of the influence of *APOE* genotypes. In our analysis, we found that higher plasma levels of HDL were associated with better cognitive function in the E4 (−) group. Subjects with higher plasma levels of apoE had higher cognitive scores in both E4 (−) and E4 (+) groups. The concentrations of these lipids had a substantial influence on cognitive scores.

A number of possible mechanisms may explain the observed association between HDL and cognitive function in the E4 (−) group. One plausible explanation may be found in the involvement of HDL in their cerebral vascular pathology. Particles of HDL are assumed to be linked with small-vessel disease through their role in the removal of excess cholesterol from the subendothelian space of cerebral microvessels.[19] In fact, reduced HDL levels have been observed in vascular dementia (VaD).[20] In addition, low-level HDL is thought to be a risk factor for atherosclerotic diseases, leading to ischemic lesions in the brain that contribute to the development of cognitive decline and dementia.[21,22] It has been reported that HDL might also prevent aggregation and polymerization of amyloid in human brain.[23,24] In addition, anti-inflammatory properties of HDL could prevent inflammation from neurodegenerative processes.[25] However, these factors should be carefully considered for explanation of our findings, as plasma and brain cholesterol are separated by the blood brain barrier (BBB), and intact BBB prevents cholesterol influx from the circulation into the brain. Brain cholesterol is almost entirely synthesized in situ.[26]

We found the difference in cognitive score between the E4 (+) and E4 (−) groups by the degree of HDL concentration. By ANCOVA analysis of the influence of HDL level and ApoE genotype on the cognitive score, we found the interaction between them. When we added the plasma apoE level as covariate to the ANCOVA analysis, the interaction between HDL level and genotype failed to reach significance. ($F_{[2,1381]} = 3.25$. p = 0.04→$F_{[2,1380]} = 2.59$. p = 0.08). This interaction between HDL level and genotype on cognitive function may suggest the presence of interaction between HDL and apoE in cognitive function of the elderly. Considering the positive relationship of the apoE level with cognitive function in our study, it is possible that HDL might prevent the progression of cognitive decline via its influence on apoE.

Recent studies presented evidence of the involvement of internalized triglyceride-rich lipoprotein

(TRL)-derived apoE in the regulation of cellular cholesterol transport and HDL metabolism.[27] The greater portion of TRL-derived apoE forms a complex with cholesterol and remains in peripheral recycling endosomes. This pool of TRL-derived 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 HDL-induced recycling of apoE is accompanied by cholesterol enrichment of HDL and cholesterol efflux, and it may maximize the removal of cholesterol from the periphery.[28] Thus, HDL may prevent the progression of atherosclerosis and cognitive decline via apoE recycling, thereby reducing cholesterol accumulation. Our finding of the positive association between plasma apoE level and cognitive function is in agreement with the earlier-described hypothesis of the influence of apoE recycling. Further, it has been reported that elevated levels of plasma apoE reduce inflammation, endothelial dysfunction and lipid oxidation within lesions.[29] An antioxidant role of apoE in promoting the regression of atherosclerosis has also been reported.[30]

However, the absence of an association of HDL and cognitive function in the E4 (+) group remains a question to be addressed. Recent study showed that HDL-induced recycling of TRL-derived apoE4 is impaired and is associated with decreased cholesterol efflux.[31] In agreement with this finding, previous studies showed that apoE4 is less efficient in comparison with apoE3 in promoting cholesterol efflux from the periphery.[32,33] In our data, we found a lower concentration of apoE in the E4 (+) than in the E4 (−) group, perhaps reflecting the impaired recycling of apoE4. Examining the correlation between the levels of HDL and apoE, we found a significant positive relationship in the E4 (−) group ($r = 0.28$, $p < 0.001$, $df = 1,116$), but not in the E4 (+) group ($r = 0.08$, $p = 0.15$, $df = 275$). This finding may reflect the impairment of HDL-induced recycling of apoE4. This impairment might reduce the preventive role of HDL on atherosclerosis and at least partly account for the lack of the association of the HDL level with cognitive function in the E4 (+) group.

The present study has limitations. Three hundred seventy participants had no blood sampling data and/or cognitive data, and these participants were excluded from our analysis. When we compared the demographic characteristic data of excluded (n = 370) and included subjects (n = 1395), significance was found in older age (excluded versus included subjects: 76.4 ± 7.6 versus 73.6 ± 5.8 years), shorter education (9.0 ± 2.7 versus 10.0 ± 2.7 years), higher GDS score (3.3 ± 3.2 versus 2.6 ± 2.9) and higher ratio of a medical history of CVD (7.7% versus 3.7%). There is a possibility that the excluded subjects produced some distortions in the results.

Two hundred sixty-one participants required a face-to-face testing procedure, whereas the other 1,134 participants had tests with the group-setting procedure. There is a possibility that this difference in testing procedure had some confounding effect, although composite cognitive scores were not different between the groups (group versus face-to-face testing; 38.6 ± 12.1 versus 39.8 ± 12.2, $F_{[1,1385]} = 1.86$. $p = 0.17$), and the results did not change when we added the difference of testing procedure as a confounding factor in all of the performed statistical analyses (data not shown).

The sample size of E4 (+) was only about a quarter of that of E4 (−), and it is possible that the insignificant result in the E4 (+) group is affected by its small sample size. However, effect size was less than 0.01 or near 0.01 in all of the influences of lipids on cognitive scores in the E4 (+) group except that of apoE. This means that there was no or nearly negligible influence of lipids (except apoE) on cognitive scores in the E4 (+) group.

In conclusion, our findings suggest that plasma apoE have a positive influence on cognitive function in both the E4 (−) and E4 (+) groups, whereas the positive influence of plasma HDL was shown only in the E4 (−) group. The interaction between HDL level and *APOE* genotype on cognitive function may suggest the possible interaction between HDL and apoE. High-density lipoprotein may prevent the progression of atherosclerosis and cognitive decline via apoE recycling, which reduces cholesterol accumulation. However, HDL-induced recycling of apoE4 may be impaired. Although further longitudinal study is needed for sufficient basis for conclusions, the identification of the influences of *APOE* genotype and the intracellular linkage among apoE, cellular cholesterol transport, and HDL metabolism is hoped for new preventive and therapeutic strategies for cognitive decline in the elderly.

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□研究論文

認知症患者に対するコンピューターを用いた認知機能向上訓練の効果

―前頭連合野機能を基盤とし個人の能力・興味にテーラーメイド可能な訓練の開発と試行から―

竹田　里江[*1,*2]　竹田　和良[*3]　池田　　望[*1]
松山　清治[*1]　石合　純夫[*2]　船橋新太郎[*4]

要旨：ワーキングメモリ機能，目的志向的行動の計画や実行など前頭連合野機能を基盤にし，個人の興味・関心や遂行能力にテーラーメイド可能な訓練を開発した．今回，アルツハイマー型認知症の1症例に施行したところ，語の流暢性，抑制コントロール，記憶機能に向上を認めた．また，日常生活面での記憶，見当識，会話に改善が得られ，うつ状態評価尺度や症例の感想から情動面の改善も示唆された．本訓練は実生活に密着した内容で，対象に合わせて課題の難易度や題材を設定できる．単なる反復的な記憶訓練ではなく過去の記憶やアイディアの創出を刺激することを意図している．こうした特徴が症例の認知・情動の両側面の機能改善に寄与したと考えられた．

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Effects of cognitive rehabilitation using computers on a dementia patient: Development and trial of a tailor-made training program based on prefrontal function

*1 札幌医科大学保健医療学部作業療法学科
Satoe Ichihara-Takeda, OTR, PhD, Nozomu Ikeda, OTR, PhD, Kiyoji Matsuyama, MD, PhD: Department of Occupational Therapy, School of Health Sciences, Sapporo Medical University
*2 札幌医科大学医学部リハビリテーション医学講座
Satoe Ichihara-Takeda, OTR, PhD, Sumio Ishiai, MD, PhD: Department of Rehabilitation, School of Medicine, Sapporo Medical University
*3 国立精神・神経医療研究センター病院
Kazuyoshi Takeda, MD, PhD: Department of Psychiatry, National Center Hospital, National Center of Neurology and Psychiatry
*4 京都大学こころの未来研究センター
Shintaro Funahashi, PhD: Kokoro Research Center, Kyoto University

緒　　言

近年の神経科学の進歩により認知症，統合失調症，うつ病などの症状の神経科学的背景が明らかになりつつある[1)]．その中で，記憶・認知・情動機能の障害が患者の生活や予後の問題に強く関与していることが示され[1)]，認知機能障害に対するリハビリテーションがますます重要視されている．認知症のリハビリテーションにおいて，記憶障害に対する直接的介入は短期

的効果を認めたとしても日常生活への汎化が難しく，患者の心理的負担が大きい場合があるとされている[2]．一方，メモやカレンダーなどの外的補助具の使用や環境調整は比較的効果が高いとされている[3]．しかし，特に初期の認知症患者からは，忘れないための環境整備をするだけでなく，記憶障害自体の改善を希望する切実な訴えが聞かれることが少なくない[4]．また，実際に記憶障害に繰り返し介入することや患者の生活に必要な動作に領域特異的に介入することで記憶の改善が得られ，患者の自立的な生活に寄与することも報告されており[5,6]，記憶障害の改善に対して直接的に介入する方法の発展が望まれている．

我々はワーキングメモリや遂行機能を担う前頭連合野に注目し，記憶・認知・情動機能の改善をはかる方法を模索してきた．神経生理学的研究や脳機能画像研究から，前頭連合野はワーキングメモリ（作業記憶）や目的志向的行動の計画や実行，問題解決機能に深く関わっていることが知られている[7~12]．また，我々の研究から前頭連合野での情報処理は無機的に行われるのではなく，情動や動機付けといった個人の内的状況との相互作用が強いことが明らかになっている[13~15]．一方，ほど良い難易度の際に，前頭連合野が強く活動するなど，脳活動と課題の難易度に相関が認められており[16]，患者の能力に応じた関わりが必要となる．したがって，個人の遂行能力，障害からの回復段階に加え，興味や関心に応じた訓練の開発が必須となる．そこで，我々は神経生理学的研究で明らかになったワーキングメモリ機能，目的志向的行動の計画や実行，問題解決機能という前頭連合野の機能を基盤にし，遂行能力や興味・関心に合わせてコンピューターが柔軟かつ簡易に課題を抽出するなど，個々人にテーラーメイド可能なリハビリテーション訓練を開発した．今回この訓練を軽度認知症の症例に実施し，その効果を認知・情動の両側面に加え，日常生活場面においても評価することで効果を多面的に検討した．

方　法

1．症例

80代女性，右利き，アルツハイマー型認知症，介護福祉施設（以下，A施設）入居中．女手一つで育てた娘は若くして他界，その後独居となるが，孫との交流が続いている．X−8年より両膝関節症，腰痛のために入退院を繰り返す．この頃，置き忘れやそれに伴う混乱が見られ認知症と診断された．X−2年A施設に入所．他の入所者と折り合いが悪く，些細なことで興奮し暴行，暴言が見られた．介護者に他患に対する不平不満を漏らすことが多く，居室のカーテンを閉め切って生活していた．施設で実施している個別の歩行訓練（2，3回／週）や集団の活動（書道，華道，レクリエーション：1〜2回／週）には声掛けによって参加することもあったが，身体の不調や対人関係を理由に参加を中断したり，断ることが多かった．同じ質問や会話の繰り返し，置き忘れなどの物忘れ症状に加えて情動面の不安定さが目立っており，X年に介入となった．

倫理的配慮として，本研究の内容，結果の取り扱い，同意を取り消しできる権利などについて書面と口頭で本人に説明し，文書で同意を得た．なお，本研究に関して札幌医科大学倫理委員会より承認（承認番号 18-2-3）を得た．

2．初期評価

1）認知機能評価

結果を表1Aに示した．Mini-Mental State Examination（以下，MMSE）は19点で見当識（5/10点），遅延再生（0/3点），計算（2/5点）に失点を認めた．前頭葉機能検査（以下，FAB）は14点で概念化（2/3点），流暢性（1/3点），抑制コントロール（1/3点）に失点を認めた．語の流暢性検査（「か」で始まる言葉の語想起は3個，動物の想起は7個）で正常値に比べて低下を示した[17]．Wechsler記憶検査改訂版（以下，WMS-R）に収録されている数唱の順唱7点（5，6桁可能），逆唱では5点（3，4桁可能）で年齢相応であった[18]．Trail Mak-

表1 1回目介入時の認知機能・情動・日常生活評価

A. 認知機能

		①介入開始の1ヵ月前（初期評価）	②介入開始直前	③介入終了時	④介入終了時から1ヵ月後
MMSE（点）		19	19	23	21
FAB（点）		14	12	17	12
語想起	語頭「か」（個）	3	3	7	4
	動物名（個）	7	4	9	5
数唱	順唱（点）	7	5	6	5
	逆唱（点）	5	6	5	3
TMT-A（秒）		238	198	175	137
三宅式	有対語（個）	8	9	10	7
	無対語（個）	2	1	4	1
図形記憶	即時再生（点）	0	0	4	4
	5分後再生（点）	0	0	4	0

＊MMSE，FAB，数唱，三宅式，図形記憶の満点はそれぞれ30点，18点，12点，10個，10点である．①～④は図2の評価時点に相当する．

B. 情動

	①介入開始の1ヵ月前（初期評価）	②介入開始直前	③介入終了時	④介入終了時から1ヵ月後
GDS	8	8	2	7
PGC	10	10	14	10

＊GDS，PGCの満点はそれぞれ15点，17点であり，GDSは得点が低いほどうつ傾向が低いことを示す．①～④は図2の評価時点に相当する．

C. 日常生活

	1介入開始直前（初期評価）	2介入終了時	3介入終了時から1ヵ月後
N-ADL	36	37	37.5
NMスケール	44	48	42.5
CDR	0.5	0	0.5

＊得点は評価者2名の平均点を示した．N-ADL，NMスケール，CDRの満点はそれぞれ50点，50点，0点である．CDRは得点が低いほど重症度が低いことを示す．1～3は図2の評価時点に相当する．

ing Test A（以下，TMT-A）は238秒，三宅式記銘力検査（以下，三宅式）の有関係対語試験の3回目では8個，無関係対語試験の3回目では2個で正常値に比べて低下を示した[17]．浜松方式高次脳機能スケールの図形の記憶問題（以下，図形記憶）では，即時再生，5分後再生ともに0点で低下が著しかった[19]．

2）情動面評価

結果を表1Bに示した．うつ状態の評価尺度として高齢者うつ評価尺度短縮版（Geriatric Depression Scale；以下，GDS）を実施した．この検査では15項目中5項目にあてはまると，うつ傾向にあることが示唆されている[20]．本症例は，GDSが8点でうつ傾向が示唆された．個人のQOLを測定する指標として，改訂PGCモラールスケール（Philadelphia Geriatric Center；以下，PGC）を実施した．これは得点が高いほどQOLが高いことを意味する．本症例は17点中10点であった．

3）日常生活評価

結果を表1Cに示した．N式老年者用日常生活動作能力評価尺度（以下，N-ADL），N式

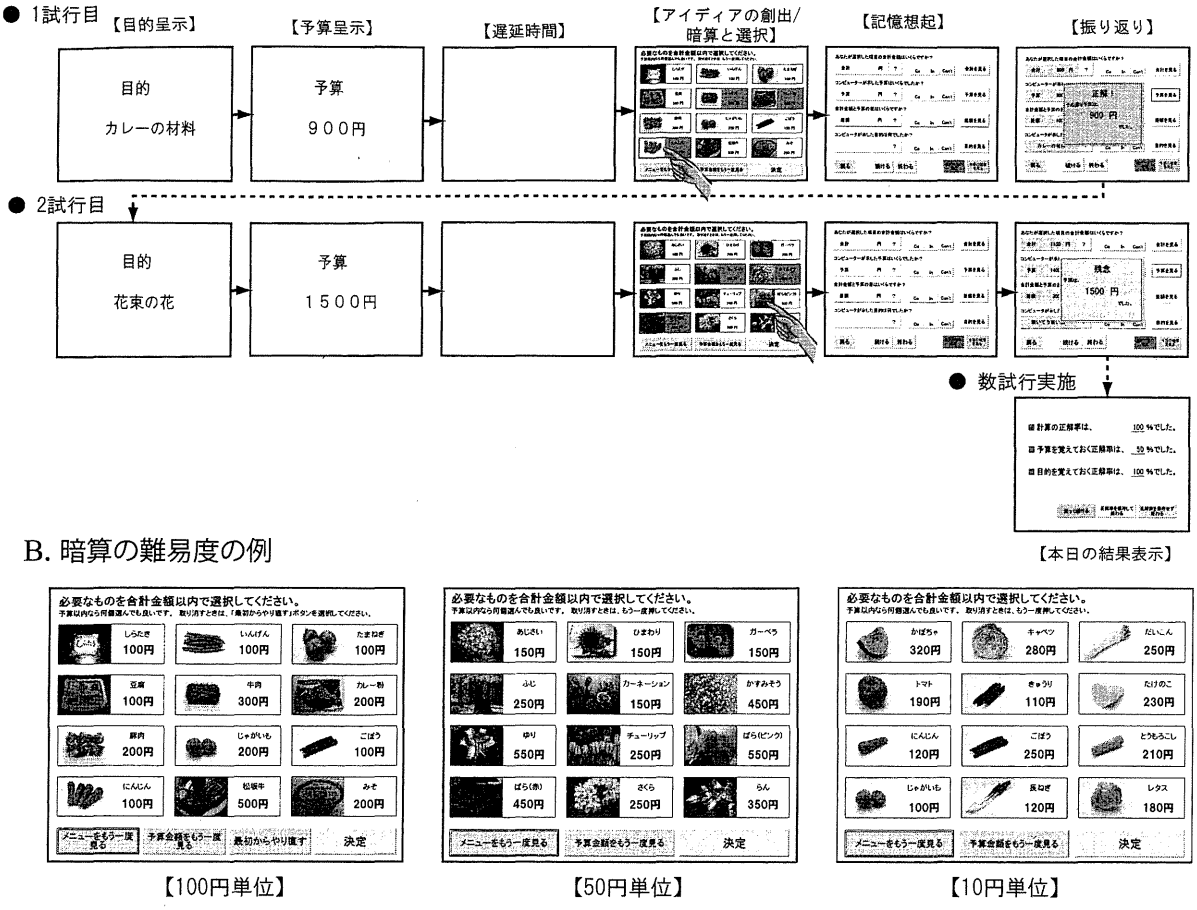

図1　目的志向的遅延反応課題（G-DR 課題）

A. 課題の流れ：コンピューター上に「目的」と「予算」が1秒間呈示されて消える．次に，患者の能力に応じて設定した遅延時間の後，選択肢が呈示される．記憶している目的と予算に応じて暗算をしながら必要項目を考え選択をする．その後，目的や予算の記憶想起が求められる．回答に対してコンピューターからフィードバックが呈示され，検者と振り返りを行う．この課題の流れを数試行繰り返すことが1回の訓練となる．訓練の終了時には，暗算，内容および予算の想起率について本日の結果が表示される．

B. 暗算の難易度の例：簡単な順に100円単位，50円単位，10円単位で設定が可能である．

老年者用精神状態尺度（以下，NM スケール），Clinical Dementia Rating（以下，CDR）を実施した．これらの検査は，病棟職員2名によって記入時の1ヵ月前から記入時の間の状態を評定した．N-ADL は36点で歩行（5/10点）と生活圏（5/10点）に主な失点を認めた．NM スケールは44点で記憶（7/10点），見当識（9/10点），会話（9/10点）に主な失点を認めた．CDR は0.5点であった．

以上の認知・情動・日常生活評価から，軽度の認知症と判断できた．

3. 課題とその特徴

今回実施した目的志向的遅延反応課題（Goal directed Delayed Response task；以下，G-DR 課題）は，コンピューターを用いて行う．1試行の流れを図1A に示した．まずコンピューターの画面上に，患者が行う作業の「目的」と作業のために使用できる「予算」がそれぞれ1秒間呈示されて消える（例えば，カレーの材料

を900円以下の予算でそろえる）．次に，患者の能力に応じて設定した時間経過（遅延時間）の後，作業の目的と関連した選択肢が呈示される．患者は記憶している作業の目的と予算をもとに，どれが必要で，予算内で準備できるか暗算をしながらタッチパネル式のパソコン画面にタッチすることで選択する．患者が必要な選択をした後，最初に呈示された作業の目的や予算の想起が求められる．次に，患者が行った回答に対してコンピューターから“正解”，“不正解”といったフィードバックが呈示される．最後に検者と患者は，「カレーを作るのに必要な品がすべて揃っていますね」，「たまねぎは欠かせないですよね」，「ちょっと予算がオーバーしてしまいましたね」など，作業の目的と選択した項目について振り返りを行う．本課題の操作は主に症例がタッチパネルにタッチすることで行うが，操作が困難な場合は作業療法士（以下，OTR）が様子を見ながら手助けした．このような流れで課題を数試行繰り返すことを1回の訓練とした．訓練の終了時には，暗算結果，目的および予算の想起について正解率が患者に示された．

G-DR課題は，前頭連合野研究で頻繁に用いられている遅延反応課題を基盤にしたものである．しかし，同じ行為の単なる反復訓練ではなく，実生活で現実に遭遇する作業を達成するために，作業の目的や実行に必要な予算を一時的に記憶し，記憶している予算額を考慮しながら必要項目を選択するという行動のシミュレーションを意図した．また，正解を一つには限定せず自由な着想やアイディアの創出を促すようにした．「目的」に示す内容や選択肢，遅延時間，暗算の難易度は個人の遂行能力や興味・関心に合わせてコンピュータが柔軟かつ簡易に課題を抽出する．また，検者により自由に調整や作成も可能で，患者の興味や能力に合わせて自由に設定できる．本症例の場合は，本人が料理と花に興味を持っていると述べたため，作業の「目的」として「カレーの材料」，「花束の花」など料理と花に関する内容を取り入れた（図1A）．暗算と遅延時間による難易度の初期設定は，訓練開始前の練習試行の正解率が60～80%であった100円単位の暗算（図1B），遅延時間3秒とした．

4. 介入期間

G-DR課題はOTRとともに機能訓練室の一角で，個別に実施した．G-DR課題を約30分間，6～8課題実施することを1回の訓練とした．週2回，約3ヵ月間（24回）実施し，この24回の実施期間を1回目介入とした．

効果を再検証するために，1回目介入終了後の1年6ヵ月後に再び介入を行った（2回目介入）．課題，介入期間，評価項目およびそのスケジュールは1回目と同様に実施した．

5. 評価項目

初期評価と同じ項目を用いて実施した．認知機能検査としては，MMSE，FAB，語の流暢性検査（「か」で始まる言葉の語想起，動物の想起），数唱（順唱，逆唱），TMT-A，三宅式，図形記憶を実施した．情動面の評価は，GDS，PGCで行った．これらの検査を介入開始の1ヵ月前（初期評価），介入開始直前，介入終了時，介入終了時から1ヵ月後に実施した（図2）．日常生活評価として，N-ADL，NMスケール，CDRを実施した．これらの検査は，病棟職員2名が介入開始直前（初期評価），介入終了時，介入終了時から1ヵ月後の時点において直近の1ヵ月の様子をもとに評定した（図2）．

結　果

1. 課題遂行の様子とその経過

介入期間における目的想起の正解率は毎回ほぼ80%，予算想起は20～70%であり，遅延時間は変化させず期間中3秒間のままとした．症例は徐々に予算を忘れやすいことを自覚し，「予算は700円だったよね」とつぶやきながら選択をする様子へと変化していった．一方，暗算は100円単位レベルでは90～100%の正解率となり，介入期間の中盤で50円単位の計算へと難易度を上げた（図1B参照）．しかし，その難易度では50%台の正解率となることもあ