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Original Research

Relationship between Lipoprotein(a) and cardiovascular risk factors—data from 4602 participants of the ELITE study

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Lipoprotein(a) (Lp(a)) is becoming increasingly important as an independent risk factor for cardiovascular disease. Since no effective therapy currently exists other than lipid apheresis, the recommendation remains to optimally adjust all other cardiovascular risk factors (CVRF). In a Northwest German population study, the frequency of elevated Lp(a) levels and all other CVRF was investigated. The aim was to investigate whether individuals with elevated Lp(a) levels were also more likely to have other CVRFs. To date, 4602 individuals have been enrolled in the study, and blood pressure, weight, lipids, diabetes, medications, and pre-existing conditions were recorded in addition to Lp(a). In addition, questionnaires assessed physical activity, psychological stress, depression, and brain dysfunction. All participants received detailed individual recommendation about their CVRF and its treatment. In the further follow-up of 5 years, it will be examined how persons with elevated Lp(a) implemented these recommendations in comparison with participants without elevated Lp(a). The first group Lp(a) $<$75 nmol/L consisted of 3550 (80.2%), the Lp(a) 75–120 nmol/L group of 341 (7.4%) and the Lp(a) $>$120 nmol/L of 538 (11.7%). 81.6% of all participants had one or more CVRF. Age, sex, and prevalence of hypertension, diabetes, smoking, obesity, and exercise did not differ among the 3 groups. As expected, LDL-Cholesterol was significantly elevated in the Lp(a) $>$120 nmol/L group despite significantly more frequent use of statins. Significantly more often hypertensive patients were found in the Lp(a) $>$120 nmol/L group who were inadequately controlled by medication and significantly less often persons without further CVRF. No differences existed in the frequency of psychological stress, depression, and mild cognitive impairment. CVRF occur with comparable frequency in individuals with elevated Lp(a) levels. However, individuals with Lp(a) above 120 nmol/L were more likely to have poorly controlled blood pressure, elevated LDL-C, and less likely to have no other risk factors. This underlines that in case of Lp(a) elevation all further CVRF should be intensively adjusted, especially in case of strongly elevated values $>$120 nmol/L. However, these recommendations have not been adequately implemented in clinical care in this population to date.

Keywords

Lipoprotein(a); Hypertension; Lifestyle; Cardiovascular risk factors; Prevention

1. Introduction

Lipoprotein(a) (Lp(a)) is increasingly important as an independent risk factor for cardiovascular disease. Numerous studies have shown that elevated Lp(a) levels are associated with higher rates of coronary heart disease, stroke, peripheral arterial disease and aortic valve stenosis. This includes patients with pre-existing cardiovascular disease. A linear risk for myocardial infarction and increasing Lp(a) levels was found, without a threshold effect [1–5]. Various pathophysiological relationships are responsible for this. Lp(a) consists not only of LDL-Cholesterol (LDL-C) particles, from which highly inflammatory oxidized LDL-C is formed after entry into the vessel wall, but also of apoliprotein(a) (apo(a)), which among other things also acts highly inflammatory and also antifibrinolytic through the inhibition of plasminogen activation. Thus, it promotes arterial thrombosis and venous thrombosis [6–8]. However, there is a lack of therapeutic options for prevention. Lifestyle modifications such as diet or physical activity do not significantly affect Lp(a) levels [9]. There is currently no approved medication for the treatment of elevated Lp(a) levels, although there are Proproteinkonvertase Subtilisin Kexin Typ 9 (PSCK9) inhibitors that can lower Lp(a) levels. Thus, a specific therapy currently exists only with lipid apheresis, which can effectively lower Lp(a) and significantly reduce the risk of cardiovascular events [10, 11]. However, lipid apheresis is essentially used only for secondary prevention. In Germany, treatment with lipid apheresis is approved only in cases of progressive cardiovascular disease despite optimal of the usual secondary prevention therapy and even then only for lipoprotein(a) levels above 60 mg/dL or 120 nmol/L.

However, patients with and without preexisting cardiovascular disease with elevated Lp(a) levels for whom apheresis is not an option are increasingly being presented for therapeutic intervention. In the absence of drug therapies, it is probably essential for this patient group to efficiently control traditional cardiovascular risk factors to minimize risk. It is also an open question whether individuals with elevated Lp(a) levels are also more likely to have other risk factors and whether they should be treated even more intensively.

The aims of this evaluation of the ELITE (Ernährung, Lebensstil und individuelle Information zur Verhinderung von Herzinfarkt, Schlaganfall und Demenz; german for: Nutrition, Lifestyle and Individual Information for the Prevention of Heart Attack, Stroke and Dementia) study were to present the frequency of elevated Lp(a) levels and to investigate the care situation and control of other risk factors in a rural population in northwestern Germany.

All participants received detailed individual and written education about their cardiovascular risk factors and their treatment. In the further follow-up of 5 years, it will be examined how persons with elevated Lp(a) implement these recommendations compared with persons with normal Lp(a) levels and how frequently cardiovascular events occur.

2. Methods

A detailed description, methods, and basic results have already been published [12, 13]. ELITE is a prospective interventional cohort study. Information about Cardiovascular risk factors (CVRF), mild cognitive impairment, psychosocial factors and Nutritional habits was prospectively collected. These CVRFs should be improved through targeted individualized prevention suggestions. The objective is to improve the health status of the participants and to identify the reasons for the lack of implementation of the prevention recommendations. The study included 4602 participants older than 16 years. Participation was called for via newspapers, sports clubs, companies or hospitals. Exclusion criteria were age under 16 years, lack of a declaration of consent, and obvious difficulties in tracking the participant. The aims of this particular evaluation were to present the frequency of elevated Lp(a) levels and to investigate the control of other risk factors in a rural population in northwestern Germany.

2.1 Data collection

Information on baseline data, school, occupation, medication, blood pressure (BP), dietary and exercise behaviors, laboratory values, daily/work life stress, and memory performance was collected through examinations, blood samples, and standardized questionnaires by trained professionals. Blood pressure was measured on both arms three times in a standardized manner after 5 minutes of rest, blood was drawn, and the previously completed questionnaire was checked, either at the study institute or with mobile teams in companies and organizations.

2.2 Data analysis

CVRF: for the purpose of this paper were defined as a Bodymass index (BMI) $\geq$30 kg/m^2, LDL cholesterol $>$130 mg/dL, smoking, diabetes mellitus, blood pressure $\geq$140/90 mmHg.

Diabetes Mellitus: Participants with antidiabetic medication, hämoglobin A1c (HbA1c) $\geq$6.5% and/or known diabetes mellitus type 1/2.

Smoking: Participants who state that they smoke regardless of the frequency.

Sports behavior: The classification of sports behavior was based on the multiple choice answers of the participant in the questionnaire to the question: "How often do you exercise?".

Regular physical activity = "1×/daily" and/or "2–3×/week".

Moderate amount of sport/moderate physical activity = "1×/week" and/or "every 2 weeks".

Sparse exercise/physical inactive= "1×/month" and/or "less often".

"All hypertensives": all participants with hypertensive values and/or antihypertensive therapy.

"Normotensive": all participants with normotensive blood pressure values and without a history of medication and/or known hypertension in the medical history.

"Untreated hypertensives": all participants with hypertensive BP and/or known hypertension without antihypertensive therapy.

"Treated hypertensives": all participants with hypertensive values or normotensive values and/or known hypertension but with antihypertensive therapy.

"Treated controlled hypertensives": all participants with normotensive BP ($<$140/90 mmHg) and antihypertensive therapy.

"Treated uncontrolled hypertensives": all participants with hypertensive BP and antihypertensive therapy.

Lp(a) values (nmol/L): Tina-quant® Lipoprotein (a) Gen. 2 assay (Roche, Basle, Switzerland). The assay is one of the first methods on a consolidated platform to follow the recommendations made in the recent clinical guidelines published by the EAS Consensus Panel, being insensitive to natural variations in Lp(a) particle size and standardized to measure Lp(a) molarity rather than Lp(a) mass [14]. Based on the recommendations of the German Lipid League, 3 groups were formed: $<$75 nmol/L (normal), 75–120 nmol/L (intermediate) and $>$120 nmol/L (german apheresis limit) [15].

Mild cognitive impairment: The Demtect (by Calabrese, Kessler and Kalb; Bochum/Cologne) as screening tool was used. Score between 0–12 points was rated as pathological and $>$13 points as physiological.

psychological stress: The question "How often do you feel you are exposed to stressful situations in your daily life?" was asked in the questionnaire. The answer options 2–3×/week and/or daily were rated as stress.

Depressive symptoms: The BDIII (by Beck, Ward, Mendelson, Mock & Erbaugh, 1961) was used to screen for

Table 1. Basic data.

	Lp(a) <75 nmol/L	Lp(a) 75–120 nmol/L	Lp(a) >120 nmol/L	*p*-value
participants n (%)	3550 (80.2)	341 (7.7)	538 (12.1)	
male n (%)	1649 (80.5)	162 (7.9)	237 (11.6)	0.517
female n (%)	1901 (79.8)	179 (7.5)	301 (12.6)	0.517
age mean (SD)	51.1 (15.65)	50.3 (15.46)	52.4 (15.26)	0.106
lipid therapy n (%)	276 (7.8)	26 (7.6)	73 (13.6)	$p < 0.001$
Family History of CAD n (%)	761 (21.4)	79 (23.2)	142 (26.4)	$p = 0.032$

SD, standard deviation; CAD, coronary artery disease.

Table 2. Blood Pressure in the different Lp(a) group.

	Lp(a) <75 nmol/L	Lp(a) 75–120 nmol/L	Lp(a) >120 nmol/L	*p*-value
Normotensives n (%)	1465 (41.3)	144 (42.2)	210 (39.0)	0.558
all Hypertensives n (%)	2085 (58.7)	197 (57.8)	328 (61.0)	0.558
Untreated Hypertensives n (%)	1029 (49.3)	91 (46.2)	161 (49.1)	0.689
treated Hypertensives n (%)	1056 (50.6)	106 (53.8)	167 (50.9)	0.689
treated controlled hypertensives n (%)	443 (42.0)	29 (27.4)	58 (34.7) (a)	$p = 0.005$
Treated uncontrolled hypertensives n (%)	613 (58.0)	77 (72.6)	109 (65.3) (a)	$p = 0.005$
Blood pressure group	Number	Lp(a) (nmol/L) mean	SD	*p*-value (b)
Normotensives	1819	40.6	59.1	0.488
Untreated Hypertensives	1281	41.9	62.9	0.488
treated controlled hypertensives	530	40.0	59.3	0.024
Treated uncontrolled hypertensives	799	48.4	71.4	0.024

(a) significant difference between controlled hypertensives with AH and uncontrolled hypertensives in Lp(a) >120 ($p = 0.005$).
(b) test between normotensives and one of the other 3 blood pressure categories.

depression. A score above 9 points was considered as depressive mood.

European society of Cardiology (ESC)-Score: According to the recommendations of the ESC, the SCORE was calculated for the 10-year risk assessment of cardiovascular events [16].

For grouped variables a cross table was formed and the Chi-square test was applied. For variables with metric values, the *T*-test was used for independent samples. When comparing more than two groups with metric characteristics, an analysis of variance was performed followed by a post-hoc test and Bonferroni correction. The α value of 0.05 was used as the significance level.

3. Results

Table 1 shows the baseline data of the cohort divided into 3 groups (Lp(a) <75 nmol/L, Lp(a) 75–120 nmol/L, Lp(a) >120 nmol/L). The group with normal Lp(a) was clearly the largest, although almost 20% had elevated Lp(a) values. The groups compared with each other were homogeneous with no significant differences in sex or age. Lipid therapy was significantly more common in the Lp(a) group with values >120 nmol/L.

The prevalence of cardiovascular risk factors has been compared among the 3 groups in Tables 2 and 3. In Table 2, the results on BP are presented in detail. The overall prevalence did not vary significantly in the different groups (58.7%, 57.8% and 61%).

First, the difference between normotensive participants (all participants with BP values <140/90 mmHg) and all hypertensive participants was analyzed. Here, there were no significant differences in frequency between the Lp(a) groups.

Then, all hypertensives (all participants with high BP and/or antihypertensive medication and/or history of hypertension) were analyzed in more detail and divided into drug-treated hypertensives ("treated hypertensives") and drug-untreated hypertensives ("untreated hypertensives"). Again, there were no significant differences in the Lp(a) groups. Finally, the group of treated hypertensives was again divided into well-controlled hypertensives (treated controlled hypertensives, i.e., with drug therapy and blood pressure <140/90 mmHg) and poorly controlled hypertensives ("treated uncontrolled hypertensives", i.e., with drug therapy and BP ≥140/90 mmHg). Interestingly, "treated uncontrolled hypertensives" have significantly more often high Lp(a) values >120 nmol/L than the "treated controlled hypertensives". This is also reflected in the mean Lp(a) values (Table 2). Here, the mean values of Lp(a) in the different BP groups were compared with the normotensives. Only the treated uncontrolled hypertensives group had significantly higher mean Lp(a) values compared with normotensives.

Table 3 shows the other risk factors in the Lp(a) groups. Only LDL-C differs significantly between the groups in each case. The "soft" risk factors like depression and stress also showed no significant difference.

Table 3. Cardiovascular risk factors in the different Lp(a) groups.

	Lp(a) <75 nmol/L	Lp(a) 75–120 nmol/L	Lp(a) >120 nmol/L	*p*-value
Diabetes n (%)	180 (5.1)	23 (6.7)	32 (5.9)	0.321
HbA1c mean (SD)	5.32 (0.57)	5.38 (0.63)	5.36 (0.54)	0.060
Smoking n (%)	476 (13.4)	48 (14.1)	66 (12.3)	0.702
BMI mean (SD) (kg/m^2)	26.52 (4.48)	26.92 (4.8)	26.6 (4.37)	0.295
Regular physical activity n (%)	1490 (42)	136 (39.9)	227 (42.2)	0.745
Moderate and sparse physical activity n (%)	2060 (58)	205 (60.1)	311 (57.8)	0.745
LDL-C (mg/dL) mean (SD)	129.30 (35.92)	129.81 (33.08)	139.22 (36.96)	$p < 0.001$
LDL-C <100 mg/dL (%)	20.6	18.8	14.0	$p < 0.001$
LDL-C 100–130 mg/dL (%)	32.1	34.1	26.5	$p < 0.001$
LDL-C ≥130–160 mg/dL (%)	28.0	30.3	32.7	$p < 0.001$
LDL-C >160 mg/dL (%)	19.3	16.8	26.7	$p < 0.001$
Mild cognitive impairment n (%)	278 (7.8)	40 (11.7)	44 (8.2)	0.4
psychological stress n (%)	2198 (61.9)	213 (62.5)	313 (58.2)	0.115
Depressive symptoms n (%)	991 (27.9)	99 (29.0)	141 (26.4)	0.797

Table 4. Number of cardiovascular Risk factors (CVRF) and ESC risk in different Lp(a) groups.

	Lp(a) <75 nmol/L	Lp(a) 75–120 nmol/L	Lp(a) >120 nmol/L	*p*-value
No additional CVRF n (%)	678 (19.7)	68 (20.5)	70 (13.4)	
1 CVRF n (%)	1183 (34.4)	100 (30.1)	188 (35.9)	
2 CVRF n (%)	1026 (29.8)	112 (33.7)	184 (35.1)	
3 or more CVRF n (%)	551 (16)	52 (15.6)	82 (15.7)	
				$p = 0.008$
ESC-Score				
10 Year risk <5% n (%)	2881 (84.2)	275 (83.3)	442 (83.6)	
10 Year risk 5–10% n (%)	363 (10.6)	30 (9.1)	54 (10.2)	
10 Year risk >10% n (%)	176 (5.1)	25 (7.6)	33 (6.2)	
				$p = 0.325$

Nevertheless, there are significant differences in the number of cardiovascular risk factors per participant in the 3 Lp(a) groups (Table 4). 2 other risk factors were found significantly more frequently in the Lp(a) >120/nmol/L group, whereas no other risk factors were less frequent in this group than in the Lp(a) <75 nmol/L and Lp(a) 75–120 nmol/L groups.

This is not reflected in a different ESC risk of a cardiovascular event in 10 years. Here, there are no significant differences in the groups ($p = 0.325$). The laboratory values in Table 5 showed no significant differences except for LDL-C and total cholesterol.

4. Discussion

In this Northwest German Cohort Study, the frequency of elevated Lp(a) and the correlation of Lp(a) levels with other CVRF were investigated. No frequency studies have previously been performed for this region.

The frequency of elevated Lp(a) was 19.8% with no significant differences between women and men. Among them, 7.7% were above the normal value of 75 nmol/L and 12.1% were above 120 nmol/L. From this value, patients with progressive atherosclerosis can apply for apheresis treatment in Germany. Thus, the frequency is within the previously published range [14, 17]. For Europe, North America and Australia, elevated values above 50 mg/dL or above 125 nmol/L are reported in 20%, in Africa even in 30%, in China in 10% [18–20].

The question of this work was whether other cardiovascular risk factors are also more frequent in individuals with elevated Lp(a) than with normal Lp(a) levels.

In summary, there was no significant difference in the prevalence of other CVRF such as arterial hypertension, Smoking, HDL- cholesterol triglycerides, uric acid, and diabetes mellitus. Also, physical activity, brain dysfunction, depressive symptoms, psychological stress, or age were not different in the three Lp(a) groups. Only LDL-C was significantly more prescriptions of statins in the group with the despite, which was largely due to the methodical co-recording and measurement of the LDL-C fraction in lipoprotein(a). The number of participants treated with statins was also significantly higher in this group, so that the difference in LDL-C was originally even higher. As expected, the group with Lp(a) levels above 120 nmol/L was significantly more likely to have a positive family history of coronary heart disease.

A common clinical question is how to proceed in patients with elevated Lp(a) and not yet manifest cardiovascular disease, especially with a positive family history. Previous guidelines recommend Lp(a) measurements in defined patient groups [21, 22].

Table 5. Labroratory results.

	Lp(a) <75 nmol/L	Lp(a) 75–120 nmol/L	Lp(a) >120 nmol/L	*p*-value
HbA1c (%) mean (SD)	5.32 (0.57)	5.38 (0.63)	5.36 (0.54)	0.06
Cholesterol (mg/dL) mean (SD)	204.79 (38.90)	202.73 (35.81)	214.80 (39.60)	$p < 0.001$
Triglyceride (mg/dL) mean (SD)	152.10 (102.75)	150.04 (98.16)	149.46 (90.58)	0.814
High density liprotein (HDL) (mg/dL) mean (SD)	61.14 (18.79)	59.30 (17.79)	61.69 (18.12)	0.156
LDL-C (mg/dL) mean (SD)	129.30 (35.92)	129.81 (33.08)	139.22 (36.96)	$p < 0.001$

An isolated assessment of cardiovascular risk only by means of high Lp(a) and the subsequent setting of individual thresholds for LDL-C is not yet mentioned in the guidelines. Lp(a) should currently only be used as a decision aid in patients between moderate and high risk of cardiovascular events [21]. It is problematic that even when the ESC score is used for risk assessment, the attributive risk of Lp(a) elevation is not detected. Thus, currently, in the absence of drug therapy, the logical consequence remains to optimally adjust all other risk factors.

Therefore, the frequency of other cardiovascular risk factors was evaluated in this study. This is of particular importance, because in this study participants with Lp(a) had significantly more frequent two risk factors - especially in the group with Lp(a) >120 nmol/L. In particular, the question arises as to the clinical significance and therapeutic consequence of elevated LDL-C in conjunction with elevated Lp(a). Overall, it must be assumed that patients with Lp(a) >120 nmol/L are at moderate to high cardiovascular risk and thus, according to guidelines, should achieve an LDL-C target value of at least below 100 mg/dL (or even <70 mg/dL). However, this classification has to be put up for discussion, because the guidelines on dyslipidaemia do not consider Lp(a) for risk assessment. The LDL-C mean value of this group in our study is 139.22 mg/dL. A controlled LDL-C is essential for this risk group. Nevertheless, in our survey only 14% of the participants in this group were in the target range of below 100 mg/dL, while almost 59.4% were above 130 mg/dL. Only 13.6% in the Lp(a) >120 nmol/L were receiving lipid lowering therapy. The Jupiter Trial or the AIM-High Trial confirm a continued increased cardiovascular risk despite controlled LDL-C, although potentially lower than uncontrolled LDL-C [23, 24]. A meta-analysis by Tsimikas *et al.* [25] provides evidence for a significant increase in Lp(a) by statins . Up for debate is whether this elevation partially explains the residual cardiovascular risk with statin therapy. It has been shown that increased Lp(a) leads to a linear increase in cardiovascular risk even with statin therapy [26].

In addition to LDL-C, all other CVRFs must of course be adjusted [27]. There is impressive evidence that the cardiovascular risk of elevated Lp(a) further increases in the presence of additional CVRF [28–30]. Saeed *et al.* [28] found a significantly increased risk of cardiovascular events over 15 years when diabetes or prediabetes was present. Smoking also significantly increased the risk [29, 30]. Hypertension, as one of the major CVRFs, was not adequately controlled in all 3 groups. In the "high-risk" group Lp(a) >120 nmol/L, only 17.7% of all hypertensive patients were controlled (<140/90 mmHg). While the mean Lp(a) values of untreated hypertensives and treated controlled hypertensives did not differ significantly from normotensives, treated uncontrolled hypertensives showed significantly increased Lp(a) values. Thus, the most prognostically unfavorable hypertensive group showed the highest Lp(a) values.

The significance and cause are unclear. Also, these results need to be confirmed. One could discuss that the high BP levels in combination with high Lp(a) might have led to inflammation with endothelial damage. It may also be speculated that mechanisms such as fibrinolysis inhibition contributed to this. The compliance of patients with a lot of different medication could also be a problem in this group.

5. Conclusions

Overall, the strict cessation of further classical CVRF is of paramount importance. Nevertheless, this study shows that the recommendations of professional societies are not currently implemented in the general population.

This analysis shows that recognition of the hazardous nature of elevated Lp(a) does not lead to better adjusted traditional cardiovascular risk factors. As a consequence, high-risk patients may need to be much better educated and monitored with respect to their individual cardiovascular risk profile. In ELITE, participants are revisited annually and detailed individual prevention recommendations are made. Evaluation of follow-up data at 1 year and endpoints at 5 years will show whether intensive written recommendations can help to better control cardiovascular risk factors in patients with high Lp(a).

Author contributions

BS, JS, ASh, ASc and SL drafted the manuscript, BV was responsible for the statistical evaluation and described the statistical analyses, AE, MK and HH advised on the design of the study and improved the manuscript of this paper. BS, JS and SL designed the ELITE study. The decision to submit the manuscript for publication was made jointly by all authors, who also guarantee the completeness and correctness of the data and the study conduct.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted

in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of University of Göttingen (approval number: 34/6/14).

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Conflict of interest

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