Lipoprotein(a) and Cognitive Performances in an Elderly White Population
Cross-Sectional and Follow-Up Data

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Background and Purpose—Elevated lipoprotein(a) [Lp(a)] serum levels have been associated with an increased risk of vascular diseases, and preliminary observations suggest that they are a risk factor for vascular dementia. The relationship between Lp(a) levels and cognitive performances in the general population has never been investigated. Our aim was to evaluate the effect of elevated Lp(a) levels on cognitive functions in the elderly.

Methods—Cognitive performances were assessed by means of the Mini-Mental State Examination (MMSE), the Babcock Short Story, and the Matrix Test in a population sample of 435 white subjects aged 65 to 84 years who were evaluated at baseline and after 3 years. Lp(a) levels were determined by ELISA.

Results—No statistically significant difference was found in neuropsychological test scores between subjects with and without elevated Lp(a) levels, although subjects with elevated Lp(a) levels had slightly better cognitive performances. This difference reached a statistical significance level only in a subscore of the Matrix Test (number of correct responses) when adjusted for age, sex, education, smoking, and history of stroke. At follow-up, no statistically significant difference was found in cognitive performances between subjects with and without elevated Lp(a) serum levels in either univariate or multivariate analyses. Subjects with and without elevated Lp(a) showed a similar decline rate during follow-up.

Conclusions—In this sample of elderly white subjects, elevated Lp(a) levels were not associated with poorer cognitive performances or with an increased rate of cognitive decline. Elevated Lp(a) levels do not appear to be a major determinant of cognitive impairment in the elderly. (***Stroke***. 2001;32:1678-1683.)

Key Words: aging ∎ cognitive disorders ∎ lipoproteins ∎ neuropsychological tests

Lipoprotein(a) [Lp(a)] is a molecule formed by an LDL bound to a glycoprotein called apolipoprotein(a) [apo(a)].[1] Although the physiological function of Lp(a) is still unknown, elevated Lp(a) serum levels have been found to be associated with an increased risk of coronary,[2–7] peripheral artery,[8,9] and cerebrovascular[10–16] diseases. This association is presumably mediated by the procoagulant[17] and the proatherogenic[18] effects of Lp(a).

Because cardiac and cerebrovascular diseases are recognized risk factors for dementia,[19,20] the study of Lp(a) in relation to cognitive functions seemed worthy of investigation. Although preliminary data from 2 controlled series of hospitalized patients have indicated that Lp(a) is a possible risk factor for vascular dementia,[21,22] the effect of Lp(a) levels on cognitive functions has never been investigated in large population-based surveys.

As part of a study aimed at evaluating the effect of elevated Lp(a) serum levels on the prevalence of vascular diseases in

an elderly (65 to 84 years old) white population cohort,[23] we were able to study the relationship between Lp(a) levels and cognitive performances assessed at baseline and after 3 years.

Subjects and Methods

The study was conducted in Impruneta, Florence, which is 1 of the 8 centers participating in the Italian Longitudinal Study on Aging (ILSA).[24,25] ILSA is a population-based, longitudinal study of the health status of Italians aged 65 to 84 years. The main objective of ILSA is the study of prevalence and incidence rates of age-related diseases in the elderly Italian population and the identification of their risk and protective factors. ILSA is also aimed at assessing age-associated physical and mental functional changes. All individuals from 65 to 84 years of age who were living at home or institutionalized and residing in the study areas at the start of the prevalence study (March 1, 1992) were eligible for inclusion. In each of the participating centers, a random sample of 704 individuals, stratified by age and sex, was selected from the demographic records of the registry office of each municipality according to an equal allocation strategy: 88 subjects of each sex from 4 age groups (65 to 69, 70 to 74, 75 to 79, and 80 to 84 years).

Cross-Sectional Study

The prevalence survey was conducted from March 1, 1992, to June 30, 1993. Cases of a given disease were identified in the study cohort by way of a 2-phase design. In the screening phase, a questionnaire and a series of brief tests to identify suspect cases for further investigation were administered to each subject in the sample. In the confirmation phase, suspect cases were clinically confirmed, and a differential diagnosis of specific disorders within a syndrome was formulated. A detailed protocol of the study has been published elsewhere.[24,25]

As part of the screening phase, a short battery of neuropsychological tests was administered by a physician. The tests assessed global cognitive functions (Mini-Mental State Examination [MMSE]),[26] selective attention [Matrix Test],[27] and episodic memory [immediate and delayed recall of the Babcock Short Story[28]). The Matrix Test (scores range from 0 to 60) has a basic format with 3 different matrices made up of 13 strings of 10 digits (0 to 9 in random sequence); each line includes 0 to 5 targets, and digits must be crossed out within a time limit (45 s/matrix). Through a 21-unit story, the Babcock Short Story (scores range from 0 to 16) measures immediate and delayed (10 minutes) recall and their sum; an event-weighed, hierarchical scoring system was used that rewarded the degree of organization of the subject's oral recollection.

The presence of cognitive impairment/no dementia (CIND) was assessed in all the subjects who scored <24 on the MMSE in the screening phase. In the ILSA Study, a diagnosis of CIND was made on the basis of a clinical and neuropsychological examination, informant interview, and assessment of the subject's functional activities. The details of the method are reported elsewhere.[29] The CIND definition is consistent with a more recent one of mild cognitive impairment.

Characteristics of Subjects Investigated in the Cross-Sectional Study

The original study cohort was a random population sample, selected according to the above sampling design in the municipality of Impruneta, a hilly area on the outskirts of Florence, Italy, that has 15 237 inhabitants, most of whom are engaged in agricultural, handicrafts, and tertiary activities. On March 1, 1992, the percentage of persons >65 years of age in this municipality was 16.7%. Of the total of 704 subjects in the original randomized cohort, 6 died before the start of the survey and 154 refused (refusal rate 22.06%) to participate. Due to a delay in starting the Lp(a) assessment, Lp(a) serum levels were determined in only 446 of the 544 subjects who had agreed to participate.[23] Because the survey was to start with examination of the oldest subjects first, those who, because of this delay, missed Lp(a) determination were mainly in the 80- to 84-year-old age group. The mean age of subjects with (n=446) and without (n=252) Lp(a) determination was 74.5 ± 5.7 and 75.4 ± 5.8 years, respectively (*t* test $P=0.035$), with no significant difference in sex distribution [among subjects with and without Lp(a) level assessment, 51.8% and 46.4% were men, respectively; χ^2 $P=0.173$]. In addition, the subjects who refused to participate in the ILSA survey were mainly those in the oldest age groups. These exclusions led to a younger mean age of this study cohort compared with the original one. We were unable to explore whether further selection biases occurred in regard to subjects who were lost due to their refusal to participate in the population survey, because apart from age and sex, we had no other information related to either determinants or outcomes. On the other hand, we were able to analyze the differences in the prevalence of risk factors between participants with Lp(a) determination (n=446) and those who, although participants of the survey, did not have a Lp(a) determination (n=98). No substantial differences were observed in the prevalence of stroke, myocardial infarction, angina, or diabetes (χ^2 P 0.163 to 0.694). There was only a significant difference in smoking [36.9% versus 20.4% in subjects with and without Lp(a) assessment, respectively; $P=0.002$] and a trend difference in hypertension [68.5% versus 58.4% in subjects with and without Lp(a) assessment, respectively; $P=0.068$].

Four hundred thirty-five of 446 subjects with Lp(a) assessment and 97 of 98 subjects without Lp(a) assessment underwent neuropsychological testing. The 97 subjects scored worse than the 435 subjects. As expected, because the subjects without Lp(a) determination were older, these differences were no longer significant after correction for age.

Lp(a) Assessment

A blood sample was taken after a 12-hour fast for several laboratory investigations to determine baseline values. Serum concentration of Lp(a) was quantified with an ELISA (Biopool).

Normal values of Lp(a) levels are not known for the general population >65 years of age. Given that a number of studies have suggested that the risk associated with Lp(a) is confined to the upper quartile,[2,30,31] we chose the 75th percentile as a cutoff to define subjects with elevated Lp(a) levels. As in another population-based study,[31] in our cohort the 75th percentile differed significantly between male (310 mg/L) and female (400 mg/L) subgroups; therefore, the subjects were considered as having elevated Lp(a) concentration when the level exceeded the 75th percentile for their sex.

Follow-Up Study

The follow-up survey of the ILSA Study was started on September 1, 1995. Screening and confirmation procedures were the same as those for the cross-sectional survey. Of the 435 patients with a Lp(a) determination and a complete neuropsychological examination at baseline, 49 died before the follow-up neuropsychological evaluation; we were unable to make a comparison between follow-up and baseline cognitive assessment for an additional 73 subjects who either were not assessable (n=24) or refused to actively participate in the follow-up study (n=49). Thus, 313 subjects were available for cognitive reexamination.

Statistical Analysis

To examine the effect of Lp(a) on cognitive function, we analyzed the score differences for each of the 3 tests (MMSE, Matrix Test, Babcock Short Story) administered in the 2 study phases and compared the subgroups of subjects within each of the 4 quartiles of Lp(a) and the 2 subgroups of subjects with and without an elevated ($\geq$75th percentile) Lp(a) level. The significance was tested by means of ANOVA and *t* test for independent samples, respectively. Because age, educational level, history of stroke, and smoking were the factors that had been found to alter cognitive functions in the total ILSA population,[29] we examined the possible confounding or modifying effect of these factors used as covariate variables in the ANOVA. We defined as a smoker each subject with a pack-year index of >10 (pack-years was defined as packs of cigarettes per day multiplied by the number of years the subject smoked). The relationship between Lp(a) levels and baseline neuropsychological test scores was analyzed by means of Pearson's correlation.

Baseline neuropsychological test scores of the total sample were compared with the follow-up results, and the statistical significance of the differences was analyzed by *t* test for independent samples. All the scores were also corrected for age, educational level, history of stroke, smoking, and baseline score (ANOVA).

For the 66 subjects who were unable to complete the MMSE test at baseline due to motor, visual, or hearing deficits or illiteracy, a ratio was calculated between the score obtained and the maximum score obtainable. This ratio was then multiplied by 30 to normalize it with the scores of other subjects.

The relative prevalence of CIND in subjects with and without elevated Lp(a) levels was examined, and the statistical significance assessed by χ^2 test.

Version 9.0 of SPSS software for Windows was used for these analyses.[32]

Results

The demographic characteristics and educational level of the study cohort are given in Table 1.

TABLE 1. Demographic Characteristics and Educational Level of Subjects

	Lp(a) Level			
	<75th Percentile (n=327)	≥75th Percentile (n=108)	Total Sample (n=435)	P
Age, y	74.62±5.72	73.95±5.82	74.46±5.75	0.293*
Male sex, n (%)	172 (52.6)	56 (51.9)	228 (52.4)	0.893†
Education, y	4.54±3.50	4.32±3.25	4.49±3.44	0.575*

*t test.
†χ^2.

No statistically significant difference was found in neuropsychological test scores between the 2 groups of subjects with (≥75th percentile) and without (<75th percentile) elevated Lp(a) levels, although subjects with elevated Lp(a) levels had slightly better cognitive performances in all the tests (Table 2). This difference reached statistical significance in the number of correct responses in the Matrix Test after control for age, sex, education, smoking, and history of stroke (Table 2). No correlation was found between Lp(a) levels and the neuropsychological test score (Pearson's correlation P 0.364 to 0.625).

The rate of subjects with elevated Lp(a) levels was equally distributed in the group of subjects available and in the group of subjects lost at follow-up (24.9% of available subjects versus 24.6% of lost subjects). No statistically significant difference in sex distribution was found (for men, 52.1% of available subjects versus 53.3% of subjects lost at follow-up, χ^2 $P=0.453$). Compared with the 313 available subjects, the 122 subjects lost at follow-up were older (mean age 76.3±5.8 versus 73.7±5.6 years, t test $P=0.0001$) and at the cross-sectional assessment had significantly higher rates of dementia (17.2% versus 2.2%, χ^2 $P<0.001$), myocardial infarction (13.9% versus 7.4%, $P=0.029$), and heart failure (10.7% versus 1.9%, $P<0.001$) and nonsignificantly higher rates of stroke (7.4% versus 3.8%, χ^2 $P=0.100$) and intermittent claudication (8.6% versus 5.5%, χ^2 $P=0.208$).

Table 3 shows the mean test scores among the subgroups of subjects classified according to the 4 quartiles of Lp(a) determination. No statistically significant difference was found in score variations between baseline and follow-up assessments in each Lp(a) class level.

At follow-up, the neuropsychological test scores showed no statistically significant difference between subjects with and without elevated Lp(a) levels at baseline in either the univariate or the multivariate analysis (Table 4). Table 4 also shows the differences between the neuropsychological test scores at baseline and at follow-up assessment. The cognitive performances of subjects with and without elevated Lp(a) levels worsened over the follow-up period with a similar trend.

In our sample, a CIND diagnosis was made in 25 subjects. No significant difference was found in the prevalence of CIND between subjects with and without elevated Lp(a) serum levels (4.9% versus 6.6%, respectively; χ^2 $P=0.533$).

Discussion

In our population cohort of elderly white subjects, we did not detect any significant difference in the cognitive performances between the groups of subjects with and without elevated Lp(a) levels. Overall, the slightly better cognitive profile of subjects with elevated Lp(a) levels detected at baseline was nonsignificant from a statistical and, in our opinion, a clinical point of view. Moreover, the significant difference seen at baseline in a subscore of 1 of the 3 neuropsychological tests was not confirmed at follow-up. Thus, we conclude that in our population sample, the serum level of Lp(a) did not influence a subsequent rate of cognitive decline.

TABLE 2. Baseline Neuropsychological Test Scores (Mean±SD) According to Serum Level of Lp(a)

	Lp(a) Level			
	<75th Percentile (n=327)	≥75th Percentile (n=108)	P*	P†
MMSE	25.36±4.4	26.04±3.7	0.155	0.064
Babcock Short Story				
Immediate recall	4.28±2.3	4.46±2.3	0.478	0.251
Delayed recall	4.91±2.6	5.36±2.4	0.114	0.072
Matrix Test				
Correct responses	35.67±12.4	38.34±12.6	0.062	0.005
Omissions	11.01±7.2	11.07±8.1	0.948	0.699
False alarms	0.27±0.9	0.26±1.2	0.936	0.205

Values are mean±SD.
*Univariate analysis (t test).
†Adjustment for age, education, history of stroke, and smoking (ANOVA).

TABLE 3.   Neuropsychological Test Scores According to Lp(a) Level Quartiles at Baseline and Follow-Up

Neuropsychological Test	Lp(a) Level Quartile	Baseline	P*	Follow-Up	P*
MMSE	<25th	26.0±4.0		25.1±4.9	
	25th–50th	25.0±4.8	0.142	24.4±5.0	0.254
	50th–75th	25.0±4.5		24.3±5.5	
	>75th	26.0±3.7		25.7±4.0	
Babcock Short Story					
Immediate recall	<25th	4.7±1.9		4.4±2.1	
	25th–50th	4.2±2.4	0.176	3.9±2.2	0.192
	50th–75th	4.0±2.5		4.0±2.1	
	>75th	4.5±2.3		4.5±2.1	
Delayed recall	<25th	5.3±2.3		4.7±2.3	
	25th–50th	4.7±2.7	0.139	4.5±2.5	0.274
	50th–75th	4.8±2.7		4.9±2.0	
	>75th	5.4±2.4		5.2±2.2	
Matrix Test					
Correct responses	<25th	37.8±13.7		35.7±13.2	
	25th–50th	34.5±10.6	0.049	35.8±11.5	0.500
	50th–75th	34.8±12.6		36.2±13.0	
	>75th	38.3±12.6		38.6±12.3	
Omissions	<25th	9.8±6.8		8.7±6.1	
	25th–50th	11.5±6.9	0.294	9.7±6.3	0.715
	50th–75th	11.6±7.9		9.7±6.0	
	>75th	11.0±7.4		9.2±6.4	
False alarms	<25th	0.22±0.7		0.36±1.1	
	25th–50th	0.25±0.7	0.798	0.25±1.0	0.696
	50th–75th	0.35±1.0		0.19±0.6	
	>75th	0.26±1.2		0.23±0.7	

Values are mean±SD.
*ANOVA.

Because elevated Lp(a) levels have been reported to be associated with an increased risk of coronary artery and cerebrovascular diseases, our original hypothesis was that an elevated Lp(a) level could also be a risk factor for poorer cognitive performances. Although a previous study on the same population did not disclose any association between elevated Lp(a) levels and vascular diseases,[23] we decided to analyze the effect of elevated Lp(a) levels on cognitive

TABLE 4.   Cognitive Performances in Subjects Available at Follow-Up and Differences Versus Baseline

	Lp(a) Level <75th Percentile (n=235)	Lp(a) Level ≥75th Percentile (n=78)	P*	P†	ΔLp(a) <75th Percentile	ΔLp(a) ≥75th Percentile	P*	P†
MMSE	24.64±5.1	25.70±4.0	0.098	0.823	1.6±3.8	1.4±3.1	0.682	0.823
Babcock Short Story								
Immediate recall	4.05±2.1	4.47±2.1	0.144	0.119	0.5±2.2	0.3±1.8	0.541	0.162
Delayed recall	4.66±2.3	5.1±2.3	0.157	0.114	0.6±0.6	0.6±0.6	0.827	0.175
Matrix Test								
Correct responses	36.08±12.4	38.11±12.7	0.238	0.284	1.4±7.3	2.9±7.2	0.123	0.284
Omissions	9.48±6.2	9.42±6.5	0.945	0.443	1.1±5.9	0.5±7.0	0.506	0.443
False alarms	0.26±0.9	0.20±0.7	0.588	0.568	−0.1±1.0	0.1±1.5	0.225	0.568

Values are mean±SD.
Δ indicates differences between baseline and follow-up scores.
*Univariate analysis (*t* test).
†Adjustment for age, education, history of stroke, smoking, and baseline score (ANOVA).

functions for the possibility that silent cerebrovascular disease (not assessable because the ILSA protocol does not include a neuroimaging evaluation) might be found in this population. There are at least 2 studies that show an association between elevated Lp(a) levels and silent cerebral infarction[33] or subcortical vascular encephalopathy.[34] The results of our study on an aged (>65 years) cohort do not support the original hypothesis. One should bear in mind, however, that the association between vascular diseases and elevated Lp(a) has been found mainly in subjects <60 years of age[35–38] and that elevated Lp(a) levels alone did not represent, as in our cohort, a risk factor for vascular diseases.[23] Thus, the putative detrimental effect of Lp(a) on cognitive performance could be similarly undetectable in older subjects of the general population. Because apo(a) molecular weight has been recently regarded as the main determinant of the harmful effect of Lp(a),[39] it could be hypothesized that subjects with elevated Lp(a) levels who survive to older age carry a less risky type of Lp(a) and thus are protected from its deleterious effect.

To the best of our knowledge, this study is the first to have evaluated the effect of Lp(a) levels on cognitive performances in the general population. In 2 Japanese studies,[21,22] elevated Lp(a) levels were found to be a risk factor for dementia. In the first study, higher Lp(a) levels were observed in patients with vascular dementia and large artery stroke compared with patients with Alzheimer's dementia, cerebral hemorrhage, and lacunar infarcts.[21] In the second study, the Lp(a) levels of patients with cerebrovascular disease and dementia were higher than those of age-matched control subjects.[22] Both studies focused on vascular dementia and used hospital-based patient series. In our population study, Lp(a) levels did not appear to influence the prevalence or subsequent rate of dementia, but we had a very small number of cases and we chose not to present these data. In our sample, only 1 of 6 subjects with a diagnosis of vascular dementia had an elevated Lp(a) level.

On the other hand, the influence of Lp(a) levels on cognitive performances in whites has not been previously investigated. As shown in a biracial population study,[40,41] the effect of elevated Lp(a) serum levels on vascular diseases may be dissimilar in different races: compared with whites, blacks have twice as high mean Lp(a) levels but carry the same or even a lower disease risk. One can assume that the effect of Lp(a) on cognition may also vary according to race.

Concerning the methodological issues of our study, Lp(a) was not assessed in nonresponders (the nonresponse rate of 20% can be considered acceptable for such population-based surveys) and in the previously mentioned group of individuals because of the delay in Lp(a) determination. Both these circumstances lowered the mean age of the study cohort due to the exclusion of older subjects but probably did not result in a systematic selection bias. In fact, apart from age and smoking, there was no difference in the prevalence of the diseases and risk factors being investigated between the group of subjects with and without Lp(a) level determination. The multivariate analysis showed that the worse neuropsychological performances of subjects without Lp(a) determination were mainly due to their older age.

We arbitrarily chose the 75th percentile to separate subjects with and without an elevated Lp(a) level. This was supported by data showing that the vascular risk associated with Lp(a) is confined to the upper quartile.[2,30,31] The 75th percentile for Lp(a) level in our study was slightly higher than that of previously quoted studies, and therefore it is unlikely that it could be below a putatively dangerous level. A repeat of the same analyses with the 70th, 80th, and 90th percentile cutoff limits or with a common 75th percentile for men and women did not change the significance of the results.

The battery of neuropsychological tests used to evaluate cognitive performances in this population sample originated from the general protocol of the ILSA Study.[24] This protocol included the MMSE along with the Babcock Short Story and the Matrix Test to screen subjects in this population suspected of having mental decline. The MMSE was chosen because it is the test most widely used and validated for the neuropsychological screening of large population-based studies. The choice of the other 2 tests was dictated by the need to expand the exploration of cognitive functions omitted by the MMSE and by these tests being rather easily administered in terms of time and compliance by the subjects under investigation (also in consideration of the low educational level of this Italian 65- to 84-year-old age group). Although the screening battery of tests used in the ILSA Study cannot be regarded as comprehensive (information regarding selective dysfunction related to age such as language and planning capacity is lacking), the Matrix Test and the Babcock Short Story are highly focused in finding alterations in attention and episodic memory, respectively. However, we cannot exclude that the use of a more comprehensive battery of neuropsychological tests and a longer follow-up period would have led to different results.

In conclusion, according to our data, elevated Lp(a) levels cannot be considered among the factors that influence cognitive performances in elderly whites. Future longitudinal observation studies should be aimed at evaluating the role of Lp(a) in relation to cognitive performances in younger age groups and in different racial groups.

Acknowledgments

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