Chapter 5

Association between high-density lipoprotein and cognitive impairment in the oldest old

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ABSTRACT

Background Low HDL-cholesterol is associated with an increased risk for cardiovascular disease and stroke. At the same time, cardiovascular disease and stroke are important risk factors for dementia. We assessed the association between total- and fractionated cholesterol and cognitive impairment, and explored whether observed associations were dependent or independent of atherosclerotic disease.

Methods In a population-based study, total-cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol were measured in 561 subjects aged 85 years, and grouped in three equal strata representing decreasing serum concentrations. History of cardiovascular disease and stroke was determined. All subjects completed the Mini-Mental State Examination (MMSE) and presence of dementia was determined.

Results Median MMSE scores were significantly lower in subjects with low HDL-cholesterol (25 *vs.* 27 points, $p < 0.001$). No differences in MMSE scores were found for other lipids and lipoproteins. MMSE scores in subjects with and without cardiovascular disease was 26 and 27 points ($p=0.007$) and in subjects with and without stroke 21 and 26 points ($p<0.001$). The associations between low MMSE scores and low HDL-cholesterol remained significant after excluding subjects with cardiovascular disease or stroke. Comparing subjects with low HDL-cholesterol with subjects with high HDL-cholesterol, the odds ratio for dementia was 2.3 (95% CI 1.2-4.3) and in subjects without cardiovascular disease or stroke it was 3.3 (95% CI 1.1-10.3). All odds ratios were unaffected by education, LDL-cholesterol, triglycerides, and survival.

Conclusion Low HDL-cholesterol is associated with cognitive impairment and dementia. At least part of the association between HDL-cholesterol and cognitive function is independent of atherosclerotic disease.

Introduction

Several risk factors for cardiovascular disease, such as hypertension and diabetes mellitus, are linked with cognitive impairment[1,2]. The association of serum total cholesterol concentrations and cognitive impairment, however, has yielded conflicting results[3-7].The amount of evidence relating to a possible association of triglycerides, low-density lipoprotein-cholesterol (LDL-cholesterol), and high-density lipoprotein-cholesterol (HDL-cholesterol) on cognitive impairment is even more limited[5,6,8].

Lipids and lipoproteins may directly affect neurodegeneration. In-vitro studies have shown that both cholesterol and HDL-cholesterol can influence the formation of amyloid-beta[9-12], the main constituent of amyloid plaques. There is also indirect support for a link between HDL-cholesterol and cognitive function via atherosclerotic disease. It has been shown that atherosclerotic disease is associated with clinical and subclinical ischemic diseases in the brain, which contributes to the development of late onset dementia[13,14]. At the same time low serum concentrations of HDL-cholesterol have been associated with an increased risk of stroke[15,16] and patients who suffered a stroke have an increased risk of developing Alzheimer's disease[17].

The primary goal of our study was to examine the association between adverse lipid profiles and cognitive impairment. Furthermore, we explored whether observed associations between individual components of the adverse lipid profiles and cognitive impairment were dependent or independent of atherosclerotic disease.

Methods

Subjects

The Leiden 85-plus Study is a population-based study of inhabitants of Leiden, the Netherlands. There are no selection criteria for health or demographic characteristics. Between September 1997 and September 1999 all members of the 1912 to 1914-birth cohort were contacted by mail in the month after their 85th birthday. They were then contacted by telephone and subsequently visited at home. Subjects were visited three times at their place of residence. At the first two visits face to face interviews were administered and an electrocardiogram was obtained. At the third visit a venous blood sample was drawn. All subjects gave informed consent to participate in the study. For cognitively impaired subjects informed consent was obtained from a guardian. The Medical Ethical Committee of the Leiden University Medical Center approved the study.

Medical history

In the Netherlands general practitioners provide medical care for people of all ages within a small catchment area. Virtually all inhabitants living in the Netherlands register with a general practitioner, who acts as the gatekeeper to further medical care. Hence the general practitioner has a complete medical history of all of his or her patients. The only exception are institutionalised subjects who are treated by a nursing home physician. Five percent of 85-year-olds in Leiden live in a nursing home. All subjects' general practitioners and nursing home physicians were interviewed to obtain a full medical history.

Lipid profile

Serum total cholesterol and triglycerides concentrations were analysed on a fully automated Hitachi 747. HDL-cholesterol was measured with a Hitachi 911. LDL-cholesterol was estimated using the Friedenwald equation: LDL-cholesterol = total cholesterol – HDL-cholesterol – (triglycerides/2.2), whereby 5 subjects with a triglyceride concentration higher than 5 mmol/l were excluded. Concentrations of serum lipids and lipoproteins were grouped into three equal strata representing decreasing concentrations of lipids and lipoproteins. This was done separately for women and men, since women have higher lipids and lipoproteins concentrations than men.

Cognitive function

The Mini-Mental State Examination (MMSE)[18] was administered in all subjects. Cognitive impairment was classified as a MMSE score of 18 points and lower[18]. Clinical diagnosis of dementia was obtained from the medical records of subjects' general practitioner or nursing home physician[19].

Possible confounders

History of cardiovascular disease, history of stroke, and educational level were considered possible confounders. Subjects were classified as having cardiovascular disease when they had a positive history of myocardial infarction, angina pectoris, arterial surgery, or intermittent claudication, as obtained form the medical records. Coronary artery disease was also considered present when the ECG, performed at the home visit, revealed a myocardial infarction (Minnesota codes 1-1, 1-2, and 1-3)[20] or myocardial ischaemia (Minnesota codes 4-1, 4-2, 4-3, 5-1, 5-2 and 5-3)[20]. Subjects were classified as having a history of stroke, when the medical records of the general practitioner or nursing home physician indicated a history of stroke. Subjects were divided into two educational levels: a lower education level (subjects without schooling or with primary school only) and a higher education level (more than 6 years of schooling).

Statistical analysis

Distribution of MMSE-scores was skewed to the left, therefore data are presented as medians with corresponding 95% confidence intervals (95% CI)[21]. Such intervals represent the range of plausible values that include the "true" median. Groups were compared with non-parametric tests that do not assume an underlying normal distribution of the data. As the non-parametric equivalent of the one-way ANOVA procedure, we used the Jonckheere-Terpstra test[22] to determine the p-value for trend between MMSE-scores and the strata representing decreasing lipid and lipoprotein concentrations. Univariate and multivariate odds ratios were obtained by logistic regression analysis.

First, we determined the association between MMSE-scores over strata of decreasing concentrations of lipids and lipoproteins. Second, we determined whether the observed associations were independent of atherosclerotic disease by restricting the analysis to subjects without cardiovascular disease and/or subjects without stroke. Third, the presence of cognitive impairment (MMSE score < 18 ponits and lower) or clinical diagnosis of dementia were used as dichotomous endpoints in a logistic regression

model. All odds ratios were adjusted for level of education. We tested for trend using the log-likelihood statistic with one degree of freedom. In a final analysis we created a restricted sample of subjects who survived the first year of follow-up, and repeated all previous statistical analyses.

Results

Between September 1997 and September 1999 a total of 705 inhabitants of Leiden reached the age of 85 years and were thus eligible for inclusion in the study. Fourteen subjects died before they could be contacted. Of the remaining 691 subjects, 599 subjects participated (response rate 87%). There were no significant differences for various demographic characteristics between the 599 respondents and the source population.

The lipid profile of 38 subjects could not be determined because seven subjects died before a blood sample could be obtained and 31 subjects refused to give a blood sample. Table 1 shows the demographic and clinical characteristics of the remaining 561 subjects. More than half of all subjects (60%) had a history of cardiovascular disease, while 10% had a history of stroke. The median HDL-cholesterol concentration was 1.23 mmol/l in subjects with a history of cardiovascular disease compared to 1.31 mmol/l in those without a history of cardiovascular disease (Mann-Whitney, p=0.01). HDL-cholesterol concentrations in subjects with and without stroke were 1.14 mmol/l and 1.29 mmol/l, respectively (Mann-Whitney, p=0.004). There were no differences when concentrations of total cholesterol, LDL-cholesterol, or triglycerides were compared.

Table 1 *Demographic and clinical characteristics of study participants.*

Characteristic	Total (n=561)	
	No.	%
Female	373	67%
Low level of education *	333	63%
History of cardiovascular disease	335	60%
History of stroke	56	10%
Cognitive impairment		
MMSE $\leq$ 18 points	91	16%
Dementia	73	13%

** Low level of education is defined as subjects without schooling or those who finished primary school only. All subjects were aged 85 years. MMSE; Mini-Mental State Examination.*

Table 2 shows the median MMSE scores for the three strata of decreasing serum concentrations of lipids and lipoproteins. There was no association between MMSE scores and serum concentrations of total cholesterol, triglycerides, and LDL-cholesterol. A significant association was observed for HDL-cholesterol and MMSE score. Subjects with a low HDL-cholesterol concentration had a median MMSE score of 25 points compared to 27 points for subjects with a high HDL-cholesterol concentration (p for trend <0.001). The association between HDL-cholesterol and MMSE scores was equally strong in men and women, and in subjects with a high and a low level of education.

Table 2 *MMSE scores in strata of lipid and lipoprotein concentrations.*

	Strata of lipid or lipoprotein *			
	High (n=188)	Intermediate (n=185)	Low (n=188)	p for trend
Total cholesterol (median, mmol/l)	6.79	5.73	4.64	-
MMSE score (median, 95% CI)	26 (25-27)	26 (26-27)	26 (25-27)	0.4
Triglycerides (median, mmol/l)	2.21	1.34	0.90	-
MMSE score (median, 95% CI)	26 (25-26)	26 (25-27)	26 (26-27)	0.2
LDL-cholesterol (median, mmol/l)	4.57	3.64	2.75	-
MMSE score (median, 95% CI)	26 (25-27)	26 (26-27)	26 (25-27)	0.4
HDL-cholesterol (median, mmol/l)	1.65	1.28	0.93	-
MMSE score (median, 95% CI)	27 (26-27)	26 (25-27)	25 (24-26)	<0.001

* *Concentrations of serum lipids and lipoproteins were grouped into three equal strata representing decreasing concentrations of lipids and lipoproteins. This was done separately for women and men, since women have higher lipids and lipoproteins concentrations than men.*

MMSE scores of subjects with and without cardiovascular disease were 26 versus 27 points, respectively (Mann-Whitney, p=0.007). MMSE scores of subjects with and without a history of stroke were 21 versus 26 points, respectively (Mann-Whitney, p< 0.001). Since we found an association between HDL-cholesterol and cardiovascular disease and history of stroke, and an association between MMSE scores and cardiovascular disease and history of stroke, we explored whether the observed relation between low HDL-cholesterol concentration and cognitive impairment was due to the presence of cardiovascular disease and stroke. When subjects with cardiovascular disease (n=335) were excluded from analysis, the decrease on the MMSE score over strata of HDL-cholesterol

concentrations was still significant (table 3). When subjects with a history of stroke (n=56) were excluded, the decrease on the MMSE score over the three strata still remained significant. After excluding subjects with either a history of cardiovascular disease or stroke (n=356), the trend over strata of HDL-cholesterol concentrations was still observed. When the same analyses were carried out for total cholesterol, triglycerides, and LDL-cholesterol, no such associations were observed.

Table 3 *MMSE scores in strata of HDL-cholesterol concentrations.*

	Strata of HDL-cholesterol			
	High	Intermediate	Low	p for trend
All subjects				
N	188	185	188	
MMSE score (median, 95% CI)	27 (26-27)	26 (25-27)	25 (24-26)	<0.001
Subjects without CVD				
N	86	70	70	
MMSE score (median, 95% CI)	27 (26-28)	26 (24-28)	26 (24-27)	0.03
Subjects without history of stroke				
N	178	161	164	
MMSE score (median, 95% CI)	27 (26-27)	27 (26-27)	26 (25-26)	0.002
Subjects without CVD and without history of stroke				
N	83	62	62	
MMSE score (median, 95% CI)	27 (26-28)	27 (25-28)	26 (25-27)	0.1

CVD ; cardiovascular disease

Table 4 presents odds ratios for cognitive impairment (MMSE score < 19 points) and clinical diagnosis of dementia in relation to decreasing concentrations of HDL-cholesterol. The odds ratios are adjusted for level of education and not distorted by gender or age since stratification was dependent on gender and all subjects were 85 years. The odds ratio for cognitive impairment increased to 2.4 (95% CI 1.3-4.5) when subjects with a low concentration of HDL-cholesterol were contrasted with subjects with a high concentration of HDL-cholesterol. The odds ratios were unaffected by excluding subjects with cardiovascular disease or history of stroke. The odds ratio for subjects with a clinical diagnosis of dementia gradually increased over decreasing strata of HDL-cholesterol to 2.3 (95% CI 1.2-4.3).

The odds ratio was 3.3 (95% CI 1.1 to 10.3) when subjects with cardiovascular disease or history of stroke were excluded. All odds ratios for cognitive impairment or a clinical diagnosis of dementia were unaffected when we adjusted for LDL-cholesterol and triglyceride concentrations.

Finally, all analyses were carried out in a restricted sample where subjects who died within the first year of follow-up (n=36) were excluded. All observed associations between HDL-cholesterol and cognition remained similar.

Table 4 *Odds ratios for cognitive impairment and clinical diagnosis of dementia in relation over strata of HDL-cholesterol concentrations*

	Strata of HDL-cholesterol		
	High (n=188)	Intermediate (n=185)	Low (n=188)
Cognitive impairment			
All subjects	1*	1.7 (0.9-3.3)	2.4 (1.3-4.5)
Subjects without CVD	1*	1.6 (0.6-4.3)	2.5 (1.0-6.4)
Subjects without history of stroke	1*	1.4 (0.7-2.9)	2.2 (1.1-4.4)
Subjects without CVD and without history of stroke	1*	1.5 (0.5-4.2)	2.5 (0.9-6.6)
Dementia			
All subjects	1*	1.1 (0.6-2.3)	2.3 (1.2-4.3)
Subjects without CVD	1*	1.6 (0.5-5.0)	3.6 (1.3-10.0)
Subjects without history of stroke	1*	1.0 (0.5-2.2)	2.0 (1.0-4.0)
Subjects without CVD and without history of stroke	1*	2.2 (0.7-7.2)	3.3 (1.1-10.3)

** Reference category. Poor cognitive function, defined as MMSE ≤ 18 points. All odds ratios are adjusted for level of education. CVD ; cardiovascular disease*

Discussion

The aim of the present study was to explore the association between adverse lipid profiles and cognitive impairment. We found that low serum concentration of HDL-cholesterol was linked with cognitive impairment and dementia. Serum concentrations of cholesterol, triglycerides, and LDL-cholesterol showed no association with cognitive impairment or dementia. Serum HDL-cholesterol concentration and cognitive function was lower in subjects with cardiovascular disease and in subjects with stroke. In subjects without cardiovascular disease or stroke, low serum concentration of HDL-cholesterol was still associated with poor cognitive function and dementia. The specific association of low HDL-cholesterol and cognitive impairment was not confounded by level of education, LDL-cholesterol, triglycerides, or survival.

We measured cognitive function in a population based study using the Mini-Mental State Examination and obtained a clinical diagnosis of dementia from the medical records of the subjects' general practitioners and subjects' nursing home physicians. General practitioners tend to underreport dementia[20]. We therefore may have classified subjects as free from dementia, while in fact they were demented. This possible misclassification results in underestimates of the association between HDL-cholesterol and dementia.

It is difficult to infer causality from cross-sectional studies because it is unable to establish the temporal relationship and it is possible that the subjects' HDL-cholesterol serum concentrations show a decrease as a result of the cognitive impairment. However, when underlying disease in subjects with poor cognitive function or dementia would be the explanation for the observed association, we would have expected that the association between HDL-cholesterol and cognitive impairment to disappear when subjects who died early were excluded from the analysis. Since the association between low HDL-cholesterol and cognitive impairment was still present in subjects who survived one year, we think that the association can be regarded as causal and independent of underlying disease.

A possible explanation of the association between HDL-cholesterol and cognitive function may lie in the unifying hypothesis that atherosclerotic disease, i.e. cardiovascular disease and cerebrovascular disease, causes clinical and subclinical ischaemic lesions in the brain which contribute to the development of dementia[13]. Many studies showed an association between high total cholesterol, high LDL-cholesterol, high triglycerides, and low HDL-cholesterol and the risk of cardiovascular disease. These associations were absent or much weaker for high total cholesterol, high LDL-cholesterol, and high triglycerides and stroke. In line with other studies[15,16] we found that only low HDL-cholesterol is associated with stroke. Data from a randomised controlled trial, studying the effects of gemfibrozil, strongly suggests that increasing HDL-cholesterol decreases the risk for stroke[23]. These findings might explain why we found a specific association between low HDL-cholesterol concentrations and cognitive impairment, and why no associations were found when we studied the relation between total cholesterol, LDL-cholesterol, and triglycerides and cognitive impairment.

As expected, subjects with cardiovascular disease or stroke had lower MMSE scores compared with subjects without cardiovascular disease. When analysing subjects without cardiovascular disease or history of stroke, the association between HDL-cholesterol and cognitive function, however, was unaffected. This indicates that the observed association of HDL-cholesterol and cognition was not only due to a history of cardiovascular disease or stroke. When HDL-cholesterol is related to cognitive impairment via the occurrence of atherosclerotic disease, one would have expected odds ratios close to unity when excluding subjects with cardiovascular disease or stroke. Nevertheless, we cannot exclude that the relation we found between low HDL-c and cognitive impairment in subjects without cardiovascular disease or stroke is due to subclinical stroke.
There are two other hypotheses that may explain the observed association between HDL-cholesterol and cognitive impairment. First, HDL-cholesterol is the predominant lipoprotein in the human brain[11], where it can prevent aggregation and polymerisation of amyloid beta protein[11,12]. This might slow or even prevent the development of dementia. Second, HDL-cholesterol has anti-inflammatory properties[24,25]. Inflammatory responses are increasingly recognised as being important in neurodegenerative processes[26]. Markers of inflammation are found in and around amyloid plaques[26,27]. Moreover, various studies have shown that use of anti-inflammatory drugs protect against dementia[26,28,29].

In conclusion, in very old subjects low serum concentration of HDL-cholesterol is associated with cognitive impairment and clinical diagnosis of dementia. Serum concentrations of cholesterol, triglycerides, and LDL-cholesterol were not associated with cognitive impairment and dementia. The association between low HDL-cholesterol and cognitive impairment was not merely due to the presence of cardiovascular disease and stroke. These findings are of great clinical importance since they suggest that increasing HDL-cholesterol rather than lowering total cholesterol might prevent the development of cognitive impairment and dementia. New preventive and therapeutic strategies should identify the effects of HDL-cholesterol on cognitive function in the elderly.

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