Published in final edited form as:
J Alzheimers Dis. 2013 January 1; 34(1): 273–279. doi:10.3233/JAD-121138.

Very old adults with better memory function have higher low-density lipoprotein cholesterol levels and lower triglyceride to high-density lipoprotein cholesterol ratios: KOCOA project

Yuriko Katsumata[a], **Hidemi Todoriki**[b], **Yasushi Higashiuesato**[c], **Shotoku Yasura**[d], **Yusuke Ohya**[e], **D. Craig Willcox**[d], and **Hiroko H. Dodge**[a]

[a]Department of Neurology, Oregon Health & Science University, Portland, OR, USA

[b]Department of Public Health and Hygiene, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

[c]Clinical Laboratories, University of the Ryukyus Hospital, Okinawa, Japan

[d]Department of Human Welfare, Okinawa International University, Okinawa, Japan

[e]Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

Abstract

We examined cross-sectionally which lipid profiles are associated with better cognitive function among those aged 80 and older-free of dementia (Clinical Dementia Rating ≤ 0.5), functionally independent and community-dwelling. Our cohort consisted of 193 participants from the "Keys to Optimal Cognitive Aging (KOCOA) Project", a prospective cohort study in Okinawa, Japan. Higher low-density lipoprotein cholesterol levels and lower triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratios were associated with higher scores in memory performance after controlling for confounders. Further research is required to clarify the associations among LDL-C levels, TG/HDL-C ratios, and healthy cognitive aging.

Keywords

Lipoprotein cholesterol; Aged 80 and over; Memory Disorders

INTRODUCTION

Facing a growing number of those affected by dementia, prevention of cognitive decline is becoming increasingly important. The identification of modifiable factors associated with healthy cognitive aging is of significant importance in designing effective preventive strategies against cognitive impairment.

There are conflicting results regarding the association between dyslipidemia and cognitive impairment [1-7], which appear to depend on the age when the lipids were assessed, whether at middle-age or older-ages. Longitudinal studies have shown consistently that low high-density lipoprotein cholesterol (HDL-C), high total cholesterol (TC), and high low-density

CORRESPONDING AUTHOR: Yuriko Katsumata, Department of Neurology, Oregon Health & Science University, Mail Code: CR131, 3181 SW Sam Jackson Park Rd., Portland, OR 97239-3098, TEL: 503-494-7616, FAX: 503-494-7499, katsumat@ohsu.edu.

There are no personal conflicts of interest for any of the authors.

lipoprotein cholesterol (LDL-C) in midlife are associated with higher risk of cognitive decline in later life [1, 2]. On the other hand, there are no consistent findings among older people to show that low HDL-C, high TC, and high LDL-C are associated with subsequent cognitive decline or dementia. Low HDL-C, high TC, and high LDL-C have been associated with increased risk of cognitive impairment or dementia in some studies [3-5, 7], but no association in others [8, 9]. Furthermore, Mielke et al. reported that high TC in late life was associated with decreased dementia risk [10], while West et al. found a positive association between elevated LDL-C and better memory function among the oldest old [11].

Additional lipid indices derived from the standard lipid measures, such as higher non-HDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, and triglyceride (TG)/HDL-C ratio, are considered risk factors for cardiovascular disease (CVD) [12-16]. Non-HDL-C, which is calculated by simply subtracting HDL-C from the TC, has an association with risk of CVD [12]. The TC/HDL-C ratio is one of the predictors of future coronary heart disease (CHD) [13], and changes in TC/HDL-C ratio and LDL-C/HDL-C ratio are better predictors of lowered CHD risk [14, 15] than TC, LDL-C and HDL-C alone. The high TG/HDL-C ratio is closely correlated with the concentration of small, dense LDL-C particles [18] which are widely acknowledged as a major risk factor of CVD [16, 17]. While recent studies suggest that cardiovascular risk factors are also important risk factors for Alzheimer's disease (AD) [1, 2, 19], to our knowledge, there have been few reports on the association between these ratios and cognitive function among very old subjects, such as those aged 80 and older.

In this study we examined cross-sectionally which lipids and ratios contribute to better cognitive function among community dwelling older people aged 80 and older who are functionally independent and free from dementia.

METHODS

Study design and subjects

Data came from the Keys to Optimal Cognitive Aging Project (KOCOA), a prospective pilot cohort study of community-dwelling older people aged 80 years and older living in Okinawa, Japan. A detailed description of the recruitment process has been presented elsewhere [20, 21]. Briefly, researchers visited 22 senior centers, explained the study protocol, and asked them to participate in the study. A request to join the study was made at the conclusion of each presentation. We recruited community-dwelling older people aged 80 and older who were functionally independent (no or partial assistance required for any activities of daily living). The study was conducted annually between November 2007 and March 2010. Using baseline data from this study, we analyzed the cross-sectional associations of three key cognitive domains (global, executive and memory functions) with each lipid level as well as each lipid ratio (TC/HDL-C, LDL-C/HDL-C, and triglyceride (TG)/HDL-C ratios). Of 194 consented subjects who completed a face-to-face interview at baseline, one participant with frank dementia (Clinical Dementia Rating scale (CDR) [22] = 1.0) was excluded. The remaining 193 participants with CDR ≤ 0.5 were used in this study. The study was approved by the Ethics Committee of the University of the Ryukyus, and the Institutional Review Board at Oregon Health and Science University. Informed consent was obtained from all participants prior to enrollment in the study.

Measures

Cognitive function was assessed by a trained interviewer using the Japanese version of the Mini-Mental State Examination (J-MMSE) [23], the Verbal Fluency Initial Letter (VFL) [24], and the Scenery Picture Memory Test (SPMT) [25]. The J-MMSE is a measure of global cognitive function and ranges from 0 to 30 points, with higher scores representing

better cognitive function [23, 26]. The VFL was used to measure executive function. This test requires the participant to generate words beginning with the letter "Ka" (in Japanese) in 60 seconds, and has been validated as an equivalent test to Initial Letter Fluency by Lezak [24]. The SPMT is a measure to assess memory function using a scenery picture, combined with verbal answers. We selected SPMT because it was found to be sensitive to detect mild cognitive impairment (MCI) and easy to administer and valid for use among those with lower educational levels. In the SPMT, the participants were first shown a scenery picture of a living room containing 23 familiar objects for 60 seconds and were instructed to memorize the items. Next, digits forward test (four digit strings consisting of 4, 5, 6 and 7 digits, respectively) was conducted to distract the participants. After the filler test, the participants were then asked to recall the objects in the scenery picture without time limit. The number of objects recalled was the score for the SPMT. The SPMT has good test-retest reliability ($r = 0.898$), inter-rater reliability ($r = 0.750$), and content validity [25].

Lipid levels and lipid lowering drugs

Venous blood samples were collected in the morning after an overnight fast. Serum was separated by centrifugation at 3000 r.p.m. for 15 min and stored at −80 °C until analysis. The laboratory analyses were performed by SRL Inc. (Tokyo, Japan), using standard laboratory protocols. The LDL-C and non-HDL-C levels were calculated using the formula of Friedewald et al [27] and as TC minus HDL-C, respectively. Use of lipid-lowering drugs was assessed by asking each participant to show their medication bottles. Lipid-lowering drugs were grouped into 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitor (statin) and non-statin. Statins were further classified as lipophilic or hydrophilic statins.

Other covariates

The history of stroke and heart diseases (myocardial infarction, angina pectoris, heart failure) were ascertained by a question: "Have you ever had a stroke/heart diseases diagnosed by a physician?" Hypertension was defined by systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [28], or currently taking antihypertensive medication. Type 2 diabetes was defined by glycosylated hemoglobin (HbA1c) level ≥ 6.5% [29], or currently taking diabetes medication. The HbA1c value was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society (JDS) method) (%) + 0.4% [29]. Smoking and alcohol drinking status were assessed by self-report and categorized as "never/former" and "current".

Statistical analyses

Logistic regression analysis was used to estimate the odds ratio of cognitive performance associated with serum TC, HDL-C, LDL-C, and non-HDL-C levels, TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C ratios. We divided subjects into two groups for each cognitive test at baseline: the highest quartile scores (i.e., top 25%, better cognitive performance group), and the rest (remaining 75%, intermediate/poor cognitive performance group). Separate models for each lipid profile were run for each of the three cognitive tests as a binary outcome using the intermediate/poor cognitive performance group as a reference. Four lipid levels (serum TC, HDL-C, LDL-C, and non-HDL-C levels) and the three ratios (TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C ratios) were analyzed as continuous variables. We first examined unadjusted models, followed by models adjusted for age, gender, years of education, and finally the fully adjusted models including all covariates (use of lipid-lowering drugs, history of stroke and heart diseases, hypertension, diabetes, and current smoking and alcohol drinking status). Statistical significance was set as $p < 0.05$ with Bonferroni adjusted p-value in the footnote of the results table. Model fitness was examined

by using the Hosmer-Lemeshow goodness-of-fit test. All analyses were conducted with SAS 9.1 for Windows (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics of participants are shown in Table 1. The mean age of the participants was 85.2 years, and 73.6% were women. The mean years of education was 7.3 years. Use of lipid-lowering drugs was reported by 44 subjects. The mean cognitive test scores were 23.3 for the J-MMSE. Somewhat low cognitive test scores are expected among this group due to their advanced age and low educational attainment. The previous study, conducted in older people aged 70 and older living in Okinawa, which is the same geographical setting, and which involved subjects with similarly low educational attainment to our study, reported an optimal cutoff score of 16/17 for the J-MMSE to detect AD [30].

No associations were found between each lipid level/ratio and the J-MMSE, and VFL score. We found that lower TC was associated with a higher score of SPMT, but this significant inverse association disappeared when age, gender, and years of education were added to the model. However, higher LDL-C level and lower TG/HDL-C ratio were associated with a higher score of SPMT, even after controlling for age, gender, and years of education. These associations remained significant after controlling for use of lipid-lowering drugs, history of stroke and heart diseases, hypertension, diabetes, and current smoking and alcohol drinking status (Table 2). None of them, however, was significant under the Bonferroni adjustment. All models showed adequate fit using the Hosmer-Lemeshow goodness-of-fit test.

The association of higher LDL-C level and lower TG/HDL-C ratio with better memory function might be influenced by use of statins, which lower blood LDL-C level by inhibiting HMG CoA reductase. Since lipophilic statins could cross the blood-brain barrier more easily than hydrophilic statins, they could be more related to cholesterol metabolism in the brain. As a post-hoc analysis, we examined whether there are differences in the association of LDL-C and TG/HDL-C with memory function by type of lipid lowering drugs (lipophilic statins, hydrophilic statins and non-statins); we reran the full models with the interaction term of LDL-C level or TG/HDL-C ratio with type of lipid lowering drugs (Table 3). The interaction terms were not significant. That is, the effect of LDL-C ratio and TG/HDL-C level on memory function did not depend on use of statins or type of lipid lowering drugs.

Finally, in another post-hoc analysis, we excluded those with CDR = 0.5 (n = 54) and reran all models. The results remained as before.

DISCUSSION

In this study, we found marginally significant associations of a higher LDL-C level and a lower TG/HDL-C ratio with better memory function among community dwelling, functionally independent dementia-free older adults aged 80 years and older, even after controlling for demographic characteristics and use of lipid-lowering drugs.

Consistent with our findings, at least one study has reported an association between elevated LDL-C level and better memory function in the oldest old (aged 85 and older) [11]. One of the potential explanations for our findings is that it is possible that people aged 80 and older, who are healthy survivors, may be less susceptible to the negative effects of high LDL-C. Another possible explanation is that lower LDL-C may be an indication of preclinical dementia. A previous study in Japanese-American men found an additional decline in total cholesterol level beyond what would be expected for age associated normative decline [31].

Those with relatively better memory performance had a lower TG/HDL-C ratio compared to normal/poor memory performance group. A higher TG/HDL-C ratio has been found to be closely correlated with a higher concentration of small, dense LDL particles [18]. Small, dense LDL particles have a low affinity for the LDL receptor [32], and are readily oxidized compared with larger and more buoyant LDL particles [33]. Oxidized LDL is associated with atherosclerosis. Additionally, Barzilai et al. have shown that larger LDL particle size (i.e., lower levels of small LDL particles) is associated with a lower prevalence of CVD [34], and at least one study has shown that those with a predominance of small, dense LDL had an increased risk for development of non-insulin dependent diabetes mellitus in older people [35]. Atherosclerosis in cerebral arteries is considered one of the risk factors for AD [36, 37], and vascular factors, including diabetes mellitus, are found to be associated with not only the risk of vascular dementia, but also of AD [38]. Our results could imply that larger and more buoyant LDL might be required to maintain memory function among older people aged 80 and older.

This study has several limitations. First, these findings were not statistically significant under the Bonferroni adjustment. Therefore, the results should be interpreted with caution. Second, the cross-sectional analysis provides associations but not causal relationships. Third, our sample consisted of older people who were relatively healthy community volunteers in Okinawa, Japan. Therefore, our results may not be generalizable to other populations. Fourth, the effect sizes reported were relatively small and the statistical significance might not be clinically meaningful. Fifth, we did not examine apolipoprotein E (APOE) genotype which is known to be a genetic risk factor of AD. Since there could be a difference in the association of lipid profile with memory function between carriers and noncarriers of the APOE-ε4 allele [11], the results might be confounded or have interacted with the APOE genotype. Apolipoprotein A5 (APOA5) gene identified by Pennacchio et al [39] has been suggested to have a significant effect on TG metabolism. Of several common single-nucleotide polymorphisms of the APOA5 gene, APOA5 −1131 T>C has been associated with lipid levels [40, 41]. The frequency of the C allele, the carriers of which have higher TG levels, was reported to be much greater in Japanese than in Caucasians [40]. Therefore, our results might be influenced by polymorphisms of APOA5, as well as APOE genotype, neither of which we could confirm from the current study design. Lastly, the cognitive battery was limited to a single test in each domain. We only selected one cognitive test for measuring each cognitive domain in order to reduce interview time and test-taking stress. Additionally memory function was measured by SPMT. Although this test was validated and found to be sensitive to early stage AD [25], using other verbal or episodic memory tests could have yielded different results from our study. Further studies are required to confirm our findings using more conventional methods, including a full cognitive test battery.

In conclusion, LDL-C, especially large, buoyant LDL may be required to maintain or support memory function among older people. Lowering the TG/HDL-C ratio could be useful as a preventive strategy for cognitive impairment and dementia in advanced age. Longitudinal follow up and analysis of the current study cohort should help to further clarify the associations among LDL-C levels, TG/HDL-C ratios, and healthy cognitive aging.

Acknowledgments

This study was supported by the National Institute on Aging (K01AG023014, P30 AG008017), the Linus Pauling Institute Research Grant, and Center for Healthy Aging Pilot Grant at Oregon State University.

We would like to express our sincere appreciation to Ms. Takiko Hokama, Ms. Satsuki Ishikawa, Ms. Masayo Iha, and Mr. Daisuke Higa, who acted as study coordinators for the KOCOA project. Faculty and staff from the University of the Ryukyus Hospital were also instrumental in the successful completion of the project. We also

thank Dr. Jeffrey A. Kaye for his helpful advice. Finally, this study would not have been possible without the cooperation and support of the municipalities, public officials, families, and most importantly, the participants in our studies.

REFERENCES

[1]. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64:277–281. [PubMed: 15668425]

[2]. Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. 2001; 56:1683–1689. [PubMed: 11425934]

[3]. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol. 2002; 59:378–384. [PubMed: 11890840]

[4]. van Exel E, de Craen AJ, Gussekloo J, Houx P, Bootsma-van der Wiel A, Macfarlane PW, Blauw GJ, Westendorp RG. Association between high-density lipoprotein and cognitive impairment in the oldest old. Ann Neurol. 2002; 51:716–721. [PubMed: 12112077]

[5]. Warren MW, Hynan LS, Weiner MF. Lipids and adipokines as risk factors for Alzheimer's disease. J Alzheimers Dis. 2012; 29:151–157. [PubMed: 22232009]

[6]. Dodge HH, Chang CC, Kamboh IM, Ganguli M. Risk of Alzheimer's disease incidence attributable to vascular disease in the population. Alzheimers Dement. 2011; 7:356–360. [PubMed: 21575878]

[7]. Moroney JT, Tang MX, Berglund L, Small S, Merchant C, Bell K, Stern Y, Mayeux R. Low-density lipoprotein cholesterol and the risk of dementia with stroke. JAMA. 1999; 282:254–260. [PubMed: 10422994]

[8]. Li G, Shofer JB, Kukull WA, Peskind ER, Tsuang DW, Breitner JC, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology. 2005; 65:1045–1050. [PubMed: 16217057]

[9]. Reitz C, Luchsinger J, Tang MX, Manly J, Mayeux R. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology. 2005; 64:1378–1383. [PubMed: 15851727]

[10]. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, Skoog I. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005; 64:1689–1695. [PubMed: 15911792]

[11]. West R, Beeri MS, Schmeidler J, Hannigan CM, Angelo G, Grossman HT, Rosendorff C, Silverman JM. Better memory functioning associated with higher total and low-density lipoprotein cholesterol levels in very elderly subjects without the apolipoprotein e4 allele. Am J Geriatr Psychiatry. 2008; 16:781–785. [PubMed: 18757771]

[12]. Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study. Atherosclerosis. 2009; 203:587–592. [PubMed: 18783774]

[13]. Wang TD, Chen WJ, Chien KL, Yi Su SS, Hsu HC, Chen MF, Liau CS, Lee YT. Efficacy of cholesterol levels and ratios in predicting future coronary heart disease in a Chinese population. Am J Cardiol. 2001; 88:737–743. [PubMed: 11589839]

[14]. Natarajan S, Glick H, Criqui M, Horowitz D, Lipsitz SR, Kinosian B. Cholesterol measures to identify and treat individuals at risk for coronary heart disease. Am J Prev Med. 2003; 25:50–57. [PubMed: 12818310]

[15]. Fernandez ML, Webb D. The LDL to HDL cholesterol ratio as a valuable tool to evaluate coronary heart disease risk. J Am Coll Nutr. 2008; 27:1–5. [PubMed: 18460475]

[16]. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. JAMA. 1996; 276:875–881. [PubMed: 8782636]

[17]. St-Pierre AC, Cantin B, Dagenais GR, Mauriege P, Bernard PM, Despres JP, Lamarche B. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year

follow-up data from the Quebec Cardiovascular Study. Arterioscler Thromb Vasc Biol. 2005; 25:553–559. [PubMed: 15618542]

[18]. Fan X, Liu EY, Hoffman VP, Potts AJ, Sharma B, Henderson DC. Triglyceride/high-density lipoprotein cholesterol ratio: a surrogate to predict insulin resistance and low-density lipoprotein cholesterol particle size in nondiabetic patients with schizophrenia. J Clin Psychiatry. 2010; 72:806–812. [PubMed: 21208572]

[19]. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? Neurology. 2009; 72:368–374. [PubMed: 19171835]

[20]. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]

[21]. Dodge HH, Katsumata Y, Todoriki H, Yasura S, Willcox DC, Bowman GL, Willcox B, Leonard S, Clemons A, Oken BS, Kaye JA, Traber MG. Comparisons of plasma/serum micronutrients between Okinawan and Oregonian elders: a pilot study. J Gerontol A Biol Sci Med Sci. 2010; 65:1060–1067. [PubMed: 20643702]

[22]. Katsumata Y, Todoriki H, Higashiuesato Y, Yasura S, Willcox DC, Ohya Y, Willcox BJ, Dodge HH. Metabolic Syndrome and Cognitive Decline Among the Oldest Old in Okinawa: In Search of a Mechanism. The KOCOA Project. J Gerontol A Biol Sci Med Sci. 2012; 67:126–134. [PubMed: 22016359]

[23]. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

[24]. Lezak, MD. Neuropsychological Assessment. Oxford University Press; New York: 1995.

[25]. Takechi H, Dodge HH. Scenery Picture Memory Test: a new type of quick and effective screening test to detect early stage Alzheimer’s disease patients. Geriatr Gerontol Int. 2010; 10:183–190. [PubMed: 20446933]

[26]. Dodge HH, Meguro K, Ishii H, Yamaguchi S, Saxton JA, Ganguli M. Cross-cultural comparisons of the Mini-mental State Examination between Japanese and U.S. cohorts. Int Psychogeriatr. 2009; 21:113–122. [PubMed: 18925977]

[27]. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]

[28]. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr. Jones DW, Materson BJ, Oparil S, Wright JT Jr. Roccella EJ, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003; 289:2560–2572. [PubMed: 12748199]

[29]. Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, Tominaga M, Oikawa S, Noda M, Kawamura T, Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y, Ohashi H, Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society. International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Invest. 2012; 3:39–40.

[30]. Ogura C, Nakamoto H, Uema T, Yamamoto K, Yonemori T, Yoshimura T. Prevalence of senile dementia in Okinawa, Japan. COSEPO Group. Study Group of Epidemiology for Psychiatry in Okinawa. Int J Epidemiol. 1995; 24:373–380. [PubMed: 7635599]

[31]. Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2007; 64:103–107. [PubMed: 17210816]

[32]. Nigon F, Lesnik P, Rouis M, Chapman MJ. Discrete subspecies of human low density lipoproteins are heterogeneous in their interaction with the cellular LDL receptor. J Lipid Res. 1991; 32:1741–1753. [PubMed: 1770294]

[33]. de Graaf J, Hak-Lemmers HL, Hectors MP, Demacker PN, Hendriks JC, Stalenhoef AF. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. Arterioscler Thromb. 1991; 11:298–306. [PubMed: 1998647]

[34]. Barzilai N, Atzmon G, Schechter C, Schaefer EJ, Cupples AL, Lipton R, Cheng S, Shuldiner AR. Unique lipoprotein phenotype and genotype associated with exceptional longevity. JAMA. 2003; 290:2030–2040. [PubMed: 14559957]

[35]. Austin MA, Mykkanen L, Kuusisto J, Edwards KL, Nelson C, Haffner SM, Pyorala K, Laakso M. Prospective study of small LDLs as a risk factor for non-insulin dependent diabetes mellitus in elderly men and women. Circulation. 1995; 92:1770–1778. [PubMed: 7671360]

[36]. Roher AE, Tyas SL, Maarouf CL, Daugs ID, Kokjohn TA, Emmerling MR, Garami Z, Belohlavek M, Sabbagh MN, Sue LI, Beach TG. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. Alzheimers Dement. 2011; 7:436–444. [PubMed: 21388893]

[37]. Roher AE, Esh C, Rahman A, Kokjohn TA, Beach TG. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke. 2004; 35:2623–2627. [PubMed: 15375298]

[38]. Haan MN. Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. Nat Clin Pract Neurol. 2006; 2:159–166. [PubMed: 16932542]

[39]. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, Krauss RM, Rubin EM. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. Science. 2001; 294:169–173. [PubMed: 11588264]

[40]. Nabika T, Nasreen S, Kobayashi S, Masuda J. The genetic effect of the apoprotein AV gene on the serum triglyceride level in Japanese. Atherosclerosis. 2002; 165:201–204. [PubMed: 12417270]

[41]. Yamada Y, Kato K, Hibino T, Yokoi K, Matsuo H, Segawa T, Watanabe S, Ichihara S, Yoshida H, Satoh K, Nozawa Y. Prediction of genetic risk for metabolic syndrome. Atherosclerosis. 2007; 191:298–304. [PubMed: 16806226]

Table 1

Baseline characteristics of the 193 individuals

Characteristics	
Demographics	
Women, n (%)	142 (73.6)
Age, mean (SD)	85.2 (3.3)
Years of education, mean (SD)	7.3 (2.2)
Lipids	
TG, mg/dL, mean (SD) <median, interquartile range>	110.6 (53.3) <99, 74-131>
TC, mg/dL, mean (SD) <median, interquartile range>	202.3 (30.2) <202, 180-220>
HDL-C, mg/dL, mean (SD) <median, interquartile range>	60.0 (11.9) <59, 52-67>
LDL-C, mg/dL, mean (SD)	120.2 (26.4)
Non- HDL-C, mg/dL, mean (SD)	142.3 (29.5)
TC/HDL-C ratio, mean (SD)	3.5 (0.8)
LDL-C/HDL-C ratio, mean (SD)	2.1 (0.6)
TG/HDL-C ratio, mean (SD)	2.0 (1.3)
Use of lipid-lowering drugs, n (%)	44 (22.8)
Use of lipophilic statins, n (%)	18 (9.4)
Use of statins (lipophilic and hydrophilic)	39 (20.4)
Others	
History of stroke, n (%)	14 (7.3)
History of heart diseases, n (%)	18 (9.6)
Hypertension, n (%)	149 (77.2)
Type 2 diabetes, n (%)	25 (13.0)
Currently smoking, n (%)	8 (4.2)
Currently drinking alcohol, n (%)	25 (13.0)
Cognitive tests	
Japanese version of Mini-Mental State Examination (J-MMSE), mean (SD)	23.3 (4.0)
Verbal Fluency Initial Letter (VFL), mean (SD)	6.1 (2.9)
Scenery Picture Memory Test (SPMT), mean (SD)	7.0 (2.9)

SD = standard deviation, TG = triglyceride, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol

Table 2

Associations of three congtive function tests with total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, non- high-density lipoprotein cholesterol, total cholesterol to high-density lipoprotein cholesterol ratio, low-density lipoprotein to high-density lipoprotein cholesterol ratio and trigriceride to high-density lipoprotein ratio

	Unadjusted	Adjusted[a]	Adjusted[b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Japanese version of the Mini-Mental State Examination (J-MMSE)			
TC	1.003 (0.992 - 1.013)	0.999 (0.987 - 1.012)	1.000 (0.987 - 1.013)
HDL-C	1.007 (0.980 - 1.034)	0.998 (0.967 - 1.030)	1.003 (0.970 - 1.037)
LDL-C	1.003 (0.991 - 1.016)	1.003 (0.989 - 1.017)	1.002 (0.988 - 1.017)
Non-HDL-C	1.002 (0.991 - 1.013)	1.000 (0.987 - 1.012)	0.999 (0.986 - 1.012)
TC/HDL-C ratio	1.001 (0.666 - 1.504)	0.988 (0.629 - 1.551)	0.935 (0.584 - 1.497)
DLL-C/HDL-C ratio	1.030 (0.618 - 1.718)	1.060 (0.601 - 1.869)	0.991 (0.549 - 1.789)
TG/HDL-C ratio	0.966 (0.743 - 1.257)	0.909 (0.681 - 1.212)	0.882 (0.648 - 1.200)
Verbal Fluency Initial Letter (VFL)			
TC	1.003 (0.993 - 1.014)	1.003 (0.992 - 1.015)	1.003 (0.990 - 1.015)
HDL-C	1.011 (0.984 - 1.037)	1.011 (0.983 - 1.041)	1.003 (0.970 - 1.036)
LDL-C	1.005 (0.993 - 1.017)	1.005 (0.993 - 1.018)	1.005 (0.991 - 1.019)
Non-HDL-C	1.002 (0.991 - 1.012)	1.002 (0.990 - 1.013)	1.002 (0.990 - 1.015)
TC/HDL-C ratio	0.980 (0.659 - 1.457)	0.936 (0.616 - 1.424)	1.038 (0.663 - 1.626)
LDL-C/HDL-C ratio	1.076 (0.656 - 1.764)	1.044 (0.620 - 1.758)	1.152 (0.660 - 2.012)
TG/HDL-C ratio	0.862 (0.656 - 1.131)	0.811 (0.609 - 1.081)	0.884 (0.653 - 1.197)
Scenery Picture Memory Test (SPMT)			
TC	1.013 (1.002 - 1.024)[c]	1.010 (0.998 - 1.022)	1.007 (0.994 - 1.020)
HDL-C	1.023 (0.996 - 1.050)	1.009 (0.980 - 1.039)	1.005 (0.974 - 1.036)
LDL-C	1.019 (1.006 - 1.032)[e]	1.019 (1.005 - 1.033)[e]	1.017 (1.002 - 1.031)[c]
Non-HDL-C	1.010 (0.999 - 1.021)	1.008 (0.996 - 1.021)	1.006 (0.994 - 1.019)
TC/HDL-C ratio	0.964 (0.647 – 1.438)	1.019 (0.662 - 1.568)	1.033 (0.650 - 1.643)
LDL-C/HDL-C ratio	1.217 (0.741 - 1.997)	1.387 (0.810 - 2.374)	1.402 (0.791 - 2.485)
TG/HDL-C ratio	0.661 (0.473 - 0.925)[c]	0.629 (0.444 - 0.889)[d]	0.641 (0.444 - 0.925)[c]

TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride

[a] Adjusted for age, gender and years of education

[b] Adjusted for age, gender, years of education, use of lipid-lowering drugs, history of stroke and heart diseases, hypertension, diabetes, and current smoking and alcohol drinking status

[c] $p < 0.05$

[d] $p < 0.01$

[e] p-value significant after Bonferroni adjustment

Table 3

Association of low-density lipoprotein cholesterol or triglyceride to high-density lipoprotein ratio with memory function (Scenery Picture Memory Test score) by use of lipophilic statins, hydrophilic statins, and non-statins

	β (SE)[a]	p-value
Lipophilic statins		
LDL-C	0.011 (0.008)	0.148
Lipophilic statins	−9.841 (5.929)	0.097
LDL-C * lipophilic statins	0.072 (0.045)	0.108
TG/HDL-C raio	−0.398 (0.190)	0.037
Lipophilic statins	2.792 (2.494)	0.263
TG/HDL-C raio * lipophilic statins	−3.161 (2.170)	0.145
Statins (lipophilic and hydrophilic statins)		
LDL-C	0.010 (0.008)	0.246
Statins	−3.835 (2.568)	0.135
LDL-C * statins	0.033 (0.021)	0.104
TG/HDL-C ratio	−0.338 (0.193)	0.079
Statins	1.288 (1.099)	0.241
TG/HDL-C raio * statins	−0.830 (0.688)	0.228
Lipid lowering drugs (statins and non statins)		
LDL-C	0.010 (0.008)	0.232
Lipid lowering drugs	−3.415 (2.493)	0.171
LDL-C * lipid lowering drugs	0.030 (0.020)	0.130
TG/HDL-C ratio	−0.331 (0.194)	0.089
Lipid lowering drugs	1.257 (1.041)	0.228
TG/HDL-C ratio * lipid lowering drugs	−0.793 (0.651)	0.224

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride

[a]Adjusted for age, gender, years of education, use of lipid-lowering drugs, history of stroke and heart diseases, hypertension, diabetes, and current smoking and alcohol drinking status