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Relationship Between Low Levels of High-Density Lipoprotein Cholesterol and Dementia in the Elderly. The InChianti Study

G. Zuliani,[1,7] M. Cavalieri,[1] M. Galvani,[1] S. Volpato,[1] A. Cherubini,[2] S. Bandinelli,[4] A. M. Corsi,[4] F. Lauretani,[5] J. M. Guralnik,[6] R. Fellin,[1,7] and L. Ferrucci[3,6]

[1]Department of Clinical and Experimental Medicine, Section of Internal Medicine, Gerontology and Geriatrics, University of Ferrara, Ferrara, Italy.
[2]Department of Clinical and Experimental Medicine, Institute of Gerontology and Geriatrics, University of Perugia, Perugia, Italy.
[3]ASF Geriatric Rehabilitation, Florence, Italy.
[4]Department of Medical and Surgical Critical Care; Center for the Study at Molecular Level of Chronic Degenerative, and Neoplastic Diseases to Develop Novel Therapies, University of Florence, Florence, Italy.
[5]Geriatric-Rehabilitation Department, Geriatric Unit and Clinical Geriatric, University Hospital of Parma, Parma, Italy.
[6]Clinical Research Branch, Longitudinal Studies Section, National Institute on Aging, NIH, Baltimore, Maryland.
[7]Centro Esperto Malattia di Alzheimer-Perusini, Ferrara, Italy.

Address correspondence to Giovanni Zuliani, MD, PhD, Department of Clinical and Experimental Medicine, Section of Internal Medicine, Gerontology and Geriatrics, University of Ferrara, Via Savonarola 9, 44100 Ferrara, Italy. Email: gzuliani@hotmail.com

Background. To evaluate the association between plasma lipid fractions and the prevalence of dementia in a large sample of Italian older individuals.

Methods. A total of 1051 older community-dwelling individuals (age ≥65 years), enrolled in the InChianti study, were included. Diagnosis of dementia was established at baseline and at the 3-year follow-up using *Diagnostic and Statistical Manual of Mental Disorder* (Fourth Edition) criteria. Plasma lipids were measured by standardized methods at baseline and after 3 years.

Results. At baseline, 61 individuals (5.8%) were affected by dementia. Demented individuals showed significantly lower total cholesterol (TC), nonhigh–density lipoprotein cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels compared with controls; no differences were found in triglycerides (TG) and lipoprotein (a) levels. Of the 819 subjects reevaluated at the 3-year follow-up, 81 (9.9%) received a new diagnosis of dementia. Again, demented subjects were characterized by significantly lower TC, non-HDL-C, and HDL-C levels compared with controls, thus confirming the baseline findings. At multivariate logistic regression analysis, HDL-C levels (odds ratio: 0.96, 95% confidence interval: 0.93–0.99), but not TG and non-HDL-C, were associated with dementia independent of important confounders including age, gender, apo E phenotype, stroke, weight loss, interleukin 6 levels, and ankle–brachial index.

Conclusions. Among community-dwelling older people, individuals affected by dementia showed significantly lower TC, non-HDL-C, and HDL-C levels; however, at multivariate analysis, only HDL-C was associated with dementia. Our results suggest the existence of an independent relationship between dementia and low HDL-C levels.

Key Words: Dementia—Lipids—Elderly.

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DEMENTIA is a common disease in older individuals living in western societies. In the past years, numerous studies have suggested the existence of a relationship between lipids metabolism and dementia. However, studies that explored the relationship between plasma lipids and dementia have reported conflicting findings. Some (1,2) but not all (3,4) epidemiological studies suggested that elevated total cholesterol (TC) levels in the middle age might be a risk factor for dementia in late life. On the contrary, cross-sectional studies have consistently reported an association between low TC levels and the diagnosis of dementia in the elderly subjects (5–8). High TC levels in late life have been associated with a decreased risk of dementia (9–11); consistently decreasing levels of TC have been associated with dementia in older individuals (12–14).

Only a few studies have evaluated the association between dementia and specific lipoprotein fractions, such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL-C. This is an important issue since apo B–containing lipoproteins (LDL-C or non-HDL-C) and apo A–containing lipoproteins (HDL-C) have "opposite" functions in human physiology

and have been associated with a pro- and antiatherogenic profile, respectively.

Increased levels of LDL-C have been associated with Alzheimer's disease (AD; 15,16), as well as dementia with stroke (17), but other studies failed to confirm these associations (8,18). On the contrary, some evidence suggests that low levels of HDL-C or Apo A-I might be associated with dementia in older individuals (19,20), and in particular with vascular dementia (21,22). Accordingly, high HDL-C values appeared to be protective against dementia in some (23) although not all studies (24,25).

In the present study, we evaluated the association of different plasma lipid fractions with the prevalence of dementia in a large sample of Italian community-dwelling older individuals.

Methods

This study is part of the "Invecchiare in Chianti" (Aging in the Chianti area, InCHIANTI) study, a prospective population-based study of older people, designed by the Laboratory of Clinical Epidemiology of the INRCA, Florence, Italy.

The study included 1,260 older participants (age 65–102 years), randomly selected from the residents in two towns of the Chianti area (Greve in Chianti and Bagno a Ripoli, Tuscany, Italy). The collection of the data started in September 1998 and was completed by March 2000. Sampling procedure and data collection method has been previously published (26). The INRCA Ethical Committee ratified the entire study protocol. A total of 105 participants were excluded as they refused to provide blood at baseline (enrolled 1155). They were older individuals (mean 79.9, *SD* 8.6 years), whereas no differences in sociodemographic characteristics emerged. Complete data about plasma lipoprotein profile and cognitive status were available only for 1,051 individuals. During the 3-year follow-up, 145 subjects died, whereas 141 were lost. Of the remaining 870 individuals, 819 could be completely reevaluated, and 81 (9.9%) received a new diagnosis of dementia.

Evaluation of Cognitive Status

Cognitive status was evaluated at baseline and after 3 years of follow-up as previously described (27) by using a two-stage screening procedure. Impaired cognitive function and dementia were ascertained using a two-stage screening procedure. During the home interview, participants were first evaluated using the Mini-Mental State Examination (MMSE). Additionally, participants who reported difficulty in performing activities of daily living or instrumental activities of daily living were asked questions aimed at understanding whether the cause of abnormality was cognitive impairment. Those with a score of greater than 26 were considered nondemented, whereas those with a score of less than or equal to 21 were considered possibly demented and directly scheduled for the second-stage screening procedure. The participants with an MMSE score between 22 and 26 received additional neuropsychological tests assessing memory (paired words test), concentration/attention (digit test from the Weschler adult intelligence test) and visuospatial ability (the Caltagirone drawings). The education-adjusted normative data for these tests exist for the Italian population. If based on these additional tests, the memory of the participant was considered normal, he or she was reattributed a full score on the MMSE memory items. Analogously, we reattributed 5 points to the item "subtract seven five times from 100" and 1 point to the "pentagon drawing" when the performance in additional tests assessing analogous neuropsychological functions was considered normal. After this procedure, we reanalyzed the MMSE score. The participants for whom the new score was greater than 26 were considered "not demented," whereas those for whom the newly calculated score remained between 22 and 26 were scheduled for the second-stage screening. The second-stage screening was performed by geriatricians and a psychologist with long-standing clinical experience in the evaluation of older patients with cognitive impairment. The diagnosis of "dementia," independent of the etiology, was established using the *Diagnostic and Statistical Manual of Mental Disorder* (Fourth Edition) criteria. Differential diagnosis between degenerative dementia, mainly AD, and vascular/mixed dementia was not performed because neuroimaging was not available in all subjects.

Clinical Chemistry Parameters

Plasma lipid levels were measured on serum from fresh samples drawn after 12 hours overnight fasting. Commercial enzymatic tests (Roche Diagnostics, Basel, Switzerland) were used for determining serum TC, triglycerides (TG), and HDL-C concentrations. The interassay coefficient of variation (CV) was less than 3.8% for TC and less than 5.0% for HDL-C. For TG, the lower detection limit was 4.0 mg/dL, the intraassay CV was 3.1%, and the interassay CV was 1.8%.

Non-HDL-C was calculated by subtracting HDL-C from TC (TC − HDL-C). Lipoprotein (a) (Lp(a)) levels were measured in 1,002 individuals by enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). Fifty individuals (4.7%) were taking statins or fibrates at the time of enrolment.

Markers of Inflammation

Interleukin 6 (IL-6) was quantified by an immunoassay kit (BioSource Cytoscreen human IL-6 UltraSensitive kits, Camarillo, CA). The minimum detectable concentrations were 0.10 pg/mL. The interassay CV was 7%.

Covariates

Anthropometry.—Weight and height were measured by using standard techniques. Waist circumference was

measured to the nearest 0.5 cm by using a plastic tape at the shortest circumference of the waist between the lower rib margin and the iliac crest.

Dietary variables.—Data on dietary intake were collected by the questionnaire created for the EPIC Study (28,29). Daily caloric intake was adjusted for weight in order to normalize the value (kcal/kg).

Ankle–Brachial index.—The ankle–brachial index (ABI) was measured using a handheld Doppler stethoscope (Parks model 41-A, Parks Medical Electronics, Aloha, OR). Systolic pressures were measured twice in the right brachial artery and in each posterior tibial artery (30). ABI was considered pathological when less than 0.9.

Apo E polymorphism detection.—Apo E genotype was detected on genomic DNA from blood leukocytes by polymerase chain reaction amplification of apo E gene, a successive restriction enzyme analysis with *Hha*I as previously described by Hixson and Vernier (31).

Statistical Analysis

Continuous variables were expressed as mean (*SD*) or median (interquartile range). Means were compared by the unpaired *t* test, whereas medians were compared by the Mann–Whitney test. Prevalence was compared by the chi-square test.

Plasma lipids at baseline (T0) and after 3 years (T3) were compared by paired sample *t* test.

In order to select the variables independently associated with the risk of dementia, we calculated the odds ratio (OR) and 95% confidence interval (CI) by means of multivariate logistic regression analysis.

The variables included into the logistic model for the likelihood of having dementia at baseline were age, gender, years of education, non-HDL-C, HDL-C, TG, plasma IL-6, ε4 allele, ABI, daily alcohol consumption, stroke (yes/no), smoking (present/former/never), statin/fibrate therapy, and reported weight loss (>4.5 kg in the last year: yes/no).

Systat for Windows, version 5.0, and SPSS for Windows, version 7.0 (SPSS, Inc., Chicago, IL) statistical packages were used for the analysis.

Results

The main characteristics of the sample are reported in Table 1. Of the 1,051 participants, 61 (5.8%) were affected by dementia at baseline. Compared with normal individuals, subjects with dementia were older, had received less years of education, and had higher IL-6 levels; furthermore, ABI was lower whereas stroke prevalence was higher in these individuals. No differences were found in daily caloric intake (weight adjusted) and body mass index between the two groups. The prevalence of subjects who reported a significant weight loss during the last year was higher in subjects with dementia compared with controls.

Table 1. Principal Characteristics and Lipid Profile in 1,051 Community-dwelling Older Italian Subjects from the InCHIANTI Study, According to Diagnosis of Dementia at Baseline

	Baseline		
Characteristics	Controls ($N = 990$)	Dementia ($N = 61$)	*p* Value
Age (years)	75 ± 7.2	85 ± 7.2	.001
Female gender (%)	55.8	63.3	.25
Education (years)	5.46 ± 3.3	3.15 ± 2.0	.001
MMSE (score/30)	25.2 ± 3.25	12.0 ± 6.8	.001
Total cholesterol (mg/dL)	218 ± 39	193 ± 45	.001
Triglycerides (mg/dL)	128 ± 70	120 ± 57	.40
Non-HDL (mg/dL)	162 ± 38	145 ± 40	.001
HDL-C (mg/dL)	56 ± 15	48 ± 13	.001
Lipoprotein (a) (mg/dL)*	12.1 (0–175)	12.4 (0–109)	.66
Apo E ε4 allele carriers (%)	11.4	12.2	.82
Interleukin 6 (pg/mL)*	1.44 (0.1–90)	4.21 (0.34–31)	.001
Daily (kcal/kg)	28.5 ± 8	30.6 ± 8	.12
BMI (kg/m^2)	27.4 ± 4.0	26.5 ± 4.6	.17
Reported weigh loss (%)	5.6	9.6	.20
ABI	1.03 ± 0.19	0.96 ± 0.16	.005
CHD (%)	7.7	6.2	.43
Stroke (%)	5.9	18.5	.001
Diabetes (%)	12.2	13.6	.42
Hypertension (%)	89.4	85.4	.17
Statins/fibrates (%)	4.5	1.4	.11

Notes: ABI = ankle–brachial index; BMI = body mass index; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; MMSE = Mini-Mental State Examination.

*Median (interquartile range).

Concerning lipoprotein profile, demented individuals had lower TC, non-HDL-C, and HDL-C levels, whereas no differences were found in TG and Lp(a) levels.

After adjusting for age, gender, and education, the likelihood of having dementia was inversely associated with TC levels (OR: 0.98, 95% CI: 0.97–0.99), and with HDL-C (OR: 0.96, 95% CI: 0.94–0.98), but not with non-HDL-C (OR: 0.99, 95% CI: 0.99–1.003) or TC/HDL-C ratio (OR: 1.03, 95% CI: 0.83–1.30).

When HDL-C, non-HDL-C, and TG were included into the same logistic model, only HDL-C was associated with the diagnosis of dementia (OR: 0.95, 95% CI: 0.93–0.98; age, gender, and education adjusted).

In Table 2 are reported the results of multivariate logistic regression analysis assessing the effect of plasma lipids and other variables on the likelihood of having dementia at baseline. We found that age (OR: 1.13, 95% CI: 1.06–1.19), years of education (OR: 0.65, 95% CI: 0.53–0.80), HDL-C levels (OR: 0.96, 95% CI: 0.93–0.99), stroke (OR: 4.06, 95% CI: 1.45–11.33), apo E ε4 allele (OR: 2.48, 95% CI: 1.07–6.14), and reported weight loss (OR: 1.21, 95% CI: 1.07–1.38) were significantly associated with dementia, independent of gender, non-HDL-C, TG, IL-6, ABI, alcohol consumption, smoking, daily caloric intake, and statin/fibrate therapy.

Table 2. Multivariate Logistic Regression Analysis Exploring the Effect of Multiple Factors on the Likelihood of Having Dementia at Baseline in 1,051 Community-Dwelling Older Italian Subjects from the InChianti Study

Variable	Beta coefficient	*SE*	Odds ratio	95% CI	*p* Value
Age (years)	0.12	0.03	1.13	1.07–1.19	.001
Education (years)	−0.41	0.11	0.65	0.52–0.80	.001
HDL-C (mg/dL)	−0.39	0.01	0.96	0.93–0.99	.01
Stroke	1.40	0.52	4.06	1.45–11.33	.007
Apo E ε4 allele	0.91	0.46	2.48	1.07–6.14	.04
Reported weight loss	0.19	0.07	1.21	1.06–1.38	.001

Note: Adjusted for nonhigh-density lipoprotein cholesterol (HDL-C), triglycerides, gender, interleukin 6, ankle–brachial index, alcohol consumption, smoking, statin/fibrate therapy.

Due to the small number of individuals with prevalent dementia ($n = 61$), we could not stratify the analysis by gender. Nevertheless, we separately run the same logistic model (Table 2) in men and women and obtained similar beta coefficients for HDL-C (women: −0.34; men: −0.55). Furthermore, we tested the potential interaction between HDL-C and gender, but the interaction term in fully adjusted model was not statistically significant.

At the 3-year follow-up, 819 individuals could be completely reevaluated; of them, 81 (9.9%) received a new diagnosis of dementia.

The main characteristics of the sample at the 3-year evaluation are reported in Table 3. Compared with participants who remained nondemented, participants who developed dementia were characterized by older age and higher IL-6 plasma levels. Concerning lipoprotein profile, demented individuals showed significantly lower TC, non-HDL-C, and HDL-C levels compared with controls, thus resembling the lipid profile associated to dementia at baseline. By multivariate logistic regression analysis, we were able to confirm the results of baseline observation. Indeed, we found that among plasma lipids, only 3 years HDL-C (OR: 0.97, 95% CI: 0.95–0.99) was associated with 3 years diagnosis of dementia, independent of age, gender, years of education, alcohol consumption, smoking, stroke, apo E4, and IL-6 (data not shown).

Discussion

In this study we evaluated a large sample of community-dwelling older individuals with the aim of characterizing the lipoprotein profile of individuals affected by dementia.

When dealing with plasma lipids and dementia, it has to be kept in mind that cholesterol contained in the central nervous system (CNS) and plasma cholesterol form two independent pools, and modifications in plasma levels do not necessarily reflect modification in CNS pool. Of consequence, extreme caution is needed when considering the possible causative relationship between plasma lipids and dementia or vice versa.

Table 3. Principal Characteristics and Lipid Profile at 3-Year Follow-up in 819 Community-Dwelling Older Italian Subjects from the InCHIANTI Study, According to Whether They Received or Not a New Diagnosis of Dementia

	3-Year follow-up		
Characteristics	Controls ($N = 738$)	Dementia ($N = 81$)	*p* Value
Age (years)	73 ± 6.9	83 ± 7.2	.002
Female gender (%)	55.7	58.8	.30
Education (years)	5.6 ± 3	4.3 ± 3	.93
MMSE (score/30)	25.5 ± 3.5	15.9 ± 8.5	.001
Total cholesterol (mg/dL)	220 ± 38	185 ± 32	.03
Triglycerides (mg/dL)	131 ± 85	123 ± 62	.43
Non-HDL-C (mg/dL)	161 ± 44	131 ± 43	.001
HDL-C (mg/dL)	57 ± 15	51 ± 16	.001
Apo E ε4 allele carriers (%)	11	14	.20
Interleukin 6 (pg/mL)*	2.45 (0.80–1.99)	4.95 (1.26–3.7)	.001
Daily kcal/weight	30 ± 9	31 ± 10	.64
BMI (kg/m^2)	26.4 ± 4.0	26.0 ± 3.8	.57

Notes: BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; MMSE = Mini-Mental State Examination.

*Median (interquartile range).

At the baseline observation, we found that TC and its two major components (non-HDL-C: apo B–containing lipoproteins, and HDL-C: apo A-I–containing lipoproteins) were significantly lower in older demented participants compared with nondemented participants. These results agree with previous reports from clinical/epidemiological studies (5–8), and confirm that low TC might be a typical characteristic of late-onset dementia.

We had also the opportunity to evaluate a second group of demented individuals, that is, the subjects who were not demented at baseline but received a new diagnosis of dementia at the 3-year follow-up. Again, data from the 3-year cross-sectional observation showed that demented individuals had low TC, non-HDL-C, and HDL-C levels. These findings might be considered as confirmatory of the baseline results.

The mechanisms accounting for low TC levels in subjects with dementia remain to be explained. Several hypotheses have been proposed including the presence of systemic inflammation, poor nutritional status, the association of dementia with poor general health, the effect of selective mortality bias in subjects with high TC and non-HDL-C, and a possible protective role of cholesterol against dementia.

We successively investigated in depth the relationship between different lipoprotein fractions and dementia. Interestingly, by multivariate logistic regression analysis, we found that, both at baseline and at the 3-year follow-up, low HDL-C levels were associated with dementia independent of important confounders, whereas non-HDL-C and TG were not.

These findings suggest that (a) among plasma lipids, low HDL-C might represent a more specific marker of the disease compared with TC and non-HDL-C. Indeed, although low non-HDL-C might be a good (when lifelong) or a bad

(in sick people) finding, low HDL-C is always an unfavorable finding, whether chronically or due to a recent disease; and (b) the association between low HDL-C and dementia might be not mediated by other conditions associated with the disease.

Our data are in good agreement with previous studies reporting that low and high HDL-C values were associated with an increase (19–22) or a decrease (23) in the risk of dementia, respectively.

In a large sample of individuals from the Leiden 85 Plus Study, van Exel and colleagues found a significant association between low levels of HDL-C and cognitive impairment and dementia (19). Interestingly, the association was not merely due to the presence of cardiovascular disease or stroke.

In a previous cross-sectional study we found that older subjects with vascular dementia, but not individuals with late-onset AD, were characterized by lower levels of HDL-C compared with controls (22).

By analyzing a sample of older individuals from the Paquid Study, Bonarek and colleagues found that elevated HDL-C levels were significantly associated with a decreased risk of dementia, after adjustment for apo E status and other potential confounders (23).

The mechanisms associating low levels of HDL-C with dementia are unknown, and different explanations might be proposed. First, low HDL-C is a risk factor for atherosclerosis and stroke (32), and both these conditions have been associated with dementia (33,34). Second, a low-grade systemic inflammation has been reported in subjects with dementia (35), and during inflammation HDL-C levels significantly decrease (36). Third, HDL-C might decrease as consequence of reduced caloric intake and weight loss, as reported by the study conducted in Biosphere 2 (37). Fourth, a strong association between low HDL-C and disability has been described (38), and dementia is strongly associated with functional impairment (39).

We attempted to minimize the effect of important confounders by adjusting for several dimensions in the multivariate analysis; we adjusted for a marker of systemic inflammation (IL-6), a standardized marker of atherosclerosis (ABI), reported weight loss, and the presence of coronary heart disease/stroke. Nevertheless, we cannot exclude the possibility that some residual confounding was still present. Fifth and last, the reduction of HDL-C, as well as TC levels, might be related to the neurodegenerative pathology itself or to the associated condition of "poor health status." Indeed, it has been shown that among older individuals with low TC levels, low HDL-C predicts total mortality (40), and might represent a marker for poor health.

The mechanism/s linking dementia and low levels of TC, and in particular of HDL-C, are unknown. It is possible that in subjects with dementia a dysregulation of hypothalamic activity might cause an increase in basal metabolic rate (BMR) as an attempt of the organism to cope with the neurological and metabolic dysfunctions caused by the disease. The increase in BMR could explain the reduction both in weight and plasma lipid levels and has been associated with increased mortality in older individuals (41).

Finally, some limitations of our study must be acknowledged. First, we could not distinguish between different forms of dementia, particularly between AD and vascular dementia. Although in older age the majority of cases with dementias are the consequence of multiple pathogenetic mechanisms, this distinction might be important when dealing with plasma lipids.

Second, we did not include in our analysis information about diet composition; it is possible that some individuals significantly change their food preferences as consequence of changes in smell and taste related to dementia.

Third, because of the cross-sectional study, we cannot define any cause–effect relationship. In particular, we cannot distinguish whether, in older individuals, dementia might cause a decrease in HDL-C levels, low HDL-C might have a role in the pathogenesis of dementia, or a third unmeasured factor might cause both dementia and low HDL-C values.

In conclusion, among community-dwelling older people, individuals affected by dementia show significantly lower TC, non-HDL-C, and HDL-C levels. However, at multivariate analysis, only low HDL-C levels are associated with the disease. Our results suggest the existence of an independent relationship between dementia and low HDL-C.

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