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Lipoprotein(a) and Cardiovascular Disease in Ethnic Chinese: The Chin-Shan Community Cardiovascular Cohort Study

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BACKGROUND: Little is known about lipoprotein(a) [Lp(a)] as a predictor of vascular events among ethnic Chinese. We prospectively investigated the association of Lp(a) with cardiovascular disease and all-cause death in a community-based cohort.

METHODS: We conducted a community-based prospective cohort study of 3484 participants (53% women; age range, 35–97 years) who had complete lipid measurements and were free of a cardiovascular disease history at the time of recruitment. Over a median follow-up of 13.8-years, we documented 210 cases of stroke, 122 cases of coronary heart disease (CHD), and 781 deaths.

RESULTS: The incidences for each event increased appreciably with Lp(a) quartile for stroke and all-cause death, but not for CHD. Baseline Lp(a) concentration by quartile was not significantly associated with stroke, all-cause death, and CHD in multivariate analyses. The multivariate relative risk was significant for stroke at the 90th and 95th percentiles and for total death at the 95th and 99th percentiles.

CONCLUSIONS: Our findings suggest a threshold relationship with little gradient of risk across lower Lp(a) values for stroke and all-cause death in Chinese adults.

Lipoprotein(a) [Lp(a)][5] is a low-density lipoprotein particle in which apolipoprotein B-100 is linked by a single disulfide bridge to apolipoprotein(a), which is structurally similar to plasminogen *(1, 2)*. The dual effects of atherogenicity and thrombogenesis from Lp(a) particles make it plausible to investigate the role of Lp(a) in atherosclerosis in a population; however, although many cross-sectional studies of hospital-based populations have consistently shown that Lp(a) is related to various vascular diseases *(3–6)*, the evidence provided by many prospective cohort studies has been equivocal. In addition, previous large-scale prospective cohorts were restricted to women *(7)*, to men *(8)*, or to an older population *(9, 10)*. Moreover, most studies have specified only one vascular outcome, either coronary heart disease (CHD) or stroke, whereas some studies have combined both outcomes into just one endpoint *(9)*. Furthermore, the risk of Lp(a) with respect to cardiovascular events has varied according to ethnicity *(11)*. Few prospective studies have investigated the role of Lp(a) among ethnic Chinese, who have cardiovascular disease patterns distinct from those of Caucasians and African Americans. Therefore, we prospectively investigated the association of plasma Lp(a) concentration with cardiovascular disease and all-cause death among ethnic Chinese in Taiwan.

Materials and Methods

STUDY DESIGN AND STUDY PARTICIPANTS

The participants were enrolled in the Chin-Shan Community Cardiovascular Study, a prospective community-based study of risk factors and cardiovascular consequences in men and women 35 years of age or older sponsored by the National Science Council, Taiwan. The study was started in 1990 with an initial cohort of 3602 participants, who were recruited on the basis of official registrations. The institutional review boards of the National Taiwan University approved the study. These participants were noninstitutionalized persons who gave oral informed consent to enter and

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[5] Nonstandard abbreviations: Lp(a), lipoprotein(a); CHD, coronary heart disease; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; RR, relative risk; CI, confidence interval.

to remain in the study. Participants were eligible for enrollment regardless of whether they had a history of cardiovascular disease. The full details of the recruitment process have been published elsewhere *(12, 13)*. In brief, the study collected information regarding medical history, the results of a physical examination and laboratory tests, and an assessment of health status that included any evidence of cardiovascular disease in 1990 and 1991 and the follow-up periods *(14–16)*. We also collected detailed information about lifestyle factors, including alcohol intake, smoking, and regular exercise, as well as data regarding socioeconomic status, including marital status, educational level, and family history of CHD. We defined the cardiovascular disease at baseline according to the responses in the questionnaire about the history of stroke and CHD events. With regard to the follow-up schedule, we gathered information about cardiovascular events and deaths through monthly collections of official death certificate documents, by annual questionnaires, and by house-to-house visits.

ASCERTAINMENT OF EVENTS

The study outcomes were stroke, CHD, and all-cause death. Stroke was defined as a sudden neurologic deficit of vascular origin that lasted longer than 24 h that was supported by evidence from an imaging study. Transient ischemic attacks were not included in this definition. Incident CHD cases were defined as nonfatal myocardial infarction, fatal CHD, and hospitalization for percutaneous coronary intervention and coronary artery bypass surgery. Fatal CHD was considered to have occurred if fatal myocardial infarction was confirmed by hospital records, if CHD was listed as the cause of death on the death certificate or was the underlying and most plausible cause of death, or if evidence of previous CHD was available. Deaths from any cause were identified from official certificate documents and further verified by house-to-house visits.

MEASUREMENTS OF BIOCHEMICAL VARIABLES

The procedures of blood sampling have been reported elsewhere *(15, 17)*. In brief, all venous blood samples drawn after a 12-h overnight fast were immediately refrigerated and transported within 6 h to the National Taiwan University Hospital. Serum samples were then stored at −70 °C before batch assay of total cholesterol, triglycerides, and HDL cholesterol (HDL-C). Standard enzymatic tests for serum cholesterol and triglycerides were used (Merck 14354 and 14366, respectively). HDL-C concentrations were measured in supernatants after precipitation with magnesium chloride/phosphotungstate reagents (Merck 14993). The LDL cholesterol (LDL-C) concentration was calculated as the total cholesterol concentration minus the concentration of cholesterol in the supernatant obtained with the precipitation method (Merck 14992) *(18)*. The concentrations of apolipoproteins A-I and B were measured by turbidimetric immunoassay *(19)* with commercially available kits (Sigma-Aldrich). The concentration of non-HDL cholesterol was calculated by subtracting the HDL-C concentration from the concentration of total cholesterol. Lp(a) was measured by isoform-independent ELISA (Organon). The CV for Lp(a) measurements was 5%. In this study, we included 3484 participants who had complete Lp(a) measurements and were free from cardiovascular disease at baseline.

STATISTICAL ANALYSIS

Participants were classified by quartile of Lp(a) concentration, and continuous variables were presented as the mean (SD) or the median; categorical data were presented in contingency tables. ANOVA and the χ^2 test were used to test differences between quartiles. Relationships between baseline Lp(a) concentrations and other obesity and lipid markers were evaluated with age- and sex-adjusted Spearman partial correlation coefficients.

Incidence rates for stroke, CHD, and all-cause death were calculated for each Lp(a) quartile by dividing the number of cases by the number of person-years of follow-up. The relative risk (RR) of an event was calculated by dividing the incidence rate for each quartile by the rate in the first quartile. We used Cox proportional hazards models to adjust for potential confounding variables. We specified 5 models for estimating the RRs of events in higher Lp(a) quartiles relative to the lowest quartile. In model 1, we estimated the univariate RR of Lp(a) concentration with the first quartile as the reference. In model 2, we adjusted for age group (35–44, 45–54, 55–64, 65–74, or ≥75 years) and sex variables. In model 3, we additionally adjusted for body mass index (<18, 18–20.9, 21–22.9, 23–24.9, or ≥25 kg/m^2), lifestyle factors [including alcohol intake (nondrinker/current), smoking, (yes/no) and exercise (yes/no)], and socioeconomic status [including marital status (single, married, or divorced/separated), educational level (<9 years/≥9 years), occupation (no work, manual work, or professional), and family history of CHD (yes/no)]. In model 4, we adjusted for the presence/absence of hypertension and diabetes at baseline along with adjustments for the variables in model 3. In model 5, we included the continuous variables of HDL-C and LDL-C concentrations. In all analyses, we modeled Lp(a) concentrations as quartiles to avoid the assumption of linearity and to reduce the effects of outliers. Furthermore, we used median Lp(a) concentrations for the categories to test for linear trends across quartiles. We categorized the data ac-

cording to the 90th, 95th, and 99th percentiles and performed threshold analyses. We also used the test of Hosmer and Lemeshow to evaluate the goodness of fit of the data to the models *(20)*.

All statistical tests were 2-tailed with a type I error of 0.05, and *P* values <0.05 were considered statistically significant. Analyses were performed with SAS software (version 9.1; SAS Institute) and Stata software (version 9.1; Stata Corporation).

Results

The participants in the highest Lp(a) quartile were less likely to drink alcohol and more likely to be in less professional jobs, compared with participants in the lower quartiles (Table 1). Participants had similar distributions across quartiles for female sex, the presence of smoking, regular exercise, marital status, and educational level. In addition, the participants had similar rates across Lp(a) quartiles for hypertension and diabetes at baseline and for a family history of CHD. A higher Lp(a) concentration was associated with an older age and higher total cholesterol, LDL-C, and non-HDL cholesterol concentrations but was associated with a lower body mass index and a lower triglyceride concentration. We found no statistically significant differences in mean values for HDL-C, apolipoprotein A-I, or apolipoprotein B across Lp(a) quartiles.

Over a median follow-up of 13.8 years (interquartile range, 13.5–14.6 years) for the 3484 participants, we documented 210 cases of stroke (including 184 nonhemorrhagic and 26 hemorrhagic strokes), 122 cases of CHD, and 781 deaths (including 165 cardiovascular deaths). The incidence rates for each event increased appreciably with Lp(a) quartile for stroke and all-cause death, and the rates were approximately the same across quartiles for CHD (Table 2). The RRs for individuals in the highest quartile of Lp(a) concentration compared with those in the lowest quartile were 1.56 [95% confidence interval (CI), 1.07–2.28; *P* for trend = 0.003] for stroke and 1.26 (95% CI, 1.03–1.54; *P* for trend = 0.007) for all-cause death. In multivariate analyses adjusted for potential confounding variables, baseline Lp(a) quartile values were not significantly associated with stroke, all-cause death, or CHD; however, in an evaluation of the risks of Lp(a) concentrations greater than or equal to the 90th, 95th, and 99th percentiles (i.e., cutoff concentrations of 0.3443 g/L, 0.4708 g/L, and 0.6930 g/L, respectively), the multivariate RR increased with the cutoff value and was statistically significant for stroke at the 90th and 95th percentiles and for all-cause deaths at the 95th and 99th percentiles (Table 3). However, the RRs for CHD showed a statistically nonsignificant increasing trend, with little power.

To address the possibility that the associated risks of Lp(a) concentration vary by sex and age group, we performed stratified analyses according to participant sex and age and found no modification of the relationship between Lp(a) concentration and stroke after adjusting for these variables (all interaction *P* values >0.1; data not shown). Among participants older than 65 years, the association between Lp(a) concentration and stroke remained marginally significant after we adjusted for multivariate risk factors, with the RR increasing from the second through the fourth quartiles (RRs, 1.05, 1.24, and 1.59, respectively; *P* for trend = 0.055); however, these patterns were not apparent among participants younger than 65 years.

Discussion

Our data suggest a threshold relationship, with little gradient of risk for stroke and all-cause death across Lp(a) values among Chinese individuals. We found a marginally significant association between Lp(a) concentration and stroke only in men 65 years of age and older. Moreover, the strength of the association of Lp(a) with stroke was attributable to the ischemic subtype of stroke.

Different observational studies have provided conflicting evidence about the role that Lp(a) concentration plays in stroke. Rigal and colleagues conducted a case-control study of young adults (18–55 years) consisting of 100 cases of ischemic stroke and 100 matched controls and found that the relationship of Lp(a) concentration with stroke remained significant in men (odds ratio, 3.55; 95% CI, 1.33–9.48, for the comparison of the highest and lowest tertiles) but not in women (odds ratio, 0.42; 95% CI, 0.14–1.26) *(21)*. In another case-control study of Japanese individuals, a high Lp(a) concentration was associated with ischemic stroke *(22)*. The weakness of these studies, however, is that the small sample sizes and the few adjustments for confounding variables may have invalidated the results. Nested case-control studies that retrospectively measured Lp(a) concentrations in stored samples, which may have been unstable, still did not prove a significant association with further stroke *(8, 23)*. Among the 198 incident stroke cases and 198 controls from 7.5 years of follow-up of a cohort of nearly 15 000 healthy male physicians, Ridker and colleagues found no association between Lp(a) concentration and the incidence of stroke *(8)*.

Table 1. Distribution according to Lp(a) quartile for various demographic, lifestyle, and socioeconomic factors at baseline in the Chin-Shan Community Cardiovascular Study cohort (1990–1991).

	Quartile of Lp(a) concentration				
	1 (n = 871)	2 (n = 871)	3 (n = 871)	4 (n = 871)	*P*
Sex, %					0.67
Men	48.1	47.1	45.8	45.5	
Women	51.9	52.9	54.2	54.5	
Current smoker (yes), %	37.8	34.2	35.9	35.9	0.49
Alcohol drinking (yes), %	34.3	28.1	27.6	29.3	0.008
Marital status, %					0.10
Single	2.8	3.6	2.4	2.4	
Living with spouse	88.0	85.5	85.8	84.1	
Divorced or separated	9.2	10.9	11.8	13.5	
Educational level, %					0.14
<9 years	93.3	93.2	95.2	95.1	
≥9 years	6.7	6.8	4.8	4.9	
Job status, %					<0.0001
No job	46.2	49.6	51.9	53.3	
Manual labor	33.8	33.1	34.6	34.8	
Professional	20.1	17.3	13.6	11.9	
Regular exercise (yes), %	14.6	13.7	17.3	14.5	0.15
Family history of CHD, %	11.1	9.8	8.2	9.6	0.22
Hypertension, %	30.8	28.4	29.7	32.2	0.37
Diabetes, %	15.1	12.0	12.3	13.9	0.19
Age, years[a]	53.2 (11.5)	54.2 (12.5)	55.6 (12.2)	56.6 (12.8)	<0.0001
Body mass index, kg/m^2[a]	24.0 (3.6)	23.5 (3.4)	23.2 (3.3)	23.2 (3.3)	<0.0001
TC[b], mmol/L[a]	4.95 (1.11)	5.04 (1.16)	5.15 (1.18)	5.32 (1.21)	<0.0001
Triglycerides, mmol/L[a]	1.65 (1.315)	1.46 (1.144)	1.32 (0.931)	1.28 (0.802)	<0.0001
HDL-C, mmol/L[a]	1.22 (0.36)	1.22 (0.32)	1.23 (0.31)	1.24 (0.31)	0.3
LDL-C, mmol/L[a]	3.39 (1.09)	3.49 (1.12)	3.61 (1.15)	3.76 (1.19)	<0.0001
Non–HDL-C, mmol/L[a]	3.72 (1.13)	3.82 (1.17)	3.92 (1.18)	4.07 (1.22)	<0.0001
TC/HDL-C[a]	4.39 (1.62)	4.40 (1.52)	4.42 (1.42)	4.53 (1.50)	0.2
Apo A-I, g/L[a]	1.360 (0.544)	1.323 (0.285)	1.338 (0.264)	1.327 (0.263)	0.1
Apo B, g/L[a]	0.953 (0.465)	0.941 (0.316)	0.978 (0.454)	0.969 (0.665)	0.4
Apo B/Apo A-I[a]	0.73 (0.40)	0.73 (0.25)	0.75 (0.34)	0.75 (0.52)	0.6

[a] Data are expressed as the mean (SD).
[b] TC, total cholesterol; Apo, apolipoprotein.

Results based on prospective cohort studies are still inconsistent with respect to the relationship between Lp(a) concentration and cardiovascular events. Ariyo and colleagues tracked cardiovascular and death events for 3972 older Caucasian adults 65 years and older during 7.4 years of follow-up. These investigators found that Lp(a) concentration remained a significant predictor of stroke in men but found no relationship with CHD *(9)*. Furthermore, they found no significant association between Lp(a) concentration and cardiovascular outcomes among older women. In 3.2 years of follow-up of a cohort of 5732 elderly Caucasian men and women who had received statin treatment, Gaw and colleagues found no statistically significant associ-

Table 2. Incidence cases, person-years, incidence rates, and RRs for stroke, CHD, and all-cause death outcomes during a median follow-up of 13.6 years, according to quartile of Lp(a) concentration at baseline (1990–1991) in the Chin-Shan Community Cardiovascular Study.[a]

	Quartile of Lp(a) concentration at baseline				
	1	2	3	4	*P*, trend
Stroke					
Cases, n	47	42	48	68	
Person-years, n	11 044	10 986	10 852	10 578	
Incidence rate	4.3	3.8	4.4	6.4	
RR, model 1	1	0.92 (0.60–1.40)	1.04 (0.69–1.57)	1.56 (1.07–2.28)	0.003
RR, model 2	1	0.85 (0.55–1.29)	0.87 (0.58–1.31)	1.19 (0.81–1.74	0.12
RR, model 3	1	0.85 (0.55–1.30)	0.89 (0.58–1.34)	1.23 (0.84–1.81)	0.09
RR, model 4	1	0.88 (0.58–1.36)	0.90 (0.60–1.37)	1.21 (0.83–1.79)	0.13
RR, model 5	1	0.87 (0.56–1.34)	0.90 (0.59–1.37)	1.20 (0.81–1.78)	0.14
CHD					
Cases, n	33	25	30	31	
Person-years, n	11 086	11 058	10 865	10 693	
Incidence rate	3	2.3	2.8	2.9	
RR, model 1	1	0.76 (0.45–1.28)	0.93 (0.57–1.52)	0.98 (0.60–1.60)	0.74
RR, model 2	1	0.71 (0.42–1.20)	0.82 (0.50–1.34)	0.81 (0.49–1.32)	0.68
RR, model 3	1	0.76 (0.45–1.27)	0.84 (0.51–1.40)	0.89 (0.54–1.47)	0.95
RR, model 4	1	0.77 (0.46–1.30)	0.86 (0.52–1.42)	0.89 (0.54–1.47)	0.92
RR, model 5	1	0.77 (0.45–1.30)	0.82 (0.49–1.37)	0.81 (0.48–1.35)	0.62
All-cause death					
Cases, n	175	170	193	211	
Person-years, n	11 216	11 151	10 978	10 764	
Incidence rate	15.6	15.2	17.6	19.6	
RR, model 1	1	0.98 (0.79–1.21)	1.13 (0.92–1.39)	1.26 (1.03–1.54)	0.007
RR, model 2	1	0.88 (0.71–1.09)	0.91 (0.74–1.12)	0.93 (0.76–1.13)	0.78
RR, model 3	1	0.88 (0.71–1.09)	0.90 (0.73–1.11)	0.91 (0.74–1.12)	0.68
RR, model 4	1	0.89 (0.72–1.11)	0.91 (0.74–1.12)	0.91 (0.74–1.12)	0.61
RR, model 5	1	0.88 (0.71–1.09)	0.92 (0.74–1.13)	0.91 (0.73–1.12)	0.62

[a] Incidence rates are presented per 1000 person-years, and RRs are presented as RR (95% CI). Model 1, univariate; model 2, adjusted for age group (35–44, 45–54, 55–64, 65–74, ≥75 years) and sex; model 3, model 2 plus body mass index (<18, 18–20.9, 21–22.9, 23–24.9, or ≥25 kg/m^2), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status (single, married and living with spouse, or divorced/separated), educational level (<9 years/≥9 years), occupation (no work, manual labor, or official/business), regular exercise (yes/no), and family history of CHD (yes/no); model 4, model 3 plus hypertension (yes/no) and diabetes mellitus (yes/no); model 5, model 4 plus HDL-C and LDL-C concentrations.

ation of log-transformed Lp(a) concentration with stroke and coronary events in a univariate analysis *(10)*. Among 27 791 healthy, mostly Caucasian women in the Women's Health Study who were followed for 10 years, a clear threshold effect was seen for Lp(a) concentration *(7)*; that is, the association of Lp(a) with total cardiovascular events remained significant only at extremely high Lp(a) concentrations. Virtually no risk gradient was seen among these women at the lower Lp(a) quintiles. Ohira and colleagues examined the association between Lp(a) concentration and ischemic stroke in a biracial population of 14 221 middle-aged adults followed up for 13.5 years and found an appreciable association in African Americans and Caucasian women, but not in Caucasian men *(11)*. Our data suggest a threshold effect for stroke: the risks of stroke above the 90th and 95th Lp(a) percentiles were significant, implying that atherosclerotic burdens increased appreciably among individuals with extremely high Lp(a) concentrations.

Table 3. Multivariate RRs for stroke, CHD, and all-cause death outcomes during a median follow-up of 13.6 years according to the 90th, 95th, and 99th percentiles of Lp(a) concentration at baseline (1990–1991) in the Chin-Shan Community Cardiovascular Study.[a]

	RR (95% CI)	*P*
Stroke		
≥90th/<90th percentile	1.50 (1.01–2.22)	0.045
≥95th/<95th percentile	1.75 (1.04–2.93)	0.035
≥99th/<99th percentile	0.60 (0.08–4.34)	0.62
CHD		
≥90th/<90th percentile	1.24 (0.73–2.13)	0.43
≥95th/<95th percentile	1.71 (0.89–3.30)	0.11
≥99th/<99th percentile	2.11 (0.51–8.73)	0.30
All-cause death		
≥90th/<90th percentile	1.17 (0.93–1.45)	0.18
≥95th/<95th percentile	1.39 (1.04–1.86)	0.025
≥99th/<99th percentile	1.96 (1.10–3.49)	0.022

[a] Adjusted variables included age group (35–44, 45–54, 55–64, 65–74, or ≥75 years), sex, body mass index (<18, 18–20.9, 21–22.9, 23–24.9, or ≥25 kg/m^2), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status (single, married and living with spouse, or divorced/separated), educational level (<9 years/≥9 years), occupation (no work, manual labor, or official/business), regular exercise (yes/no), family history of CHD (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), and HDL-C and LDL-C concentrations.

Our negative results with respect to the relationship of Lp(a) concentration to CHD are comparable with those of previous cohort studies of Caucasian and African American populations *(9, 10)* but are not consistent with the positive association reported in the nested case-control study *(24)*. Rifai and colleagues conducted a nested case-control study and collected Lp(a) and apolipoprotein(a) data from 195 men who developed severe coronary atherosclerosis during a 5-year follow-up and 195 matched controls in the Physicians' Health Study *(24)*. Although 2 metaanalyses indicated a significant association between Lp(a) concentration and the risk for CHD, the results may not be valid for different populations because of heterogeneity in participant characteristics and the study *(25, 26)*.

The inconsistency of the findings among these different studies is troublesome and begs explanation *(27)*. One proposed explanation has been that Lp(a) interacts with age with respect to further cardiovascular events. Sex, a younger or older age, and the presence of high LDL-C and triglyceride concentrations have been reported to modify the association of Lp(a) concentration with cardiovascular events *(3, 7, 9, 11, 21, 24)*. Our data suggest a potential relationship among older Chinese men that is compatible with the findings of the Cardiovascular Health Study *(9)*. A specific high-risk population that includes type 2 diabetes and hypercholesterolemia may provide new evidence for the role of Lp(a) in cardiovascular disease *(28)*.

To our knowledge, this investigation is the first extensive study of Lp(a) and the risks of stroke, CHD, and all-cause death among ethnic Chinese. Because of the prospective cohort design, the baseline measurements of all cohort members were unlikely to have been affected by storage and laboratory issues that might be raised in some nested case-control studies. The use of a homogeneous community-based population may have reduced the possibility of selection bias. We also included important socioeconomic status and lifestyle factors in the models to control for potential confounding factors. Finally, because few of the participants (<1%) reported taking cholesterol-lowering medications, our results were minimally affected by statins and other cholesterol-lowering drugs.

Our study had several potential limitations. First, the incident cases of stroke and CHD were relatively few, even with a median follow-up of 13.8 years, and this fact would reduce the power to detect subtle differences in effects between Lp(a) concentrations and make RR estimation unstable. Second, because Lp(a) concentrations were measured only once, our results might be attenuated by intraindividual variations.

In conclusion, our data do not support the hypothesis that an increase in Lp(a) concentration, over most of its range, is significantly associated with stroke, CHD, or all-cause death among ethnic Chinese adults. Only a small proportion of people with extremely high Lp(a) concentrations were at excess risk. These findings limit the use of Lp(a) as a biomarker for the comprehensive evaluation of risk for cardiovascular disease in Chinese populations; however, a single measure of Lp(a) concentration to identify the small subgroup with extreme values may have some utility.

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