

Plasma Lipid Levels in the Elderly Are Not Associated with the Risk of Mild Cognitive Impairment

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Key Words

Plasma lipid levels · Mild cognitive impairment

Abstract

Background: There are conflicting data relating plasma lipids to the risk of Alzheimer's disease (AD). We explored the association of plasma lipids to mild cognitive impairment (MCI), a transitional stage between normal cognition and dementia, in a prospective community-based cohort study among randomly sampled Medicare recipients ≥ 65 years. Baseline data were collected from 1992 to 1994, follow-up data were collected at 18-month intervals. **Methods:** Multivariate proportional hazards regression was used to relate plasma lipid levels to incident total MCI, amnestic MCI and nonamnestic MCI in 854 persons without MCI or dementia at baseline. **Results:** There were 324 cases of incident MCI, 153 cases of amnestic MCI and 171 cases of nonamnestic MCI during 4,189 person-years of follow-up. Higher levels of total cholesterol and LDL were associated with a decreased risk of total MCI in models adjusting for age and sex. However, these associations were attenuated after adjusting for ethnicity, education, APOE ϵ 4 and vascular risk factors. There was no association between lipids and the risk of amnestic

or nonamnestic MCI, and there was no effect of lipid-lowering treatment on MCI risk. **Conclusions:** Plasma lipid levels or lipid-lowering treatment in the elderly are not associated with the risk of MCI.

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Introduction

Mild cognitive impairment (MCI) has become the focus of intense research interest, as a target of early detection and prevention of Alzheimer's disease (AD). Persons with MCI convert to AD at an annual rate of 10–12% in contrast to 1–2% in the elderly population without MCI [1].

It remains unclear whether dyslipidemia, a modifiable risk factor with a high prevalence in western societies, is associated with a higher risk of cognitive impairment or dementia. More than 50% of the US population aged 20 years or older suffer from cholesterol 200 mg/dl or higher, and more than 18% show cholesterol levels equal to or over 240 mg/dl [2]. Cholesterol alters the degradation of the amyloid precursor protein, which plays a major role in the pathogenesis of AD [3]. However, studies relating

plasma lipids or lipid-lowering treatment with the risk of dementia have been inconsistent [4]. We previously reported associations between high levels of low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C) and vascular dementia [5], but no association between LDL-C and AD, or between plasma lipids and cognitive test performance over time [6].

The objective in the present study was to explore whether plasma lipid levels are associated with the risk of incident total MCI, or amnesic or nonamnesic forms of MCI in the elderly.

Methods

Subjects and Setting

Participants were enrolled in a longitudinal cohort study by a random sampling of Medicare recipients 65 years or older residing in northern Manhattan [7]. Each participant underwent an interview of general health and function, medical history, a neurological examination and a neuropsychological battery [8]. Baseline data were collected from 1992 to 1994. Follow-up data were collected at sequential intervals of 18 months.

Participants eligible for this study were those without prevalent MCI or dementia at baseline, with information on plasma lipids and with sufficient information to ascertain MCI by the Petersen criteria [1]. Of the 1,772 participants with a complete neuropsychological examination, 643 (36.3%) were excluded due to prevalent dementia or MCI, 64 (3.7%) due to missing lipid levels and 211 (11.9%) due to loss to follow-up. The final analytic sample included 854 individuals. Compared to the original cohort of 1,772 participants, the final sample was younger at baseline (mean age 75.8 vs. 77.3 years; $p < 0.001$), had a similar proportion of women (68.7 vs. 69.4%) and African Americans (33.0 vs. 32.6%), a lower proportion of Hispanics (44.7 vs. 47.0%; $p < 0.001$) and a higher proportion of Whites (22.3 vs. 20.4%; $p = 0.01$). Compared to the original cohort, the prevalence of diabetes was lower (23.5 vs. 26.4%; $p = 0.002$), and the prevalences of hypertension (68.6 vs. 53.9%; $p < 0.0001$), heart disease (34.1 vs. 26.8%; $p < 0.0001$) and current smoking (10.9 vs. 8.2%; $p < 0.0001$) were higher in the final sample.

Clinical Assessments

Data were available from medical, neurological and neuropsychological evaluations [8]. All participants underwent a standardized neuropsychological test battery examining multiple domains at baseline and subsequent assessments using the Mini Mental State Examination, the Boston Naming Test, the Controlled Word Association Test, category naming, the Complex Ideational Material and Phrase Repetition subtests from the Boston Diagnostic Aphasia Evaluation, the WAIS-R Similarities subtest, the Mattis Dementia Rating Scale, the Rosen Drawing Test, the Benton Visual Retention Test, the multiple choice version of the Benton Visual Retention Test and the Selective Reminding Test [8].

Diagnosis of Dementia and MCI

Dementia was diagnosed by consensus of neurologists, psychiatrists and neuropsychologists based on DSM-IV criteria [9]. Consistent with standard criteria [1] for all subtypes of MCI, those considered for MCI were required to have: (1) memory complaint, (2) objective impairment in at least one cognitive domain based on the average of the scores on the neuropsychological measures within that domain and a 1.5 SD cutoff using normative corrections for age, years of education, ethnicity and sex, (3) essentially preserved activities of daily living, and (4) no dementia.

The Petersen criteria [10], which focus on memory impairment, were expanded to include mutually exclusive subtypes based on cognitive features. MCI amnesic (MCI-A), corresponds most closely to the original Petersen definition, and was defined as a memory score < 1.5 SD below the demographically corrected mean on an average composite of the following measures: (1) total recall from the Selective Reminding Test, (2) delayed free recall from the Selective Reminding Test and (3) recognition from the Benton Visual Retention Test. Performance on composite scores from all other cognitive domains was required to be within normal limits. Other MCI subtypes were classified that allowed for impairment in a single nonmemory domain if performance on composite scores from all other cognitive domains was within normal limits. MCI executive function (MCI-E) was defined by an average composite measure comprising the following measures: (1) Letter Fluency; (2) Category Fluency, and (3) the WAIS-R Similarities subtest. MCI language (MCI-L) was defined as isolated impairment on an average composite measure comprising: (1) Boston Naming Test; (2) Boston Diagnostic Aphasia Evaluation Repetition, and (3) the Boston Diagnostic Aphasia Evaluation Comprehension test. MCI visuospatial (MCI-V) was assigned if impairment was demonstrated on an average composite score comprising: (1) Rosen Drawing and (2) Benton Visual Retention Test matching. Finally, we allowed for impairment in multiple cognitive domains in the absence of dementia. MCI multiple cognitive domains with memory impairment (MCI-MCDM) was defined by objective impairment on the memory domain composite score and if there was impairment on at least one other cognitive domain. MCI multiple cognitive domains without memory impairment (MCI-MCDN) was assigned if there was impairment in 2 or more of the 3 nonmemory domains, and if the memory domain composite score was within normal limits. Again, classification into the 6 subtypes was mutually exclusive. We used 3 outcomes for these analyses: (1) total MCI; (2) amnesic MCI, which included MCI-A and MCI-MCDM, and (3) nonamnesic MCI, which included MCI-E, MCI-L, MCI-V and MCI-MCDN. The rationale for grouping MCI-A and MCI-MCDM is that they equally predict the development of AD in our cohort, and that MCI-MCDM is thought to be a more advanced form of MCI-A involving other cognitive domains.

Lipids and Lipid-Lowering Treatment (Statins)

All subjects were asked to fast for at least 8 h prior to blood drawing. Fasting plasma total cholesterol and triglyceride levels were determined from frozen samples using standard techniques. HDL-C levels were determined after precipitation of apolipoprotein B containing lipoproteins with phosphotungstic acid. LDL-C was recalculated using the formula of Friedewald et al. [11]. At baseline, all participants were asked if they had ever been treated with statins.

Table 1. Comparison of demographic and clinical characteristics by MCI status in 854 subjects (Washington Heights-Inwood Columbia Aging Project, New York, N.Y., 1992–2003)

	No MCI (n = 530)	Incident total MCI (n = 324)	Incident amnesic MCI (n = 153)	Incident nonamnesic MCI (n = 171)
Women	364 (68.7)	225 (69.4)	106 (69.3)	119 (69.6)
Age, years	75.5 ± 6.0	76.3 ± 5.7	76.9 ± 5.7	75.7 ± 5.7
Education, years	9.1 ± 4.5	8.6 ± 4.6	9.1 ± 4.5	8.3 ± 4.7
Ethnic group				
White/non-Hispanic	115 (21.7)	69 (21.3)	39 (25.5)	30 (17.5)
Black/non-Hispanic	176 (33.2)	106 (32.7)	50 (32.7)	56 (32.7)
Hispanic	233 (44.0)	149 (46.0)	64 (41.8)	85 (49.7)
APOE genotype 4/- or 4/4	144 (27.2)	96 (29.7)	49 (32.0)	47 (27.5)
Total cholesterol, mg/dl	200.6 ± 41.2	195.5 ± 40.9	194.1 ± 39.4	196.7 ± 42.4
HDL-C, mg/dl	47.6 ± 15.8	46.9 ± 15.5	47.7 ± 15.9	46.2 ± 15.1
Triglycerides, mg/dl	163.5 ± 88.5	157.5 ± 87.5	149.6 ± 72.2	164.7 ± 99.1
LDL-C, mg/dl	120.2 ± 36.4	116.6 ± 34.3	116.5 ± 33.6	116.7 ± 35.1
Stroke	76 (14.3)	50 (15.4)	26 (17.0)	24 (14.0)
Diabetes	112 (21.1)	89 (27.5)*	41 (26.8)	48 (28.1)*
Hypertension	336 (63.4)	250 (77.2)*	113 (73.9)*	137 (80.1)*
Heart disease	180 (34.0)	111 (34.3)	53 (34.6)	58 (33.9)
Current smoking	61 (11.5)	32 (9.9)	16 (10.5)	16 (9.4)
Treatment with statins	65 (12.3)	53 (16.4)	25 (16.3)	28 (16.4)

Figures in parentheses indicate percentages; some are based on an incomplete sample due to small amounts of missing data. Ethnic group classified by self-report using the format of the 1990 US census [13]. * $p \leq 0.05$: significant versus no-MCI group. Values for continuous variables are mean ± standard deviation.

Other Covariates

At baseline, all participants were asked whether they had a history of hypertension or diabetes at any time during their life. If affirmative, they were asked whether they were under treatment and the specific type of treatment. Stroke was defined according to WHO criteria. The presence of stroke was ascertained from an interview with participants and their informants. Persons with stroke were confirmed through their medical records, 85% of which included results of brain imaging. The remainder was confirmed by direct examination. Heart disease was defined as a history of arrhythmia, myocardial infarction, congestive heart failure or angina pectoris at any time during life. APOE genotypes were determined as described by Hixson and Vernier [12] with slight modification. We classified persons as homozygous or heterozygous for the APOE $\epsilon 4$ allele or not having any $\epsilon 4$ allele.

Statistical Methods

We evaluated plasma lipid levels, demographic distributions and clinical characteristics at baseline. Then we used Cox proportional hazard models to estimate the association of plasma lipid levels with incident total MCI, amnesic MCI and nonamnesic MCI. Plasma lipids were analyzed as a logarithmic transformed continuous variable and grouped into quartiles. The time-to-event variable was age at onset of MCI. Among individuals who did not develop MCI, those who developed dementia were censored at the time of dementia diagnosis, and those who did not develop dementia, who died or who were lost to follow-up owing to relocation before development of MCI were censored at the

time of their last evaluation. After adjusting for sex and age, we additionally adjusted for education, diabetes, heart disease and hypertension as these variables were at a 0.1 α level associated with the risk of MCI and thereby potential confounders. To explore the independence of a potential effect of a plasma lipid from stroke, which theoretically may be in the casual pathway, we then repeated all analyses additionally adjusting for stroke. To compare the effect of plasma lipid levels on the risk of MCI between persons with and without diabetes, we finally repeated all analyses stratifying by presence of diabetes at baseline.

Results

There were 324 cases of incident MCI, 153 cases of amnesic MCI and 171 cases of nonamnesic MCI during 4,189 person-years of follow-up. The mean age of the sample was 75.8 ± 5.9 years, 69.0% were women, 22.2% were non-Hispanic White, 33.0% non-Hispanic Black and 44.8% Hispanic. The mean of years of education was 8.9 ± 4.5 , and 68.6% had hypertension, 23.5% diabetes and 34.1% heart disease. 28.1% of the sample were APOE $\epsilon 4$ carriers, 118 subjects (13.8%) used statins. Persons who developed total MCI or nonamnesic MCI during follow-up had at baseline a higher prevalence of diabetes and

Table 2. Hazard ratios (HR) and 95% confidence intervals (in parentheses), relating quartiles of plasma lipid levels and the risk of incident MCI (Washington Heights-Inwood Columbia Aging Project, New York, N.Y., 1992–2003)

Quartiles and ranges	Incident total MCI				Incident amnesic MCI				Incident nonamnesic MCI			
	n	%	model 1 HR	model 2 HR	n	%	model 1 HR	model 2 HR	n	%	model 1 HR	model 2 HR
<i>Cholesterol</i>												
1 (≤ 171.00 mg/dl)	88	26.3	1.0	1.0	48	30.0	1.0	1.0	40	23.0	1.0	1.0
2 (171.01–197.00 mg/dl)	96	28.7	1.1 (0.81–1.45)	1.1 (0.84–1.52)	39	24.4	0.8 (0.54–1.25)	0.8 (0.54–1.29)	57	32.8	1.4 (0.93–2.09)	1.5 (0.99–2.25)
3 (197.01–223.25 mg/dl)	73	21.9	0.8 (0.59–1.11)	0.9 (0.62–1.18)	35	21.9	0.7 (0.45–1.11)	0.7 (0.46–1.14)	38	21.8	0.9 (0.60–1.47)	1.0 (0.64–1.59)
4 (≥ 223.26 mg/dl)	77	23.1	0.7 (0.57–1.06)	0.8 (0.57–1.11)	38	23.8	0.7 (0.46–1.09)	0.6 (0.41–1.05)	39	22.4	0.9 (0.55–1.34)	1.0 (0.61–1.58)
Trend test			p = 0.04	p = 0.08			p = 0.09	p = 0.06			p = 0.2	p = 0.5
<i>HDL-C</i>												
1 (≤ 37.00 mg/dl)	88	26.3	1.0	1.0	37	23.1	1.0	1.0	51	29.3	1.0	1.0
2 (37.01–45.00 mg/dl)	66	19.8	0.8 (0.59–1.12)	0.8 (0.61–1.17)	30	18.8	0.9 (0.53–1.41)	0.9 (0.54–1.44)	36	20.7	0.8 (0.50–1.19)	0.8 (0.53–1.25)
3 (45.01–55.00 mg/dl)	77	23.1	0.9 (0.63–1.17)	0.9 (0.67–1.27)	41	25.6	1.1 (0.69–1.71)	1.1 (0.72–1.79)	36	20.7	0.7 (0.46–1.06)	0.8 (0.49–1.19)
4 (≥ 55.01 mg/dl)	103	30.8	0.8 (0.61–1.09)	0.9 (0.65–1.20)	52	32.5	1.0 (0.64–1.51)	1.0 (0.63–1.55)	51	29.3	0.7 (0.47–1.04)	0.8 (0.54–1.22)
Trend test			p = 0.2	p = 0.5			p = 0.8	p = 0.8			p = 0.07	p = 0.3
<i>Triglycerides</i>												
1 (≤ 98.25 mg/dl)	92	27.5	1.0	1.0	46	28.8	1.0	1.0	46	26.4	1.0	1.0
2 (98.26–142.50 mg/dl)	81	24.3	0.9 (0.65–1.18)	0.8 (0.62–1.15)	38	23.8	0.8 (0.54–1.27)	0.8 (0.53–1.27)	43	24.7	0.9 (0.60–1.39)	0.9 (0.57–1.32)
3 (142.51–197.50 mg/dl)	72	21.6	0.8 (0.58–1.03)	0.7 (0.52–1.01)	36	22.5	0.8 (0.49–1.19)	0.7 (0.47–1.14)	36	20.7	0.7 (0.48–1.16)	0.7 (0.44–1.06)
4 (≥ 197.51 mg/dl)	89	26.6	0.9 (0.72–1.28)	0.9 (0.65–1.18)	40	25.0	0.9 (0.57–1.34)	0.8 (0.47–1.19)	49	28.2	1.0 (0.69–1.56)	0.9 (0.64–1.49)
Trend test			p = 0.6	p = 0.2			p = 0.5	p = 0.2			p = 0.9	p = 0.7
<i>LDL-C</i>												
1 (≤ 95.40 mg/dl)	90	26.9	1.0	1.0	40	25.0	1.0	1.0	50	28.7	1.0	1.0
2 (95.41–116.00 mg/dl)	80	24.0	0.8 (0.61–1.12)	0.9 (0.64–1.17)	39	24.4	0.9 (0.59–1.43)	0.9 (0.61–1.48)	41	23.6	0.8 (0.50–1.15)	0.8 (0.53–1.21)
3 (116.01–141.75 mg/dl)	84	25.1	0.8 (0.63–1.14)	0.9 (0.67–1.22)	43	26.9	1.0 (0.63–1.48)	1.0 (0.64–1.54)	41	23.6	0.8 (0.49–1.14)	0.8 (0.54–1.25)
4 (≥ 141.76 mg/dl)	80	24.0	0.7 (0.54–0.99)*	0.8 (0.54–1.04)	38	23.8	0.8 (0.49–1.21)	0.7 (0.44–1.16)	42	24.1	0.7 (0.46–1.04)	0.8 (0.51–1.19)
Trend test			p = 0.06	p = 0.1			p = 0.3	p = 0.2			p = 0.09	p = 0.3

Model 1: adjusted for sex and age; model 2: adjusted for sex, age, education, diabetes, heart disease and hypertension. * $p \leq 0.05$.

hypertension than persons remaining free of MCI, and persons developing amnesic MCI reported more often a history of hypertension (table 1). Women and persons with hypertension were slightly more likely to receive lipid-lowering treatment than men and persons without hypertension.

The mean age at onset of MCI was 80.7 ± 5.8 years. Higher plasma levels of total cholesterol and LDL-C were associated with a decreased risk of total MCI after adjusting for age and sex (table 2). These associations were attenuated after adjusting for education, diabetes, heart disease and hypertension. Additional adjustment for

stroke did not change the associations. There was no relation between lipids and the risk of amnesic or nonamnesic MCI in either model. Treatment with lipid-lowering agents was not associated with the risk of total MCI (hazard ratio 1.0, 95% confidence interval 0.75–1.37), amnesic MCI (hazard ratio 1.0, 95% confidence interval 0.66–1.58) or nonamnesic MCI (hazard ratio 1.0, 95% confidence interval 0.67–1.52). Restriction of the analyses to persons with longer-follow up times (observation time equal or longer than the median follow-up time of 3.9 years) or stratification by median of age, ethnicity or diabetes did not change these relations.

Discussion

There were trends towards a decreasing risk of total MCI with increasing levels of total cholesterol and LDL-C in models adjusting for age and sex. However, these trends were attenuated after adjusting for education, diabetes, heart disease and hypertension. There was no relation between lipid levels and the risk of amnesic or nonamnesic MCI, and there was no effect of lipid-lowering treatment on MCI risk.

The role of dyslipidemia in the pathogenesis of cognitive impairment remains unclear. Brain cholesterol alters the degradation of amyloid precursor protein 2 [3], and there is evidence that lowering plasma cholesterol levels prevents AD development by reducing β -amyloid production [14]. However, reports indicate that cholesterol depletion induces AD-type injuries in cultured hippocampal slices [14] and that plasma cholesterol levels have no effect on brain HMG-CoA reductase activity [4].

Studies examining the role of plasma lipid levels or lipid-lowering treatments in cognitive function reported inconsistent results [4, 15–21]. Controversial results have also been obtained in animal studies [22, 23]. Most observational studies were cross-sectional, the few longitudinal studies mostly examined manifest dementia but not MCI as the endpoint. While studies have found a relation between high cholesterol during mid-life and cognitive impairment or MCI in old age [19], the Honolulu Asia Aging Study recently reported in a study with 26 years of follow-up that cholesterol levels in men with dementia at the end of follow-up declined at least 15 years before the diagnosis and remained lower than cholesterol levels in men without dementia [24]. Associations relating late-life lipids with cognitive impairment or dementia were also inconsistent.

We initially observed that higher cholesterol and LDL-C were related to a decreased risk of total MCI after adjusting for age and sex. However, these associations were attenuated after adjusting for education and vascular risk factors indicating that the initially observed inverse associations were caused by confounding. We also found no relation between HDL-C or triglyceride levels or lipid-lowering treatment with any MCI subtype. This is consistent with our previous observations of no association between lipid levels or treatment with cognitive performance in several domains over time [6], as well as other cross-sectional and longitudinal studies observing no relation with cognitive impairment [17, 18, 21].

It is important to note that lipid levels decrease with aging and may not have the same significance they have

in middle age. This implies the possibility that studies with a shorter follow-up or higher baseline age lack the ability to detect a harmful effect. We tried to eliminate this possibility by repeating all analyses restricted to persons with a longer follow-up but this did not change our results. Another potential explanation for our findings is that our study lacked statistical power to detect a small effect size. However, power calculation shows that, with a power of 80% and an α of 0.05 we were able to demonstrate relative risks for MCI of at least 1.30 for total cholesterol, 1.31 for HDL-C, 1.30 for triglycerides and 1.32 for LDL-C. If there is indeed an association between plasma lipid levels and MCI, it must be of relatively small magnitude. However, the hazard ratio and confidence intervals in our results were close to or lower than 1 and do not suggest that lack of power is an explanation for the lack of association.

Limitations include that we used only one measurement of lipid levels, which could have led to measurement error and an underestimation of the association. In some of the subjects, lipid measurements were taken in the afternoon, which may be a concern for triglycerides and LDL-C but do not affect levels of total cholesterol and HDL-C. An important strength of our study is that it is a prospective cohort study designed for the diagnosis of cognitive impairment and dementia.

It is important that our results be interpreted in the context of a highly selected cohort of elderly persons living in an urban setting in the decade of the 1990s, when the use of lipid-lowering medications was not as widespread as in the present. Our results may not apply to younger populations and those in other countries.

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