Cholesterol and Triglycerides Moderate the Effect of Apolipoprotein E on Memory Functioning in Older Adults

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We used data from the Betula Study to examine associations between total cholesterol, triglycerides, and apolipoprotein E on 10-year changes in cognitive performance. Tests assessing episodic memory (recall and recognition), semantic memory (knowledge and fluency), and visuospatial ability (block design) were administered to 524 nondemented adults (initial age of 55–80 years); multilevel modeling was applied to the data. Higher triglyceride levels were associated with a decline in verbal knowledge. Lipid levels moderated the influence of apolipoprotein E on episodic memory, such that among ε4 allele carriers, decline in recognition was noted for individuals with higher cholesterol levels. Cholesterol and triglyceride levels are pharmacologically modifiable risk factors that account for variation in normal cognitive aging.

Apolipoprotein E (APOE) is a plasma protein involved in the transport of cholesterol and other lipids. APOE has three allelic variants (ε2, ε3, ε4) and six genotypes. The ε3 allele is the most common variant, and ε4 and ε2 differ from the common ε2 allele by a single amino acid substitution. The ε4 allele influences serum lipid concentrations. Individuals with the ε4 allele have higher levels of total serum cholesterol, higher levels of low-density lipoprotein (LDL) cholesterol, and a higher risk for myocardial infarction and coronary heart disease than ε3 homozygotes.

The APOE ε4 allele is also a known risk factor for the development of Alzheimer’s disease (AD; Farrer et al., 1997), but it is less clear whether the ε4 allele is a risk factor for cognitive impairment in older adults without dementia (Bretsky, Guralnik, Launer, Alberta, & Seeman, 2003; Bunce, Fratiglioni, Small, Winblad, & Bäckman, 2004; Mayeux, Small, Tang, Tycko, & Stern, 2001; Nilsson et al., 2006; Wilson et al., 2002). A recent meta-analysis (Small, Rosnick, Fratiglioni, & Bäckman, 2004) found that in cognitively intact older persons, possession of the ε4 allele was associated with deficits in global cognitive function, episodic memory, and executive function, although the effect sizes reported were relatively small. When persons with dementia are excluded and education is controlled for, some longitudinal studies report that APOE ε4 does not influence the rate of cognitive decline (Bunce et al., participants aged 75 years and older; Winnock et al., 2002, participants aged 65 years and older), although other studies with a similar age range have found that APOE ε4 is associated with memory decline (Hofer et al., 2002, participants aged 70–94 years). In recent data from the Betula Study, a 5-year decline in episodic recall tasks was noted for APOE ε4 allele carriers aged 35 to 85 years (Nilsson et al.). Because AD is characterized by a long preclinical period with cognitive deficits already detected years prior to disease diagnosis, it is important to eliminate persons with impending dementia to determine whether the deficit is specific to the APOE gene rather than AD pathology (Small, Basun, & Bäckman, 1998). APOE alone may not be a sufficient cause of AD; rather, Gene × Environment or Gene × Gene interactions are areas to investigate in terms of both susceptibility to and progression of disease. Another reason for the inconsistent findings may be explained by the sensitivity of the cognitive tests to differentiate individuals with AD from those without it.

The exact biochemical processes by which possession of the ε4 allele is associated with cognitive deficits in old age are unclear. However, several potential mechanisms have been identified (see Smith, 2002) that focus on (a) the involvement of APOE in the production of amyloid-β and the role this plays in the formation of plaques and neurofibrillary tangles; (b) the direct influence of APOE on neurons or glial cells, and the effect on neuronal survival and neurite extension; and (c) the relation of APOE to vascular events, cerebral blood flow, and the blood–brain barrier. A central theme of these proposed mechanisms is that APOE may differentially affect the efficiency of neural processes, trigger the degeneration of neuronal structures and systems, or influence maintenance and repair processes once damage has occurred.

Genetic effects on cognitive impairment are potentially moderated by vascular factors such that the risk increases beyond what one would expect by either condition independently (Anstey & Christensen, 2000; Breteler, 2000; Bunce, in press; Nilsson et al., 2004; Wahlin, 2004). Relatedly, recent studies (Bunce, Kivipelto, & Wahlin, 2004, 2005) demonstrate that APOE ε4 carriers with low levels of vitamin B₁₂ have larger than expected performance deficits in face recognition, and also in episodic recall but only for task conditions...
providing low levels of cognitive support. Several studies have assessed variables relating to cerebrovascular and cardiovascular disease (e.g., atherosclerosis, hypertension, low blood pressure, and stroke), APOE, and cognitive function, producing contrasting results. For example, significant deficits in global cognition were found in ε4 carriers in the presence of the actual diagnosis, making directionality impossible to determine.

High lipids levels increase β-amyloid protein concentrations and may increase APOE expression, which would support the influence of cholesterol or triglycerides in cognitive impairment and AD pathogenesis (Puglielli, Tanzi, & Kovacs, 2003). Of interest is whether lipid levels and APOE have either additive or multiplicative effects on cognitive impairment. In two cross-sectional studies (Dufouil et al., 2005; Evans et al., 2000), high total cholesterol levels in non-ε4 carriers resulted in a higher risk of developing AD; this finding was later replicated in a 30-week study (Evans et al., 2004). One limitation of this study was that cholesterol was measured in proximity with the AD diagnosis, making directionality impossible to determine.

Prospective longitudinal studies are needed to examine how APOE interacts with vascular risk factors to predict specific cognitive functions in middle-aged and older adults. To our knowledge, no study to date has examined whether levels of cholesterol and triglycerides relate to 10-year changes in specific cognitive functions and whether such effects are moderated by APOE status in a population-based sample of nondemented adults. We hypothesize that lipid levels will be related to cognitive decline, with the greatest cognitive deficits appearing for middle-aged to older adults with high cholesterol or triglyceride levels. In addition, because the APOE ε4 allele is associated with higher circulatory cholesterol concentrations than the ε3 allele is, we hypothesize that middle-aged to older adults with the ε4 allele and high cholesterol levels will show the greatest cognitive deficits.

**METHODS**

**Participants**

We recruited the participants in the present study from the first sample (Sample 1) of adults with six age cohorts (aged 55, 60, 65, 70, 75, and 80 years at Time 1, or T1) from the Betula project (Nilsson et al., 1997; Nilsson et al., 2004). We excluded the four youngest age cohorts (aged 35, 40, 45, and 50 years at T1) from the analyses because they are not considered at risk for disease or cognitive decline. The initial wave of testing started in 1988–1990, and participants were tested over two follow-up periods at 5-year intervals. We excluded participants from the study if they were diagnosed with incident dementia at the first or second follow-up (n = 76). There were 524 participants (267 women and 257 men) aged 55–80 years at T1 (age, M = 66.72 years, SD = 8.51) who returned for both follow-up periods (Time 2, n = 433; Time 3, n = 344). The average level of education was 8.24 years (SD = 3.15). There were 180 APOE non-ε4 (ε3/ε3) carriers and 75 APOE ε4 (ε3/ε4, ε4/ε4) carriers. A description of the sample stratified by APOE status is provided in Table 1.

**Measures**

We administered the cognitive tasks during two test sessions, both of which lasted between 1.5 and 2 hr for each participant. We divided the episodic memory and semantic memory tasks into two categories on the basis of previous research on the factor structure of the memory tasks in the Betula project (Nyberg et al., 2003).
Episodic Memory

We used two dependent variables to assess episodic memory: (a) one recall composite (seven indicators: free recall, cued recall, four word recall tests with and without concurrent card sorting at study or test, and memory for activities), and (b) one verbal recognition composite (three indicators: name recognition, recognition of nouns–verbal task, and face recognition).

Recall.—We had two lists presented in a free recall test. For the subject-performed tasks (i.e., enactment condition), an experimenter provided participants with 16 objects, one at a time, and instructed them to perform the actions (e.g., lift the pen) in an 8-s interval. In the verbal (sentence) task (i.e., nonenactment condition), the experimenter again presented participants with 16 commands, but no object was present and no action was required. Following presentation of the last item, the experimenter gave a free recall test with an allotted 2 min for the participants to recall as many of the commands as possible (verb and noun). The number of verbs and nouns correctly recalled in the subject-performed task was the performance score.

A cued recall test of the nouns presented in the subject-performed task and sentence test followed immediately after free recall of the second list. We provided category names (e.g., animals, reading materials, kitchen utensils, and articles of clothing) of the nouns as retrieval cues. We had four categories from each of two lists presented, and the experimenter instructed participants to recall as many target items as possible from each category in a 3-min period. In a second test condition, occurring approximately 45 min after the category cue test, we had the verbs of the commands presented as retrieval cues. The performance score was the number of nouns correctly recalled in the subject-performed task when the category name was presented as a retrieval cue.

In the word recall task, the experimenter auditorily presented the participants with four word lists with 12 items in each list. The experimenter gave a concurrent card-sorting (distractor) task for three of the four conditions. The card-sorting task consisted of sorting a deck of playing cards into two piles, that is, one red pile and one black pile. For one list, the experimenter provided a card-sorting task as a distractor both at study and test. For two other lists, the experimenter gave the card-sorting task either at study or at test only. For the fourth list, the experimenter provided a no-card-sorting condition. In all four lists, the performance score was the number of correctly recalled words from the study list.

The experimenter also asked participants to recall in any order all tests that they had performed during the test session. The performance score was the number of activities (memory for activities) identified as previously performed.

Recognition.—In the face recognition test, we had participants presented with 16 color photographs of faces of 10-year-old children. Following presentation, the experimenter administered a free-choice (yes or no) recognition test. The performance score was hits minus false alarms. In the recognition test of the subject-performed task and verbal task, the experimenter presented 16 nouns from two recall lists and 16 distractor nouns from the same categories as those for the target nouns in a free-choice recognition. To adjust for response bias, we used hits minus false alarms for the performance score. In the name recognition test, the presentation of 16 first and last names of the 16 faces was followed by a four-alternative forced-choice recognition task of the first and last name. The experimenter instructed participants to remember the faces and the last names for a later recognition test. The performance score was the number of correctly recognized first and last names.

Semantic Memory

We used two dependent variables to assess semantic memory: (a) one vocabulary test, and (b) one semantic fluency composite (three indicators).

Verbal knowledge.—We used a revised 30-item multiple-choice synonym test (Dureman, 1960) as an index of semantic knowledge. The task involved selecting the synonym of each target word from among five alternatives in a 7-min time frame. The performance score was the number of correctly identified synonyms.

Verbal fluency.—We had three fluency tasks administered in which the experimenter instructed participants to generate aloud as many words as possible in 1 min. The differences in the tasks concerned what words to generate. The first task was to produce words beginning with the letter A. The second task required the generation of words beginning with the letter M and containing five letters. The third task was to produce names of professions beginning with the letter B.

Block Design

We administered and scored a block design, which is a standardized test of visuospatial ability from the Wechsler Adult Intelligence Scale—Revised, according to the standard procedure (Wechsler, 1991).

Lipid Profile

We had blood samples collected from participants at T1. We had total serum cholesterol and triglyceride concentrations analyzed by the chemical laboratory at Umeå University Hospital. The units are presented in millimoles per liter. (To convert millimoles per liter of cholesterol to milligrams per deciliter, multiply by 39. To convert millimoles per liter of triglycerides to milligrams per deciliter, multiply by 89.) We treated cholesterol and triglycerides as continuous variables. Means and standard deviations for total cholesterol and triglyceride levels by age group are listed in Table 2.

Cardiovascular Disease

We used a self-report questionnaire to assess the cardiovascular health of the participants. We coded responses as yes or no with respect to the presence of a heart infarction, heart disease, or circulation disorders at T1. Sixty participants had cardiovascular disease (CVD; 195 did not) at T1.

APOE Genotyping

We determined APOE genotype by means of a polymerase chain reaction (PCR) procedure, using 200 ng of genomic DNA as a template in a 25-ml reaction mixture containing 20 pmol of PCR primers APOE-A (5′-TCC-AAG-GAG-CTG-CAG-GCG-GCG-CA-3′) and APOE-B (5′-ACA-GAA-TTC-GCC-CCG-GCC-TGG-TAC-ACT-GCC-A-3′), 0.2 U of Taq
DNA polymerase (GibcoBRL, Gaithersburg, MD), 1.0 mM of MgCl$_2$, 75 mM of Tris-HCl (pH 9.0), 20 mM of (NH$_4$)$_2$SO$_4$, and 10% dimethyl sulfoxide (Sundström et al., 2004). The PCR amplification consisted of 35 cycles of 30 s at 94 °C, 30 s at 65 °C, and 30 s at 72 °C. PCR products were digested by the use of 5 U of Hhal (Life Technologies Inc., Rockville, MD) by incubating for 3 hr at 37 °C. We separated bands on a 5% agarose gel and visualized them on an ultraviolet transilluminator after we put them through ethidium bromide staining. Alternatively, we performed electrophoresis by using ExcellGel gels (Pharmacia, Piscataway, NJ) and the MultiphorII electrophoresis system (Pharmacia), and we visualized the bands by means of silver staining.

**Statistical Analyses**

We converted all cognitive measures to $z$ scores. We used the means and standard deviations from T1 to create standardized scores at Time 2 and Time 3. This method preserves longitudinal changes, the main effect for time, in the scores. We created composite scores for recall (seven tasks), recognition (three tasks), and fluency (three tasks) by summing and averaging across all relevant measures. Knowledge and block design were single indicator variables. We entered cholesterol and triglyceride levels as continuous variables. We recoded APOE to a dichotomous variable ($e$4 carriers, $e$3/$e$4 and $e$4/$e$4, non-$e$4 carriers, $e$3/$e$3). We omitted the $e$2 allele carriers from the analyses ($n = 81$; exclusive of the original sample description) because of the complex association between the $e$2 and $e$4 alleles. However, in our preliminary analyses we did not detect differences in results when we included $e$2/$e$3 genotype carriers in the analyses.

After controlling for age, sex, education, and CVD, we used multilevel analyses in the form of hierarchical linear modeling (HLM; Raudenbush & Bryk, 2002) to examine sources (i.e., cholesterol, triglycerides, and APOE × Cholesterol and APOE × Triglyceride interactions) of individual differences in level and change in five cognitive abilities: recall, recognition, fluency, vocabulary, and visuospatial. Because only three waves are available, quadratic models were not possible. These HLM models are as follows.

At Level 1, each person’s development is represented by an individual growth trajectory (an intercept, $b_0$, and a slope, $b_1$). At Level 2, these parameters become the outcome variables that depend on stable between-person sources of variation. Essentially, these variables represent an intercept ($b_0$) and slope ($b_1$) as outcome model. We analyzed separate two-stage models for each cognitive variable. A sample description (using cholesterol level as a predictor) of a Level 2 (between-person model) equation is illustrated here:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}(\text{cholesterol}) + U_{0i},$$  \hspace{1cm} (1)

$$\beta_{1i} = \gamma_{10} + \gamma_{11}(\text{cholesterol}) + U_{1i}.$$  \hspace{1cm} (2)

In Equation 1, we modeled a given person’s score at the first wave of measurement, $\beta_{0i}$, as a function of the average level across all participants in the first wave, $\gamma_{00}$ (fixed effect), the average group difference in cognitive performance for cholesterol ($\gamma_{01}$), plus a random effect of how the individual varies around the grand mean (i.e., initial individual differences), $U_{0i}$. The random effect estimated whether there are significant interindividual differences after we controlled for initial status and cholesterol. Parameter $\gamma_{01}$ estimates the cross-sectional cholesterol effect. In Equation 2, we modeled the linear average rate of change in cognitive performance for a given person, $\beta_{1i}$, as a function of the sample average change in cognitive performance after we controlled for cholesterol, $\gamma_{10}$, the effect of cholesterol, $\gamma_{11}$ (average difference in change) on the rate of change, plus a random effect, $U_{1i}$, that represents between-person variability in the slopes. Stated differently, the random effect estimated whether there are significant interindividual differences in individual level change after we controlled for other parameters (i.e., occasion of measurement and cholesterol). Parameter $\gamma_{11}$ estimates the longitudinal cholesterol effect.

All HLM models at Level 2 are as follows:

$$\beta_{0i} = \gamma_{00} + \gamma_{01}(\text{age}) + \gamma_{02}(\text{sex}) + \gamma_{03}(\text{education})$$
$$+ \gamma_{04}(\text{CVD}) + \gamma_{05}(\text{APOE status}) + \gamma_{06}(\text{cholesterol}) + \gamma_{07}(\text{triglycerides}) + \gamma_{08}(\text{APOE} \times \text{cholesterol})$$
$$+ \gamma_{09}(\text{APOE} \times \text{triglycerides}) + U_{0i},$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}(\text{age}) + \gamma_{12}(\text{sex}) + \gamma_{13}(\text{education})$$
$$+ \gamma_{14}(\text{CVD}) + \gamma_{15}(\text{APOE status}) + \gamma_{16}(\text{cholesterol})$$
$$+ \gamma_{17}(\text{triglycerides}) + \gamma_{18}(\text{APOE} \times \text{cholesterol}) + \gamma_{19}(\text{APOE} \times \text{triglycerides}) + U_{1i}.$$  

**RESULTS**

A summary of the mixed modeling results are presented in Tables 3 and 4. As one can see in Table 3, there were significant 10-year changes in recall (improvement), recognition (decline), fluency (decline), and block design (decline). Fixed and random intercepts were significantly different from zero. One random slope (for block design) was marginally significant ($p = .055$), indicating some variability in change. Significant age, sex, education, and CVD-adjusted effects for cholesterol, triglycerides, and APOE × Cholesterol and APOE × Triglyceride interactions on level or changes in cognition are reported.

One method of probing interaction effects for such models is to calculate the slope for the regression of $Y$ on $X$ at levels of a given lipid level (mean centered) at each wave. We selected two values for lipids: (a) 1 SD below the mean, and (b) 1 SD above the mean. We calculated predicted values for $Y$ (cognitive variable) on the basis of the intercept ($B_0 = \gamma_{00} + \gamma_{06}$).
Block design Intercept 0.22 0.04 5.69***
Slope 0.09 0.01 6.25***
Recognition Intercept 0.23 0.04 6.20***
Slope −0.10 0.02 −4.30***
Vocabulary Intercept 0.27 0.06 4.83***
Slope 0.01 0.02 0.63
Fluency Intercept 0.23 0.05 4.65***
Slope −0.08 0.02 −4.39***
Block design Intercept 0.34 0.06 5.78***
Slope −0.03 0.02 −1.62

Notes: SE = standard error.
***p < .001.

γ₀(1) and the slope (B₁ = γ₁₀ + γ₁₁) coefficients provided in HLM. A sample equation is as follows:

Predicted \( Y = B₀ + B₁X \) (where \( X \) = time; values are \( 0 = W₁, 1 = W₂, \) and \( 2 = W₃ \)),

\( B₀ = γ₀₀ + γ₀₁ \times W \) (where \( W = \) a value of the Level 2 predictor),

\( B₁ = γ₁₀ + γ₁₁ \times W. \)

We observed a significant effect for triglycerides on the slope for verbal knowledge (indexed by vocabulary; \( γ = −2.31; \) row 16, column 5 of Table 4). The plot of the predicted values of verbal knowledge at each wave for each of the two values of triglycerides is presented in Figure 1. The slope of the line defining the time–verbal knowledge association was steeper (showing decline) among individuals with higher triglyceride levels than among those with lower triglyceride levels (showing stability). We observed one significant APOE × Lipid Marker interaction for changes in episodic memory (recognition; \( γ = −2.13; \) row 11, column 5 of Table 4). We examined follow-up mixed modeling analyses (with the same covariates) for APOE e4 and non-e4 carriers separately. For e4 carriers, higher cholesterol was associated with decline in recognition (\( γ = −0.07, SE = 0.03; T = −2.16; p < .05 \)), whereas we found no association between cholesterol and change in recognition for non-e4 carriers (\( γ = 0.01, SE = 0.03; T = 0.55; p = .59 \)). We observed no other significant interactions for the intercept or slope of the cognitive variables.

**DISCUSSION**

In the present study we examined potential associations among APOE genotype, cholesterol, triglycerides, and individual differences in level and changes in specific cognitive functions over a 10-year period. In this random population of adults aged 55 to 80 years at T1, we found that individuals with higher triglyceride levels showed a 10-year decline in verbal knowledge, after we adjusted for age, sex, education, and CVD. Previous research emanating from the Betula project has reported stability or improvement in verbal knowledge for adults until early old age, followed by decline (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Other research from the Berlin Aging Study has also found stability of performance on a vocabulary test over a 6-year period (Ghisletta & Lindenberger, 2004). The present findings add to prior research by showing that decline (for older adults) in verbal knowledge is present in individuals with higher serum concentrations of triglycerides, and this effect is independent of CVD. Other studies have reported better cognitive functioning (i.e., faster visuomotor speed; Zhang et al., 2004) in young and middle-aged men with high total cholesterol concentrations.

We noted one significant APOE Gene × Cholesterol interaction for 10-year changes in episodic memory, after we adjusted for age, sex, education, and CVD. Prior research in the Betula project (Rönnlund et al., 2005) has reported practice-adjusted stability of episodic memory in younger age groups (35–60 years). Episodic memory begins to decline in late midlife (Hultsch, Hertzog, Dixon, & Small, 1998; Rönnlund et al.). In addition, vascular risk factors in midlife and late life are associated with cognitive impairment in old age (Breiter, 2000; Kivipelto et al., 2001; Nilsson & de Frias, in press). Adults aged 65 years and older (at Time 3) who were carriers of the e4 allele and had higher cholesterol levels declined in recognition ability. Triglyceride and cholesterol levels did not moderate the effect of APOE on episodic memory for non-e4 carriers. These data are consistent with other studies reporting associations between high lipid levels and cognitive impairment in older adults or with AD risk (Atzmon et al., 2002; Kivipelto et al.; Notkola et al., 1998;
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Figure 1. Decline in vocabulary scores over a 10-year period for individuals with higher triglyceride levels. Regression lines are plotted for two values of triglycerides (i.e., −1 SD below the mean and +1 SD above the mean).

Figure 1 shows the decline in vocabulary scores over a 10-year period for individuals with higher triglyceride levels. Regression lines are plotted for two values of triglycerides (i.e., −1 SD below the mean and +1 SD above the mean).

Teunissen et al., 2003; Yaffe et al., 2002). Poorer cognitive performance of individuals with high levels of triglycerides has also been reported in mixed (demented and nondemented) samples of centenarians (Atzmon et al.).

Our multivariate, multicohort study of APOE genotype and lipid profile (total serum concentrations of cholesterol and triglycerides) shows an aging effect for episodic memory (recognition) and semantic memory (verbal knowledge). The present data indicate that such tests provide informative results.

Future research must examine the short-term and long-term consequences of reductions in lipid parameters on specific cognitive functions from midlife to old age. One limitation of our study was a lack of data on LDL and HDL cholesterol measures. It may be the case that level or changes in LDL or HDL cholesterol are more sensitive to cognitive change. A second limitation is that information about fasting prior to cholesterol and triglycerides measures was not included in the data collection. Third, given the long prodromal trajectory of AD, we cannot rule out the possibility that some participants are in the predementia state by Time 3. One important implication of our study is that cognitive resilience may be sustained by the modification of these two vascular risk factors: triglycerides and total cholesterol. Intervention strategies (e.g., use of statin drugs) may be effective for improving cognitive functioning, and they may possibly protect against AD (Yaffe et al., 2002). The protective effects of the ε2 allele have been reported, but in our study the inclusion of ε2 carriers did not have an effect on the central findings.

Several possible mechanisms through which APOE ε4 and lipids affect cognitive functioning, and possibly AD pathogenesis, include the abnormal accumulation of the β-amyloid protein (Puglielli et al., 2003), altered brain morphology (Lind et al., 2005; Persson et al., 2005), and atherosclerosis (Ross, 1999). APOE may also modify brain cholesterol homeostasis by modifying lipoprotein formation, which could increase the risk for cognitive deficits and AD pathogenesis (Puglielli et al.). APOE ε4 binds to LDL (a higher form of cholesterol), but the ε3 allele binds to HDL. Homozygotes for the ε4 allele have the greatest concentration of cholesterol in the plasma and cerebrospinal fluid (Puglielli et al.). In our study, cholesterol alone did not affect age differences in cognitive change; rather, it was the middle-aged and oldest old who were ε4 carriers and had high cholesterol who declined in cognitive performance.

Large-scale studies that test for Gene × Vascular Health interactions across the mid-to-late adult life span can inform future research on the potential early risk factors of cognitive impairment during nondemented aging. This unique study combines genetic, biological, and behavioral data by using a population-based multicohort, multivariate, mixed-modeling longitudinal design. Further research is needed to identify the biochemical or molecular mechanisms that are linked to elevated levels of serum cholesterol and triglycerides, which may account for variations in normal cognitive aging.

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REFERENCES


