Cognitive decline in late-life: biological markers and early identification of persons at risk for dementia

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Tessa Nicole van den Kommer

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Cognitive decline in late-life: biological markers and early identification of persons at risk for dementia

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ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
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ten overstaan van de promotiecommissie
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door

Tessa Nicole van den Kommer

geboren te Delft

promotoren:	prof.dr. D.J.H. Deeg
	prof.dr. C. Jonker
copromotoren:	dr. M.G. Dik
	dr. H.C. Comijs

“ ... It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair ...”

Charles Dickens, A Tale of Two Cities
English novelist (1812 - 1870)

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Chapter 6

The role of lipoproteins and inflammation in cognitive decline: do they interact?

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Abstract

The aim of this study was to examine the associations between high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides and cognition and focus on the modifying effect of inflammation. Data were collected in the population-based Longitudinal Aging Study Amsterdam and analyzed with mixed linear models. The sample comprised 1,003 persons ≥ 65 years with cognitive data on at least two occasions over six years of follow-up. Cognition was measured with the Mini-Mental State Examination (general cognition), Auditory Verbal Learning Test (memory) and Coding Task (information processing speed).

We found an independent association between high HDL cholesterol and better memory performance. In addition, low LDL cholesterol was predictive of worse general cognitive performance and faster decline on information processing speed. Furthermore, a significant modifying effect of inflammation (C-reactive protein, α1-antichymotrypsin) was found. A negative additive effect of low LDL cholesterol and high inflammation was found on general cognition and memory performance. Also, high triglycerides were associated with lower memory performance in those with high inflammation. Thus, a combination of these factors may be used as markers of prolonged lower cognitive functioning.

Keywords: Lipoproteins; Triglycerides; Inflammation; Cognitive decline; Older persons.

Introduction

Both lipoproteins, lipids and inflammation have been linked to dementia and cognitive decline, although their role is complex and mechanisms are still far from clear. In the current study, we focus on the additive effect of these biomarkers on cognitive decline in a population-based sample of older persons.

High levels of low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, both major transport lipoproteins of cholesterol, as well as high lipid levels of triglycerides have been shown to be independently associated with cardiovascular disease (CVD) (Boden, 2000; Morrison and Hokanson, 2009), which in turn is associated with an increased risk of dementia and cognitive impairment (Van Vliet et al., 2009). Inconsistent and even contrasting results have been found in studies focusing on the direct association between lipoproteins and dementia. While some studies have shown an association between high LDL cholesterol and increased dementia risk or worse cognitive functioning (Helzner et al., 2009; Lesser et al., 2009; Moroney et al., 1999; Yaffe et al., 2002), other studies found the opposite effect (Henderson et al., 2003; Packard et al., 2007) or failed to detect an independent association (Reitz et al., 2004; Romas et al., 1999; Yoshitake et al., 1995). High HDL cholesterol has been shown to be associated with better cognitive functioning (Atzmon et al., 2002; Merched et al., 2000; Van Exel et al., 2002) and has been suggested as a protective factor for dementia in most cross-sectional studies (Bonarek et al., 2000; Van Exel et al., 2002; Wolf et al., 2004), while longitudinal studies have not found a significant association with dementia, mild cognitive impairment (MCI), cognitive decline or functioning (Henderson et al., 2003; Reitz et al., 2004, 2005, 2008; Tan et al., 2003). In contrast, autopsy studies have shown that higher late-life levels of HDL cholesterol were associated with higher levels of Alzheimer's disease (AD) pathology (Launer et al., 2001) and increasing pathological certainty of AD (Lesser et al., 2009). Some studies focusing on triglycerides have shown that higher triglyceride levels were associated with cognitive decline (De Frias et al., 2007) and poorer cognitive performance (Perlmuter et al., 1988; Sims et al., 2008), while several other studies showed no association with dementia or cognitive decline (Hall et al., 2006; Romas et al., 1999; Yaffe et al., 2002). Furthermore, the metabolic syndrome (MetS), which is defined as a cluster of low HDL cholesterol, high triglycerides, abdominal obesity, impaired fasting glucose and/or hypertension (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), has been linked to increased risk of dementia, cognitive decline and poorer cognitive functioning (Dik et al., 2007; Kalmijn et al., 2000; Solfrizzi et al., 2010; Yaffe et al., 2004). Kalmijn et al. (2000) showed that a higher level of triglycerides during midlife was significantly associated with a higher risk of dementia 25 years later. A recent study focusing on MetS, found that higher triglycerides and also lower HDL cholesterol were associated with a higher risk of cognitive impairment in Apolipoprotein E (ApoE) e4 carriers (Lee et al., 2010). Possibly, differences in sample characteristics (e.g. age, baseline cognition, outcome measure (AD, vascular dementia (VaD), cognition), level of lipoproteins, presence of CVD), and adjustment for possible

mediating or modifying factors could explain the inconsistent results regarding the role of lipoproteins and triglycerides. Moreover, we hypothesize that inflammation plays a modifying role with respect to the association between lipoproteins and cognition.

Inflammatory processes have been shown to be strongly associated with CVD (Stampfer, 2006) and may play a role in the development of dementia and cognitive decline (Peila and Launer, 2006). Furthermore, inflammatory markers including C-reactive protein (CRP), Interleukin-6 (IL-6) and α1-antichymotrypsin (ACT), have been linked to increased dementia risk (Engelhart et al., 2004) and cognitive decline (Dik et al., 2005; Weaver et al., 2002). However, associations have not been found consistently between studies.

Some previous studies have focused on the association between lipids, lipoproteins and inflammation in older persons. Both lower levels of HDL cholesterol (Arai et al., 2001; Lehtimäki et al., 2005; Zuliani et al., 2007), LDL cholesterol and total cholesterol (Lehtimäki et al., 2005) as well as acquired hypocholesterolemia (Arai et al., 2001; Ettinger et al., 1995) have been shown to be associated with higher IL-6 (Arai et al., 2001; Ettinger et al., 1995; Lehtimäki et al., 2005; Zuliani et al., 2007) and higher CRP levels (Arai et al., 2001; Ettinger et al., 1995). Furthermore, it has been hypothesized that higher HDL cholesterol may diminish dementia risk by its anti-inflammatory effects (Cockerill et al., 2001). In addition, a synergistic effect of MetS and high inflammation has been shown with respect to increased risk of VaD (Solfrizzi et al., 2010), non-amnestic MCI (Roberts et al., 2010), cognitive decline (Yaffe et al., 2004) and worse cognitive function (Dik et al., 2007). To our knowledge, no study to date has focused on the modifying or mediating effect of inflammation on each of the associations between lipoproteins, triglycerides and cognitive decline or dementia. In the current study, we focus on the interaction between HDL and LDL cholesterol, triglycerides and the inflammatory markers CRP, IL-6, and ACT with respect to the trajectory of cognitive functioning in a population based sample of older persons.

Methods

Study sample

For the present study, data were used from the ongoing population-based Longitudinal Aging Study Amsterdam (LASA). Procedures on sampling and data collection have been described in detail elsewhere (Deeg et al., 2002). In short, a random sample of men and women aged 55-85 stratified for age and sex according to the expected five-year mortality, was drawn from the population registries of eleven municipalities in three areas of the Netherlands. Data collection started in 1992/1993, main and medical interviews in which structured questionnaires were completed and tests were performed were repeated every three years. Respondents were interviewed at home by specially trained and intensively supervised interviewers. The study was approved by the Ethical Review Board of the VU University Medical Center (VUmc), and informed consent was obtained from all respondents.

In total, 3,107 persons were enrolled during the first data collection of LASA. In total, 562 persons (18.1%) were lost to follow up of whom 416 died (13.4%), 90 refused (2.9%), 38 were ineligible (1.2%) and 18 could not be contacted (0.6%) for the second data collection (1995/1996). During the second data collection, 1,509 persons aged 65 and older participated in the medical interview, of whom N = 1,331 agreed to take part in the blood drawing procedure. Blood samples were obtained in the VUmc or a health care center near the respondents' home. For respondents unable to come to the VUmc or health care center, blood samples were obtained in the home of the participant. Respondents who agreed to take part in the blood drawing procedure were significantly younger and had higher scores on cognitive tests (all $p < 0.0001$) compared to persons who refused. For the present study, subjects were included of whom triglycerides and/or lipoprotein level(s) (N = 1,296) could be determined. In addition, persons taking lipid-lowering drugs at the time of blood sampling were excluded (N = 66). Of the N = 1,230 participants included in the present study, 1,043 participated in the three-year follow-up interview in 1998/1999 (84.8%). Of the 187 subjects who were lost to follow-up, 158 died (12.8%), 12 refused (1.0%), 11 were ineligible (0.9%) and 6 could not be contacted (0.5%). Of the 1,043 persons who participated in the three-year follow-up, 854 persons participated in the six-year follow-up in 2001/2002 (81.9%). Of those lost to follow-up, 168 died (16.1%), 10 refused (1.0%), 10 were ineligible (1.0%) and 1 could not be contacted (0.1%). Persons who were lost to follow-up, were significantly older, performed worse on cognitive tests, and were more likely to be men (all $p < 0.0001$). In addition, persons lost to follow-up had higher levels of inflammation ($p < 0.05$) and lower levels of LDL cholesterol ($p < 0.05$) and total cholesterol ($p < 0.0001$). In the present study, analyses were based on persons of whom data on cognitive functioning was available on at least two occasions, which resulted in a final sample of N = 1,003. Figure 1 shows a flow chart of the study sample.

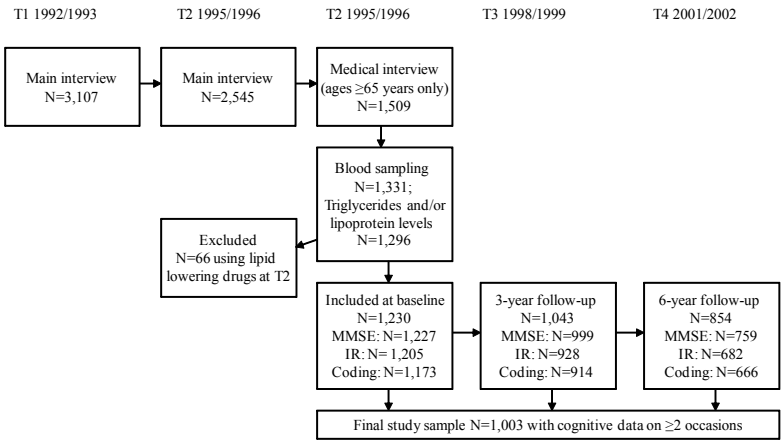

Figure 1 Flow chart of the study sample
MMSE Mini-Mental State Examination; *IR* Immediate Recall; *Coding* Information processing speed.

Cognitive functioning

Objective cognitive tasks were used to measure general cognitive performance, memory (immediate recall) and information processing speed. General cognitive performance was measured with the Mini-Mental State Examination (MMSE) (range, 0-30), a widely used and brief screening instrument to detect cognitive impairment (Folstein et al., 1975). Memory was measured with an abbreviated version of the Auditory Verbal Learning test (ALVT) (Rey, 1964) which consists of three trials instead of five. A list of 15 words is read out loud by the interviewer, after which the respondent sums up as many words as they can remember. Immediate recall was defined as the highest score out of three trials (range, 0-15). To reduce a possible practice effect parallel versions of the ALVT were used, which are applied in treatment-research (Moller et al., 1998), and have been validated and tested on parallelism (Jolles et al., 1995). Information processing speed was measured by an adapted version of the Alphabet Coding Task-15 (Piccinin and Rabbitt, 1999), a letter substitution task consisting of three identical one-minute trials in which the respondent has to combine as many characters as possible according to a given example. The mean score (i.e. number of correctly completed characters) of the three trials was used in the analyses (range, 1- 42.7).

Measurement of triglycerides and lipoprotein levels

Blood samples were kept deep frozen until analysis. Respondents were allowed to take toast and tea, but no dairy products. Serum HDL cholesterol and triglycerides were measured with a Hitachi 747 analyzer (VUmc) using enzymatic colorimetric tests (Roche diagnostics, Mannheim, Germany). The inter-assay coefficient of variation (CV) was < 2.8% for triglycerides and < 6.4% for HDL cholesterol. LDL cholesterol was calculated as: total cholesterol − HDL cholesterol − (0.456 x total triglyceride concentration) expressed in mmol/L (Friedewald et al., 1972). This formula is known to be less reliable as triglyceride concentration increases (Rifai et al., 1992), therefore it was only used if triglyceride levels were < 5.0 mmol/L. LDL cholesterol could not be calculated in nine subjects with triglycerides levels ≥ 5.0 mmol/L.

Measurement of inflammation markers

Serum levels of ACT, CRP, and IL-6 were determined using sensitive regular immunoassays (enzyme-linked immunosorbent assay (ELISA)) developed and performed at Sanquin Research, Amsterdam, the Netherlands. IL-6 was measured with an ELISA (Business Unit Immune Reagents of Sanquin Research, Amsterdam, The Netherlands) and used according to manufacturer's instructions. CRP levels were measured with a sandwich-type ELISA in which polyclonal rabbit anti-CRP antibodies were used as catching antibodies and a biotinylated mAb against CRP (CLB anti–CRP-2) as the detecting antibody (Bruins et al., 1997). ACT was measured with an ELISA in which specific mAbs against ACT were used (Rozemuller et al., 1991). Recombinant IL-6, purified CRP and pooled human plasma were used as standards in the respective assays. Results were expressed as ug/mL for CRP, pg/mL for IL-6, and % of normal plasma for

ACT. The normal human plasma pool (% NHP) used as a standard for ACT contained ~300 mg ACT per L. The inter-assay CV was < 5.2% for ACT, < 4.2% for CRP, and < 5.0% for IL-6. The intra-assay CV was 4.1% for ACT, 3.2% for CRP, and 3.3% for IL-6. The detection limits were 0.8 ng/mL for CRP, and 5.0 pg/mL for IL-6. All values were measured in duplicate, with averages being reported.

Potential confounders

The following variables were considered as potential confounders: age, sex, education, alcohol consumption, smoking, physical activity, arthritis, hypertension, ApoE e4, depressive symptoms, body mass index (BMI), use of non-steroidal anti-inflammatory drugs at baseline and follow-up, use of lipid-lowering drugs at follow-up, and ACT, CRP, IL-6 (if not significant modifiers).

Data on age and sex were derived from the population registries. Education was determined by asking for the highest educational level completed, which was converted into the total number of years of education (range, 5-18 years). Alcohol consumption was assessed by asking for the number of alcoholic units consumed per week over the past year, and the number of days of the week in which alcohol was consumed. Alcohol consumption was classified as no, middle and high according to the Netherlands Economic Institute (NEI) index (Reinhard and Rood-Bakker, 1998). Smoking status was assessed by self report and classified as never, former and current. Physical activity was measured by the LASA physical activity questionnaire (LAPAQ), which is a face-to-face questionnaire in which frequency and duration of walking outside, bicycling, light and heavy household activities and a maximum of two sports during the past two weeks are estimated. Scores were converted to total time spent on physical activities in minutes per day, and thereafter divided in three equal categories (tertiles). Diabetes mellitus was assessed by combining self-report data ($\kappa = 0.85$, nearly perfect agreement with general practitioner (GP) information) (Kriegsman et al., 1996), medication use, and records of the GP. Arthritis was determined by self report ($\kappa = 0.31$, fair agreement with GP information) (Kriegsman et al., 1996). The presence of hypertension was determined by blood pressure ($\geq$ 160/100 mmHg) and/or use of anti-hypertensive medication. ApoE phenotype was determined by isoelectric focusing of delipidated serum samples, followed by immunoblotting. The distribution of ApoE phenotypes was in Hardy-Weinberg equilibrium (ApoE e2/2: 0.8%; e2/3: 12.3%; e3/3: 61.0%; e2/4: 2.2%; e3/4: 20.9%; e4/4: 2.6%; missing: 0.2%). Persons were classified as e4 carriers (phenotypes e2/4, e3/4, e4/4) or e4 non-carriers (phenotypes e2/2, e2/3, e3/3). Depressive symptoms were assessed with the Center of Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale (range, 0-60) designed to measure depressive symptoms in the general population (Beekman et al., 1997; Radloff, 1977). BMI was calculated as: weight (kg) / (height (m))^2. Use of anti-inflammatory and lipid-lowering drugs were determined by checking medication use.

CVD (cardiac disease, peripheral arterial disease, cerebrovascular accident) was evaluated as a potential mediator. The presence of CVD at baseline and three-year follow-up was assessed

by a combination of self-report data, medication use and records of the GPs in an algorithm previously described (Bremmer et al., 2006). At six-year follow-up self-report data and medication records were used.

Data analysis

Serum levels of triglycerides, CRP, ACT and IL-6 were not normally distributed, therefore natural logarithmic (ln) transformations were performed. In addition, the MMSE score was transformed (ln (31-MMSE score)) to obtain a near-normal distribution.

To study the associations between baseline levels of HDL and LDL cholesterol and triglycerides and cognitive functioning, and the modifying effect of inflammatory markers CRP, IL-6, ACT on these associations, data were analyzed using linear mixed models in SPSS for windows, version 15.0 (SPSS incorporated, 2007, Chicago, IL). Linear mixed models takes the dependency of repeated measurements in the data into account and allows inclusion of subjects with missing data. In the present study, a random effect of time with covariance structure "unstructured" was included, taking into account within subject correlation between repeated measurements in addition to between-subject variation. The covariance structure "unstructured" allows the estimation of the variances of the random effects, in addition to their covariance (West, 2009).

First of all, the trajectories of cognitive functioning as indicated by scores on the MMSE, immediate recall and information processing speed were modelled as a function of time. Time was defined as the number of years (i.e. 0, 3 and 6 years) between the determination of lipoprotein levels and follow-up cycle. Second, in separate analyses the main predictors were added to each model and their quadratic term was tested for significance to study the presence of a non-linear association. If significant ($p < 0.10$), the quadratic term was retained in the model. Third, the interaction between the main predictor and time was tested to study whether the main predictor was associated with rate of cognitive decline. If significant ($p < 0.10$) the interaction with time was retained in the model. Hereafter, all potential confounders were added one by one to the model. Variables that showed a significant confounding effect on the studied associations, i.e. $\geq 10\%$ change in the unstandardized regression coefficient (B) of the main predictor were retained in the model.

Effect modification by the inflammatory markers CRP, ACT and IL-6 was tested in the fully adjusted model by adding the product terms (main predictor x inflammatory marker) in separate analyses. If significant ($p < 0.10$), the additive effect of the main predictor centered at different percentiles (10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th}) and the inflammatory marker centered at different percentiles on cognitive functioning was tested. Predictors and inflammatory markers were centered to test for significance of the main effects at these different levels and thus improve interpretability. Given the rigid criteria applied to the IL-6 ELISA, dichotomization around the detection limit of 5.0 pg/mL was considered the best strategy for further analyses of the modifying effect of IL-6. Thus, if a significant interaction with IL-6 was found, the effect of the main

predictor was studied in both high (> 5.0 pg/mL) and low IL-6 (≤ 5.0 pg/mL). If a significant modifying effect was not found, the inflammatory markers were added to the model one by one to test for potential confounding.

Table 1 Baseline characteristics of subjects with longitudinal data on cognitive functioning

Characteristic		Total sample (N = 1,003)
Age, years, mean (SD)		75.01 (6.39)
Female, % (N)		53.1 (533)
Education, years, mean (SD) [a]		9.03 (3.28)
Total cholesterol, mmol/L, median (IR)		5.60 (5.00 – 6.40)
HDL cholesterol, mmol/L, median (IR)		1.25 (1.03 – 1.60)
LDL cholesterol, mmol/L, median (IR) [a]		3.60 (3.10 – 4.30)
Triglycerides, mmol/L, median (IR)		1.30 (1.00 – 1.80)
ACT, % of NHP, median (IR) [a]		156.00 (133.00 – 183.00)
CRP, µmol/mL, median (IR) [a]		2.85 (1.40 – 6.10)
IL-6, pg/mL, median (IR) [a]		1.90 (1.10 – 3.10)
ApoE e4, % (N) [a]		25.8 (258)
Depressive symptoms, mean (SD) [a]		7.90 (7.60)
Hypertension yes, % (N) [a]		56.00 (557)
Diabetes mellitus yes, % (N)		7.70 (77)
Cardiovascular disease, % (N)		28.60 (287)
Rheumatic disease, % (N) [a]		10.70 (107)
Atherosclerosis, % (N) [a]		11.80 (118)
Use of anti-inflammatory medication, % (N) [a]		26.80 (268)
Physical activity (minutes/day), median (IR) [a]		143.85 (86.61 – 210.00)
Body mass index, mean (SD) [a]		26.80 (4.06)
Smoking, % (N) [a]	No	36.90 (370)
	Former	45.80 (459)
	Current	17.30 (173)
Alcohol consumption, % (N) [a]	No	23.10 (231)
	Middle	67.10 (672)
	High	9.90 (99)
MMSE, mean (SD)		27.14 (2.56)
Immediate recall, mean (SD) [a]		8.31 (2.53)
Information processing speed, mean (SD) [a]		23.69 (7.01)

[a] Missing values. *IR* interquartile range; *ACT* α1-antichymotrypsin; *NHP* normal human plasma pool; *CRP* C-reactive protein; *IL-6* Interleukin-6; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein; *ApoE* Apolipoprotein E; *MMSE* Mini-Mental State Examination.

In addition, analyses were repeated after exclusion of persons with CVD at baseline or follow-up to study the mediating effect of CVD on the associations between lipoproteins, triglycerides, inflammation and cognition.

Results

In Table 1 the baseline characteristics of the study sample with data on cognitive functioning on at least two occasions are shown.

Table 2 Associations between baseline levels of lipoproteins, triglycerides, and cognitive functioning over 6 years of follow-up

	Ln-transformed MMSE		Immediate recall		Information processing speed	
Total study sample	N = 1,003		N = 942		N = 923	
	B	p value	B	p value	B	p value
Time adjusted models						
HDL cholesterol	- 0.16	.000	0.75	.000	1.75	.001
HDL x time	0.061	.025	-	-	-	-
LDL cholesterol centered at p10	- 0.16	.000	0.55	.001	1.94	.000
LDL x LDL	0.032	.005	- 0.097	.049	- 0.50	.001
LDL x time	-	-	-	-	0.21	.008
Triglycerides	0.068	.094	- .269	.122	- 0.89	.084
Fully adjusted models						
HDL cholesterol	- 0.074 [a]	.083	0.35 [b]	.026	0.80 [a]	.072
HDL x time	0.060	.027	-	-	-	-
LDL cholesterol centered at p10	- 0.11 [c]	.001	0.24 [b]	.082	1.42 [c]	.000
LDL x LDL	0.022	.029	- 0.064	.123	- 0.38	.001
LDL x time	-	-	-	-	0.21	.009
Triglycerides	0.018 [d]	.611	- 0.19 [e]	.202	- 0.47 [f]	.277

[a] Adjusted for time, age, sex, education, alcohol; [b] Adjusted for time, age, sex, education; [c] Adjusted for time, age, education; [d] Adjusted for time, age, sex, education, alcohol, Apolipoprotein e4, body mass index; [e] Adjusted for time, age, sex, education, alcohol, body mass index; [f] Adjusted for time, age, education, alcohol, body mass index. *B* Unstandardized regression coefficients; *ln* natural log transformation; *MMSE* Mini-Mental Status Examination; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *p10* 10th percentile

Main effects

Table 2 shows the results of the longitudinal analyses in which the associations between HDL and LDL cholesterol, triglycerides and cognitive functioning were studied in the total study sample.

HDL cholesterol

In the time-adjusted models a significant positive association between baseline HDL cholesterol and performance on immediate recall and information processing speed was found. On the ln-transformed MMSE score a significant negative main effect of HDL cholesterol and positive interaction between HDL cholesterol and time was found. This latter result indicates that although a higher level of HDL cholesterol was initially associated with better general cognitive performance, this positive effect decreased over time and lost significance. With respect to the association with immediate recall and information processing speed, no significant interaction between HDL cholesterol and time was found. After adjustment for all relevant confounders, the association between HDL cholesterol and information processing speed lost significance. The positive association between HDL cholesterol and immediate recall remained significant after adjustment. Figure 2 shows the trajectory of immediate recall over time according to HDL cholesterol level. The results indicate that a higher level of HDL cholesterol was significantly associated with a higher score on immediate recall over six years of follow-up, independently of relevant confounders.

After adjustment for relevant confounders, the interaction between HDL cholesterol and time remained significant, while the main effect of HDL cholesterol on the ln-transformed MMSE score lost significance (see Table 2).

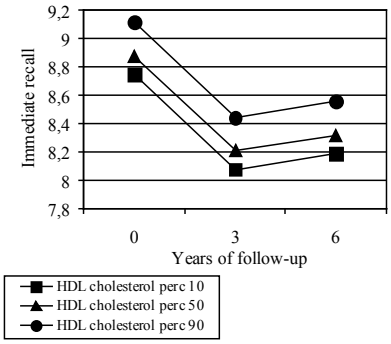

Figure 2 Six-year cognitive decline according to level of high-density lipoprotein (HDL) cholesterol
Model adjusted for time, age, sex and education.

LDL cholesterol

The results (see Table 2) show a significant negative non-linear association between LDL cholesterol and the ln-transformed MMSE score and a significant positive non-linear association between LDL cholesterol and immediate recall and information processing speed. Furthermore, a significant positive interaction between LDL cholesterol and time was found on the association with information processing speed. After additional adjustment, the association between LDL

cholesterol and immediate recall lost significance. The associations between LDL cholesterol and the ln-transformed MMSE score and information processing speed remained significant. In Figure 3, the association between LDL cholesterol and cognitive functioning as indicated by scores on the MMSE and information processing speed is shown. The results indicate that lower LDL cholesterol was independently associated with a lower level of general cognitive performance and information processing speed. In addition, lower LDL cholesterol was independently associated with faster decline on information processing speed. The association between LDL cholesterol and cognitive functioning lost significance in levels above the median of LDL cholesterol. More specifically, in the models predicting general cognitive information and decline in information processing speed a threshold effect was found of 4.2 and 3.8 mmol/L respectively, above which the main effect of LDL cholesterol lost significance.

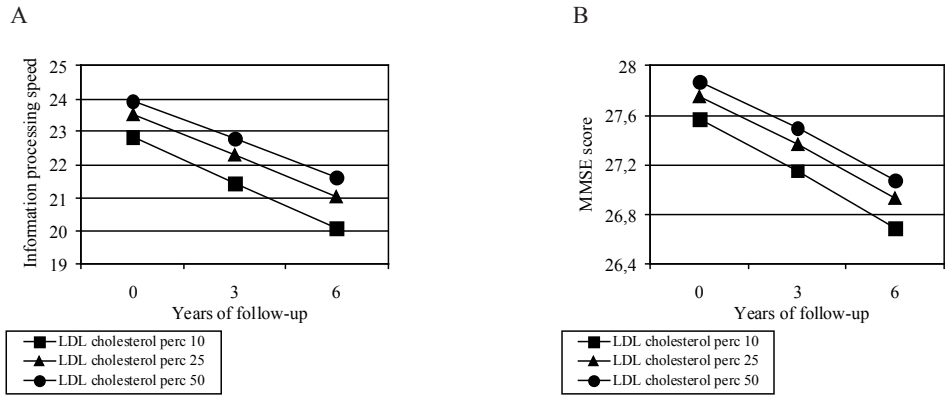

Figure 3 Six-year cognitive decline according to level of low-density lipoprotein (LDL) cholesterol
Models adjusted for time, age and education. (A) Information processing speed. (B) Mini-Mental State Examination (MMSE) score.

Triglycerides

No significant association between level of triglycerides and cognitive functioning was found in both the time- and fully adjusted models (see Table 2).

Modifying effect of inflammation

HDL cholesterol

Examining the modifying effect of inflammation in the fully adjusted models, no significant interaction between HDL cholesterol and inflammation was found (data not shown).

LDL cholesterol

Overall, the results indicate a significant modifying effect of inflammation on the associations between LDL cholesterol and cognitive functioning. More specifically, a significant interaction between LDL cholesterol and ACT as well as CRP was found on the association with general

cognitive performance and immediate recall. Figure 4 shows this additive effect of LDL cholesterol and respectively CRP and ACT on general cognitive performance and immediate recall. The negative effect of low LDL cholesterol on cognitive functioning (MMSE, immediate recall) was strongest in high levels of ACT and CRP and was associated with the lowest level of cognitive performance.

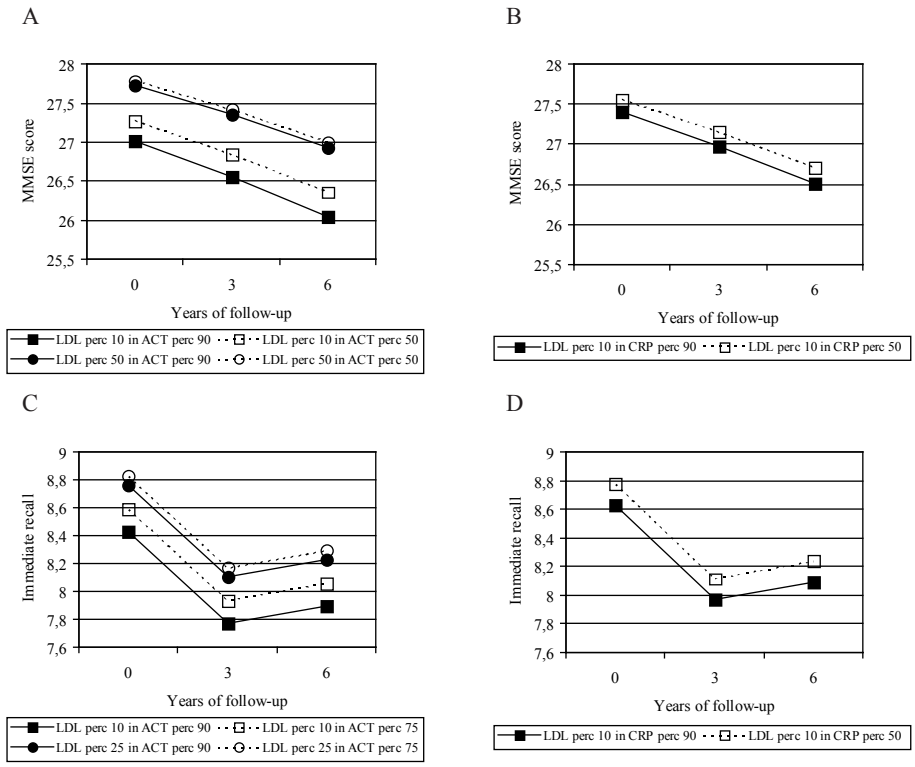

Figure 4 Six-year cognitive decline according to level of low-density lipoprotein (LDL) cholesterol and inflammation

(A and B) MMSE score; model adjusted for time, age, sex and education; (C and D) Immediate recall; model adjusted for time, age and education. *ACT* α1-antichymotrypsin; *CRP* C-reactive Protein; *MMSE* Mini-Mental State Examination.

Furthermore, a significant interaction between LDL cholesterol and IL-6 was found with respect to memory performance. However, the main effect of LDL cholesterol on immediate recall was not significant in either low or high IL-6 (data not shown).

Triglycerides

A significant interaction was found between level of triglycerides and ACT as well as CRP with respect to the association with immediate recall. Figure 5 shows the modifying effect of inflammatory markers ACT and CRP on the association between triglycerides and immediate recall.

The results show the strongest negative association between triglycerides and level of immediate recall in high ACT or CRP. This indicates that a higher level of triglycerides was associated with worse cognitive functioning in high levels of inflammation.

Also, a significant interaction was found between triglycerides and IL-6 with respect to the association with information processing speed. However, the main effect of triglycerides on information processing speed was not significant in either low or high IL-6 (data not shown).

Finally, the results show a significant interaction between triglycerides and CRP on the association with the ln-transformed MMSE score. Further analyses indicate a borderline significant ($p = 0.052$) negative effect of high triglycerides on general cognitive performance in high levels of CRP (90th percentile).

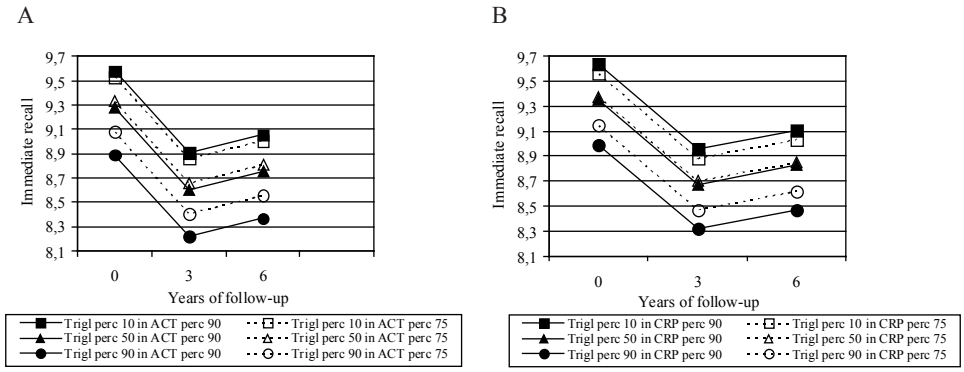

Figure 5 Six-year cognitive decline according to level of triglycerides and inflammation
Models adjusted for time, age, sex, education, alcohol, and body mass index. (A and B) Immediate recall. *ACT* α1-antichymotrypsin; *CRP* C-reactive protein; *Trigl* triglycerides.

Sensitivity analyses

To study whether CVD was a significant mediator of the associations between LDL and HDL cholesterol, triglycerides and cognitive functioning, analyses were repeated in the sample excluding persons with CVD at baseline or follow-up (N = 516). The results show no substantial change in the unstandardized B of HDL cholesterol and triglycerides with respect to the association with cognitive functioning. The strength of the association between LDL cholesterol and cognitive functioning (general cognitive performance, immediate recall) increased significantly. This indicates that the associations found could not be explained by the presence of CVD. Furthermore, exclusion of persons with CVD did not substantially change the strength of the modifying effect of inflammation on the associations between the lipoproteins, triglycerides and cognitive functioning or strengthened the associations found. This indicates that CVD could not explain the additive effect of lipoproteins, triglycerides and inflammation found on cognitive functioning.

Discussion

In the present longitudinal study we have studied the associations between HDL and LDL cholesterol, triglycerides and cognitive functioning over six years of follow-up and focused on the modifying effect of inflammation on these associations in persons aged 65 years and older. We showed a significant independent non-linear association between lower LDL cholesterol and a lower level of general cognitive performance and information processing speed, and a faster rate of decline on information processing speed. The positive effect of higher LDL cholesterol on general cognitive performance and information processing speed showed a threshold effect and was significant only at levels ≤ 4.2 mmol/L and 3.8 mmol/L, respectively. In addition, a significant modifying effect of inflammation was found. Older persons with both low LDL cholesterol and high ACT or CRP performed worst on the MMSE and immediate recall. Furthermore, we showed that higher HDL cholesterol was independently associated with better memory performance. Finally, although the results showed no significant independent association between triglycerides and cognitive functioning, a significant interaction between triglycerides and inflammation was found with respect to memory performance. It was shown that persons with both high levels of triglycerides and high levels of CRP or ACT had the lowest level of memory performance.

LDL cholesterol

The results from the current study are partially in line with the findings in the Prospective Study of Pravastin in the Elderly at Risk (PROSPER) which showed that persons with lower LDL cholesterol performed worse on a task measuring information processing speed (Packard et al., 2007). However, in their study no significant association with decline on information processing speed was detected. This may be explained by a lack of power due to the definition of the outcome measure, i.e. cognitive change score. In addition, the current findings are in agreement with the results from another prospective study in which it was shown that higher LDL cholesterol as well as an increase in LDL cholesterol in the previous three years were predictive of better performance on immediate recall in healthy women aged 52-63 years (Henderson et al., 2003). In contrast, several other longitudinal studies showed an opposite effect on cognitive functioning (Yaffe et al., 2002), cognitive decline in dementia (Helzner et al., 2009) and risk of dementia with stroke (Moroney et al., 1999). Helzner et al. (2009) concluded that higher levels of LDL cholesterol measured before dementia diagnosis, were associated with faster cognitive decline in persons with AD. However, although they found a significant negative interaction between LDL cholesterol and time, the main effect of LDL cholesterol on cognitive functioning was not significant. Furthermore, several other longitudinal studies failed to find a significant independent association between LDL cholesterol and dementia risk (Reitz et al., 2004; Romas et al., 1999; Yoshitake et al., 1995) or cognitive decline (Reitz et al., 2005). These conflicting findings could be due to differences in methods of data analysis and outcome. Previous longitudinal studies dichotomized LDL cholesterol (Reitz et al., 2005), analyzed LDL cholesterol

in quartiles (Moroney et al., 1999; Reitz et al., 2004; Romas et al., 1999; Yaffe et al., 2002) or studied continuous LDL cholesterol assuming a linear association (Helzner et al., 2009; Moroney et al., 1999; Reitz et al., 2004; Romas et al., 1999), while we found a non-linear association. In addition, in the current study mixed linear models were used to predict cognitive functioning, while in most longitudinal studies Cox proportional hazards analyses were used with age at onset of VaD or AD (Moroney et al., 1999; Reitz et al., 2004; Romas et al., 1999) or person-years to incidence (Yoshitake et al., 1995) as the outcome measure. In the study by Reitz et al. (2005) differences in rate of change in cognitive score depending on lipid level were analyzed by means of generalized estimating equations. However, LDL cholesterol was dichotomized at the median and at cutoff based on the normal limit (i.e. 4.14 mmol/L), while the findings in our study showed a ceiling effect of 3.8 - 4.2 mmol/L, above which the main effect of LDL cholesterol was no longer significant.

It has been proposed that decreased total cholesterol in late-life is a marker for decline in general health status (Brescianini et al., 2003; Stewart et al., 2007) and for early processes that reflect neurodegenerative changes and represents a risk marker for dementia and cognitive decline (Solomon et al., 2007; Stewart et al., 2007). The current finding that lower LDL cholesterol is an independent predictor of lower general cognitive performance and faster decline on information processing speed is in line with this hypothesis.

Interestingly, the present prospective study showed an additive negative effect of low LDL cholesterol and high levels of inflammation (ACT and CRP) on general cognitive performance and memory performance. To our knowledge, the moderating effect of inflammation on the association between LDL cholesterol and cognition has not been previously studied. It has been suggested by Lehtimäki et al. (2005) that because CRP binds to Apolipoprotein B-containing lipoproteins in nonagenarians with high CRP concentrations (Bhakdi et al., 1999; Taskinen et al., 2002), CRP might effectively combine with LDL cholesterol particles to form a rapidly catabolized complex (Cabana et al., 1989), resulting in decreased levels of LDL cholesterol.

HDL cholesterol

The present study showed a prolonged positive effect of higher HDL cholesterol on memory performance. This result is consistent with the findings from most cross-sectional studies in which a protective effect of HDL cholesterol was found on hippocampal volume (Wolf et al., 2004), dementia risk (Bonarek et al., 2000; Van Exel et al., 2002) and cognitive functioning (Atzmon et al., 2002; Merched et al., 2000; Van Exel et al., 2002). In contrast, results from the Heart and Estrogen-Progestin Replacement Study (HERS), which consisted of women with coronary heart disease who had all undergone a hysterectomy and were either receiving hormone replacement treatment or a placebo, showed no significant association between HDL cholesterol and cognitive functioning at the time of blood-sampling (Yaffe et al., 2002). In addition, another study showed that neither baseline levels of HDL cholesterol nor a change in HDL cholesterol were significantly associated with memory performance at the eight-year follow-up

measurement (Henderson et al., 2003). These conflicting results might be explained by the differences in sample characteristics. Furthermore, we found no main effect of HDL cholesterol on rate of cognitive decline. This is in line with the results from previous longitudinal studies showing no association between HDL cholesterol and risk of MCI (Reitz et al., 2008) or changes in cognitive functioning (Packard et al., 2007; Reitz et al., 2005). In contrast to our expectations, no significant modifying effect of inflammation on the associations between HDL cholesterol and cognitive functioning was found.

Triglycerides

In the present study no significant associations were found between triglycerides and cognitive decline. This in line with most previous studies in which no significant associations were found between triglycerides and dementia (Hall et al., 2006; Reitz et al., 2004; Romas et al., 1999) or cognitive decline (Reitz et al., 2005; Yaffe et al., 2002). Still, some have found an association between high triglyceride levels and cognitive decline (De Frias et al., 2007) and poorer cognitive functioning (Perlmuter et al., 1988; Sims et al., 2008). However, we found a significant modifying effect of inflammation on the association between triglycerides and memory performance. It was shown that higher triglycerides levels were associated with worse memory performance over six years of follow-up, only in persons with high CRP and ACT. Previously, studies have shown that in subjects with insulin-resistance syndrome, the acute-phase response, including high CRP, occurs in parallel with increased triglycerides and decreased HDL cholesterol (Pickup et al., 1997; Yudkin et al., 1999). Also, it has been shown that persons with MetS, of which high triglycerides and also low HDL cholesterol are components, and elevated levels of inflammation have an increased risk of VaD (Solfrizzi et al., 2010), non-amnestic MCI (Roberts et al., 2010) and cognitive decline (Yaffe et al., 2004), and show worse cognitive function (Dik et al., 2007), compared to those with MetS and without elevated inflammation.

Strengths and limitations

The main strength of the present study is that longitudinal data from a large population-based study were used. The trajectory of cognitive functioning based on tests most sensitive to aging was analyzed, studying performance on three occasions over six years of follow-up. To our knowledge, this is the first study focusing on the modifying effect of inflammatory markers ACT, CRP and IL-6 on the associations between lipoproteins, triglycerides and cognitive functioning. The results from the current study implicate that future research should further investigate the interaction between lipids, lipoproteins and inflammatory markers with respect to cognitive decline and dementia.

As inflammation and adverse lipid levels are known risk factors for CVD, which in turn have been shown to be associated with dementia and cognitive decline (Stampfer, 2006), analyses were repeated after exclusion of persons with CVD at baseline or follow-up to analyze the mediating effect of CVD on the associations studied. These sensitivity analyses showed that

CVD could not explain the associations found in the present study. Although we have repeated all analyses after exclusion of prevalent or incident heart disease, stroke and peripheral artery disease, the possible influence of subclinical CVD on the associations found could not be fully excluded.

A number of limitations need to be addressed. First, levels of lipoproteins, triglycerides and inflammatory markers were determined only at baseline. This may have led to measurement error and an underestimation of the strength of the associations found. Also, it was not possible to study whether a change in lipid levels and inflammation was associated with cognitive decline. Furthermore, the frailest persons with lower scores on cognitive testing refused blood sampling. Also, persons who were lost to follow-up had significantly higher levels of inflammation, lower levels of LDL cholesterol and cognitive functioning compared to those who remained in the study. This may have led to an underestimation of the strength of the associations found. In addition, a possible limitation of the current study is that a direct method of measuring LDL cholesterol was not available and LDL cholesterol levels were therefore calculated using the Friedewald formula (Friedewald et al., 1972). We can not exclude the possibility that this may have led to a certain degree of inaccuracy in LDL cholesterol levels, as has been suggested in some previous studies (Jun et al., 2008; Scharnagl et al., 2001).

Finally, the possibility that dementia pathology may have led to a change in lipid and inflammation levels can not be dismissed. In LASA a formal dementia diagnosis is not available. However, persons showing persistent cognitive decline, defined as clinically significant cognitive decline over three years of follow-up (> 2 SD below the average cognitive decline) and continued to decline during the subsequent years, were identified. Most subjects with persistent cognitive decline were likely to have developed dementia (Van den Kommer et al., 2008). In our current sample, only two persons were identified with persistent cognitive decline at the time of blood sampling, reducing the danger of reverse causality substantially.

Conclusion

In sum, the present longitudinal population-based study showed that low HDL cholesterol as well as low LDL cholesterol were independent predictors of prolonged lower cognitive functioning. Furthermore, the lowest level of general cognitive performance and memory performance was found in persons with both low LDL cholesterol and high levels of inflammation as indicated by CRP or ACT. In addition, persons with both high levels of triglycerides and high levels of inflammation showed the lowest level of memory performance. The present findings implicate that a combination of low LDL cholesterol and high inflammation as well as high triglycerides and high inflammation may be used as markers predictive of prolonged cognitive impairment.

Disclosure statement

None of the authors report any actual or potential conflicts of interest. The authors state that the institution has no contracts relating to this research through which it or any other organization may stand to gain financially now or in the future. The authors state that there are no agreements of authors or their institutions that could be seen as involving a financial interest in this work.

Informed consent was obtained from all respondents, and the study was approved by the Ethical Review Board of the VU University Medical Center (VUmc).

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References

Arai, Y., Hirose, N., Nakazawa, S., Yamamura, K., Shimizu, K., Takayama, M., Ebibara, Y., Osono, Y., Homma, S., 2001. Lipoprotein metabolism in Japanese centenarians: effects of apolipoprotein E polymorphism and nutritional status. J. Am Geriatr. Soc. 49, 1434-1441.

Atzmon, G., Gabriely, I., Greinier, W., Davidson, D., Schechter, C., Barzilai, N., 2002. Plasma HDL levels highly correlate with cognitive function in exceptional longevity. J. Gerontol. A. Biol. Sci. Med. Sci. 57A(11), M712-M715.

Beekman, A.T.F., Deeg, D.J.H., van Limbeek, J., Braam, A.W., de Vries, M.Z., van Tilburg, W., 1997. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in the Netherlands. Psychol. Med. 27, 231-235.

Bhakdi, S., Torzewski, M., Klouche, M., Hemmes, M., 1999. Complement and atherogenesis: binding of CRP to degraded, nonoxidized LDL enhances complement activation. Arterioscler. Thromb. Vasc. Biol. 19, 2348-2354.

Boden, W.E., 2000. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the veterans affairs high-density lipoprotein intervention trial. Am. J. Cardiol. 86 (12A), 19L-22L.

Bonarek, M., Barberger-Gateau, P., Letenneur, L., Deschamps, V., Iron, A., Dubroca, B., Dartigues, J.F., 2000. Relationships between cholesterol, apolipoprotein E polymorphism and dementia: a cross-sectional analysis from the PAQUID study. Neuroepidemiology 19, 141-148.

Bremmer, M.A., Hoogendijk, W.J.G., Deeg, D.J.H., Schoevers, R.A., Schalk, B.W.M., Beekman, A.T.F., 2006. Depression in older age is a risk factor for first ischemic cardiac events. Am. J. Ger. Psychiatry 14, 523-530.

Brescianini, S., Maggi, S., Farchi, G., Mariotti, M.S., Di Carlo A., Baldereschi, M., Inzitari, D., 2003. Low total cholesterol and increased risk for dying: are low levels clinical warning signs in elderly? Results from the Italian Longitudinal study on Aging. J. Am. Geriatr. Soc. 51, 991-996.

Bruins, P., te Velthuis H., Yazdanbakhsh, A.P., Jansen, P.G., van Hardevelt, F.W., de Beaumont, E.M., Wildevuur, C.R., Eijsman, L., Trouwborst, A., Hack, C.E., 1997. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation 96, 3542-3548.

Cabana, V.G., Siegel, J.N., Sabesin, S.M., 1989. Effects of the acute phase response on the concentration and density distribution of plasma lipids and apolipoproteins. J. Lipid Res. 30, 39-49.

Cockerill, G.W., Huehns, T.Y., Weerasinghe, A., Stocker, C., Lerch, P.G., Miller, N.E., Haskard, D.O., 2001. Elevation of plasma high-density lipoprotein concentration reduces interleukin-1-induced expression of E-selectin in an in vivo model of acute inflammation. Circulation 103, 108-112.

De Frias, C.A., Bunce, D., Wahlin, A., Adolfsson, R., Sleegers, K., Cruts, M., van Broeckhoven, C., Nilsson, L.G., 2007. Cholesterol and triglycerides moderate the effect of apolipoprotein E on memory functioning in older adults. J. Gerontol B Psychol Sci Soc Sci 62, 112-118.

Deeg, D.J., van Tilburg, T., Smit, J.H., de Leeuw, E.D., 2002. Attrition in the Longitudinal Aging Study Amsterdam. The effect of differential inclusion in side studies. J. Clin. Epidemiol. 55, 319-328.

Dik, M.G., Jonker, C., Hack, C.E., Smit, J.H., Comijs, H.C., Eikelenboom, P., 2005. Serum inflammatory proteins and cognitive decline in older persons. Neurology 64, 1371-1377.

Dik, M.G., Jonker, C., Comijs, H.C., Deeg, D.J.H., Kok, A., Yaffe, K., Penninx, B.W., 2007. Contribution of metabolic syndrome components to cognition in older individuals. Diabetes Care 30, 2655-2660.

Engelhart, M.J., Geerlings, M.I., Meijer, J., Kiliaan, A., Ruitenberg, A., van Swieten, J.C., Stijnen, T., Hofman, A., Witteman, J.C.M., Breteler, M.M.B., 2004. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch. Neurol. 61, 668-672.

Ettinger, W.H., Harris, T., Verdery, R.B., Tracy, R., Kouba, E., 1995. Evidence for inflammation as a cause of hypocholesterolemia in older people. J. Am. Geriatr. Soc. 43, 264-266.

Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III), 2001. Executive summary of the third report of the National Cholesterol Education Program (NCEP). JAMA 285, 2486-2497.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-Mental State. A practical method for grading cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189-198.

Friedewald, W.T., Levy, R.I., Fredrickson, D.S., 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 18(6), 499-502.

Hall, K., Murrell, J., Ogunniyi, A., Deeg, M., Baiyewu, O., Gao, S., Gureje, O., Dickens, J., Evans, R., Smith-Gamble, V., Unverzagt, F.W., Shen, J., Hendrie, H., 2006. Cholesterol, APOE genotype, and Alzheimer disease: an epidemiologic study of Nigerian Yoruba. Neurology 66, 223-227.

Helzner, E.P., Luchsinger, J.A., Scarmeas, N., Cosentino, S., Brickman, A.M., Glymour, M.M., Stern, Y., 2009. Contribution of vascular risk factors to the progression in Alzheimer Disease. Arch. Neurol. 66, 343-348.

Henderson, V.W., Guthrie, J.R., Dennerstein, L., 2003. Serum lipids and memory in a population based cohort of middle age women. J. Neurol. Neurosurg. Psychiatry 74, 1530-1535.

Jolles, J., Verhey, F.R.J., Riedel, W.J., Houx, P.J., 1995. Cognitive impairment in elderly people. Predisposing factors and implications for experimental drug studies. Drugs Aging 7, 459-479.

Jun, K.R., Park, H.I., Chun, S., Park, H., Min, W.K., 2008. Effects of total cholesterol and triglyceride on the percentage difference between the low-density lipoprotein cholesterol concentration measured directly and calculated using the Friedewald formula. Clin. Chem. Lab. Med. 46(3), 371-375.

Kalmijn, S., Foley, D., White, L., Burchfiel, C.M., Curb, J.D., Petrovitch, H., Ross, G.W., Havlik, R.J., Launer, L.J., 2000. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men: the Honolulu-Asia Aging Study. Arterioscler. Thromb. Vasc. Biol. 20, 2255-2260.

Kriegsman, D.M.W., Penninx, B.W.J.H., van Eijk, J., Boeke, A.J.P., Deeg, D.J.H., 1996. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinations of inaccuracy. J. Clin. Epidemiol. 49, 1407-1417.

Launer, L.J., White, L.R., Petrovitch, H., Ross, G.W., Curb, J.D., 2001. Cholesterol and neuropathologic markers of AD: a population-based autopsy study. Neurology 57, 1447-1452.

Lee, K.S., Jang, Y., Chung, Y.K., Chung, J.H., Oh, B.H., Hong, C.H., 2010. Relationship between the diagnostic components of the metabolic syndrome (MS) and cognition by ApoE genotype in the elderly. Arch. Gerontol. Geriatr. 50, 69-72.

Lehtimäki, T., Ojala, P., Rontu, R., Goebeler, S., Karhunen, P.J., Jylhä, M., Mattila, K., Metso, S., Jokela, H., Nikkila, M., Wuolijoki, E., Hervonen, A., Hurme, M., 2005. Interleukin-6 modulates plasma cholesterol and C-reactive protein concentrations in nonagenarians. J. Am. Geriatr. Soc. 53, 1552-1558.

Lesser, G.T., Haroutunian, V., Purohit, D.P., Beeri, M.S., Schmeidler, J., Honkanen, L., Neufeld, R., Libow, L.S., 2009. Serum lipids are related to Alzheimer's pathology in nursing home residents. Dem. Ger. Cogn. Disord. 27, 42-49.

Merched, A., Xia, Y., Visvikis, S., Serot, J.M., Siest, G., 2000. Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease. Neurobiol. Aging 21, 27-30.

Moller, J.T., Cluitmans, P., Rasmussen, L.S., Houx, P., Rasmussen, H., Canet, J., Rabbitt, P., Jolles, J., Larsen, K., Hanning, C.D., Langeron, O., Johnson, T., Lauven, P.M., Kristensen, P.A., Biedler, A., van Beem, H., Fraidakis, O., Silverstein, J.H., Beneken, J.E.W., Gravenstein, J.S., 1998. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 351, 857-861.

Moroney, J.T., Tang, M.X., Berglund, L., Small, S., Merchant, C., Bell, K., Stern, Y., Mayeux, R., 1999. Low-density lipoprotein cholesterol and the risk of dementia with stroke. JAMA 282, 254-260.

Morrison, A., Hokanson, J.E., 2009. The independent relationship between triglycerides and coronary heart disease. Vasc. Health Risk Manag. 5, 89-95.

Packard, C.J., Westendorp, R.G.J., Stott, D.J., Caslake, M.J., Murray, H.M., Shepherd, J., Blauw, G.J., Murphy, M.B., Bollen, E.L.E.M., Buckley, B.M., Cobbe, S.M., Ford, I., Gaw, A., Hyland, M., Jukema, J.W., Kamper, A.M., Macfarlane, P.W., Jolles, J., Perry, I.J., Sweeney, B.J., Twomey, C., 2007. Association between apolipoprotein E-4 and cognitive decline in elderly adults. J. Am. Ger. Soc. 55, 1777-1785.

Peila, R.. Launer, L.J., 2006. Inflammation and dementia: epidemiologic evidence. Acta Neurol. Scand. Suppl. 185, 102-106.

Perlmuter, L.C., Nathan, D.M., Goldfinger, S.H., Russo, P.A., Yates, M., 1988. Triglyceride levels affect cognitive function in noninsulin-dependent diabetics. J. Diabet. Complications 2, 210-213.

Piccinin, A.M., Rabbitt, P.M., 1999. Contribution of cognitive abilities to performance and improvement on a substitution coding task. Psychol. Aging 14, 539-551.

Pickup, J.C., Mattock, M.B., Chusney, G.D., Burt, D., 1997. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia 40, 1286-1292.

Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas 1, 385-401.

Reinhard, O., Rood-Bakker, D., 1998. Alcoholgebruik in beeld. Standaardmeetlat. Nederlands Economisch Instituut, Rotterdam (in Dutch).

Reitz, C., Tang, M.X., Luchsinger, J., Mayeux, R., 2004. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch. Neurol. 61, 705-714.

Reitz, C., Luchsinger, J., Tang, M.X., Manly, J., Mayeux, R., 2005. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology 64, 1378-1383.

Reitz, C., Tang, M.X., Manly, J., Schupf, N., Mayeux, R., Luchsinger, J.A., 2008. Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment. Dem. Ger. Cogn. Disord. 25, 232-237.

Rey, A., 1964. L'examen clinique en psychologie. Presses Universitaire de France, Paris, France.

Rifai, N., Warnick, G.R., Mcnamara, J.R., Belcher, J.D., Grinstead, G.F., Frantz, I.D., 1992. Measurement of low-density-lipoprotein cholesterol in serum: a status report. Clin. Chem. 38 (1), 150-160.

Roberts, R.O., Geda, Y.E., Knopman, D.S., Cha, R.H., Boeve, B.F., Ivnik, R.J., Pankratz, V.S., Tangalos, E.G., Petersen, R.C., 2010. Metabolic syndrome, inflammation, and nonamnestic mild cognitive impairment in older persons. Alzheimer Dis. Assoc. Disord. 24(1), 11-18.

Romas, S.N., Tang, M.X., Berglund, L., Mayeux, R., 1999. APOE genotype, plasma lipids lipoproteins, and AD in community elderly. Neurology 53, 517-521.

Rozemuller, J.M., Abbink, J.J., Kamp, A.M., Stam, F.C., Hack, C.E., Eikelenboom, P., 1991. Distribution pattern and functional state of alpha 1-antichymotrypsin in plaques and vascular amyloid in Alzheimer's disease. A immunohistochemical study with monoclonal antibodies against native and inactivated alpha 1-antichymotrypsin. Acta Neuropathol. 82, 200-207.

Scharnagl, H., Nauck, M., Wieland, H., März, W., 2001. The Friedewald formula underestimates LDL cholesterol at low concentrations. Clin. Chem. Lab. Med. 39(5), 426-431.

Sims, R., Madhere, S., Callender, C., Campbell, A., 2008. Patterns of relationships between cardiovascular disease risk factors and neurocognitive function in African Americans. Ethn. Dis. 18, 471-476.

Solfrizzi, V., Scafato, E., Capurso, C., D'Introno, A., Colacicco,, A.M., Frisardi, V., Vendemiale, G., Baldereschi, M., Crepaldi, G., Di Carlo, A., Galluzzo L., Gandin, C., Inzitari, D., Maggi, S., Capurso, A., Panza, F., 2010. Metabolic syndrome and the risk of vascular dementia. The Italian Longitudinal Study on Ageing. J. Neurol. Neurosurg. Psychiatry 81, 433-440.

Solomon, A., Kåreholt, I., Ngandu, T., Winblad, B., Nissinen, A., Tuomihelto, J., Soininen, H., Kivipelto, M., 2007. Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology 68 (10), 751–756.

Stampfer, M.J., 2006. Cardiovascular disease and Alzheimer's disease: common links. J. Intern. Med. 260 (3), 211-223.

Stewart, R., White, L.R., Xue, Q.L., Launer, L.J., 2007. Twenty-six-year change in total cholesterol levels and incident dementia. The Honolulu-Asia Aging Study. Arch. Neurol. 64, 103-107.

Tan, Z.S., Seshadri, S., Beiser, A., Wilson, P.W.F., Kiel, D.P., Tocco, M., D'Agostino, R.B., Wolf, P.A., 2003. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham study. Arch. Intern. Med. 163, 1053-1057.

Taskinen, S., Kovanen, P.T., Jarva, H., Meri, S., Pentikainen, M.O., 2002. Binding of C-reactive protein to modified low-density-lipoprotein particles: identification of cholesterol as a novel ligand for C-reactive protein. Biochem. J. 367, 403-412.

Van Exel, E., de Craen, A.J.M, Gussekloo, J., Houx, P., Bootsma-van der Wiel, A., Macfarlane, P.W., Blauw, G.J., Westendorp, R.G.J, 2002. Association between high-density lipoprotein and cognitive impairment in the oldest old. Ann. Neurol. 51, 716–721.

Van den Kommer, T.N., Comijs, H.C., Dik, M.G., Jonker, C., Deeg, D.J.H., 2008. Development of classification models for early detections of persons at risk for persistent cognitive decline. J. Neurol. 255(10), 1486-1494.

Van Vliet, P., van de Water, W., de Craen, A.J.M., Westendorp, R.G.J., 2009. The influence of age on the association between cholesterol and cognitive function. Exp. Gerontol. 44, 112-122.

Weaver, J.D., Huang, M.H., Albert, M., Harris, T., Rowe, J.W., Seeman, T.E., 2002. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology 59, 371-378.

West, B.T., 2009. Analyzing longitudinal data with the linear mixed models procedure in SPSS. Eval. Health. Prof. 32(3), 207-228.

Wolf, H., Hensel, A., Arendt, T., Kivipelto, M., Winblad, B., Gertz, H.J., 2004. Serum lipids and hippocampal volume: the link to Alzheimer's disease? Ann. Neurol. 56, 745-748.

Yaffe, K., Barrett-Connor, E., Lin, F., Grady, D., 2002. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch. Neurol. 59, 378-384.

Yaffe, K., Kanaya, A., Lindquist, K., Somonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F.A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292(18), 2237-2241.

Yoshitake, T., Kiyohara, Y., Kato, I., Ohmura, T., Iwamoto, H., Nakayama, K., Ohmori, S., Nomiyama, K., Kawano, H., Ueda, K., Sueishi, K., Tsuneyoshi, M., Fujishima, M., 1995. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 45, 1161-1168.

Yudkin, J.S., Stehouwer, C.D.A., Emeis, J.J., Coppack, S.W., 1999. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler. Thromb. Vasc. Biol. 19, 972-978.

Zuliani, G., Volpato, S., Ble, A., Bandinelli, S., Corsi, A.M., Lauretani, F., Paolisso, G., Fellin, R., Ferrucci, L., 2007. High interleukin-6 plasma levels are associated with low HDL-C levels in community-dwelling older adults: the InChianti study. Atherosclerosis 192, 384-390.