

# 行政院國家科學委員會專題研究計畫 成果報告

脂蛋白(a)在動脈硬化危險因子,代謝症候群,次臨床疾病與  
心血管疾病發生扮演的角色研究  
研究成果報告(精簡版)

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行政院國家科學委員會補助專題研究計畫  成果報告  
 期中進度報告

Role of Lipoprotein(a) in Atherosclerotic Risk Factors,  
Metabolic Syndrome, Subclinical Diseases and Incidence of  
Cardiovascular Disease

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執行單位：台大公衛學院 預防醫學研究所

中 華 民 國 97 年 10 月 22 日

## **Introduction**

Lp(a) lipoprotein 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) lipoprotein particles in basic research make it plausible to investigate the role of Lp(a) lipoprotein for atherosclerosis in population science. However, while many cross-sectional studies based on hospital-based population have consistently proven that Lp(a) lipoprotein was related to various vascular diseases(3-6), many prospective cohort studies have provided disputable arguments. In addition, previous large-scale prospective cohorts were restricted in women(7) or in men(8) or in older population(9, 10). Moreover, most studies specified only one vascular outcome, either coronary heart disease or stroke, whereas some studies combined both outcomes into just one endpoint(9). Furthermore, the risk of Lp(a) on cardiovascular events varied according to different ethnicity(11). Scant prospective studies were conducted to investigate the role of Lp(a) lipoprotein among ethnic Chinese, who had distinct cardiovascular disease patterns from Caucasians and African Americans. Therefore, we investigated prospectively the association between plasma concentrations of Lp(a) lipoprotein and 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 (CCCC), 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 non-institutionalized persons who gave oral informed consent to enter and to remain in the study. Participants were eligible for enrollment regardless of whether or not they had a history of cardiovascular disease. The full details of the recruitment process have been published elsewhere(12, 13). Briefly, information about detailed medical history, a physical examination, laboratory tests and 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 socioeconomic status, including marital status, educational level, , and family history of coronary heart disease. We defined the cardiovascular disease at baseline according to history of stroke and coronary heart disease events in the questionnaire. With regards to the schedule of follow-up, we collected the information about the cardiovascular events and death cases by monthly collection of official death certificate documents and by annual questionnaires and house-to-house visits.

### **ASCERTAINMENT OF EVENTS**

The outcomes studies were stroke, coronary heart disease and all-cause death. Stroke was defined according to the following criteria: a sudden neurological deficit of vascular origin that

lasted longer than 24 hours, with supporting evidence from image study. Transient ischemic attacks were not included in this study. Incident coronary heart disease cases were defined as nonfatal myocardial infarction, fatal coronary heart disease and hospitalization due to percutaneous coronary intervention and coronary bypass surgery. Fatal coronary heart disease was considered to have occurred if fatal myocardial infarction was confirmed by hospital records or if coronary heart disease was listed as the cause of death on the death certificate was the underlying and most plausible cause of death, or if evidence of previous coronary heart disease was available. Deaths from any cause were identified from official certificate documents and further verified by house-to-house visits.

#### MEASUREMENT OF BIOCHEMICAL VARIABLES

The procedures of blood sampling were reported elsewhere(15, 17). Briefly, all venous blood samples drawn after a 12-hour overnight fast were immediately refrigerated and transported within 6 hours to the National Taiwan University Hospital. Serum samples were then stored at -70°C before batch assay for levels of total cholesterol, triglyceride, and high density lipoprotein cholesterol (HDL-C). Standard enzymatic tests for serum cholesterol and triglyceride were used (Merck 14354 and 14366, Germany, respectively). HDL-C levels were measured in supernatants after the precipitation of specimens with magnesium chloride phosphotungstate reagents (Merck 14993). LDL-C concentrations were calculated as total cholesterol minus cholesterol in the supernatant by precipitation method (Merck 14992)(18). Apo A1 and Apo B concentrations were measured by turbidimetric immunoassay with commercial kits (Sigma). Non-HDL-C was calculated by subtracting HDL-C from total cholesterol. Lp(a) lipoprotein was determined by enzyme-linked immunosorbent assay (ELISA) (Organon) regardless of isoforms. The coefficient of variation for measuring Lp(a) lipoprotein was 5%. A total of 3484 participants with complete Lp(a) lipoprotein and free from cardiovascular disease at baseline were included in the study.

#### STATISTICAL ANALYSIS

Participants were categorized on the basis of quartiles of Lp(a) lipoprotein levels, and continuous variables were presented by mean, standard deviation or median levels; categorical data were presented in contingency table. ANOVA and the chi-square test were used to test the difference across the quartiles. Relationships between baseline Lp(a) lipoprotein and other obesity and lipid markers were examined by age and gender adjusted Spearman's partial correlation coefficients.

Incidence rates of stroke, coronary heart disease and all-cause death were calculated by dividing cases by the person-years of follow-up for each quartiles of Lp(a) lipoprotein. Relative risk of event was calculated by dividing the incidence rate of each quartile by the rate in the first quartile. We used Cox proportional-hazards models to adjust for potential confounding variables. We specified five models to estimate relative risk of events in the higher Lp(a) lipoprotein compared with the lowest quartile. First, we estimated the univariate relative risk of Lp(a) lipoprotein with the first quartile as reference in Model 1. Second, we adjusted for age groups (35-44, 45-54, 55-64, 65-74, >=75 years old) and gender variables in Model 2. In Model 3, we adjusted for additional body mass index (<18, 18 to 20.9, 21 to 22.9, 23 to 24.9, or >=25

kg/m<sup>2</sup>) and lifestyle factors, including alcohol intake (nondrinker/current), smoking, (yes/no) and exercise(yes/no), as well as socioeconomic status, including marital status(single, married, or divorced), educational level (<9 years, ≥9 years), occupation (no work, manual work, or professional), and family history of coronary heart disease (yes/no). In addition to the variables in Model 3, we further adjusted for the presence or absence of baseline hypertension and diabetes in Model 4. Moreover, we included continuous variables of HDL cholesterol and LDL cholesterol in Model 5. In all analyses, we modeled the Lp(a) lipoprotein as quartiles to avoid a linearity assumption and to reduce the effect of outliers. Furthermore, to test for linear trend across quartiles, we used the median Lp(a) lipoprotein levels for the categories. We categorized the data according to the 90<sup>th</sup>, 95<sup>th</sup> and 99<sup>th</sup> percentile values and performed threshold analysis. We also tested the goodness of fit for the model by using the Hosmer and Lemeshow test(19), and the results of the model fitted the data at an acceptable level.

All statistical tests were two-tailed with a type I error of 0.05, and *P* values < 0.05 were considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC) and Stata version 9.1 (Stata Corporation, College Station, Texas).

## **Results**

The participants in the highest Lp(a) lipoprotein quartile were less likely to be drinkers and in less professional jobs, compared with those in the lower quartiles (Table 1). Participants had similar distributions of female gender, the presence of smoking, regular exercise, marital status and education levels across quartiles. In addition, the participants had similar rates of the baseline hypertension, diabetes, and family history of coronary heart disease across different quartiles. A higher Lp(a) lipoprotein was associated with higher age, total cholesterol, LDL cholesterol, and non-HDL cholesterol, but had lower body-mass index and triglycerides, compared with lower Lp(a) lipoprotein levels. We did not find significantly different mean values of HDL-cholesterol, apolipoprotein A1 and apolipoprotein B across different quartiles of Lp(a) concentrations.

Over a median of 13.8-years' (inter-quartile range: 13.5-14.6 years) follow up among the 3,484 participants, we documented 210 cases of stroke (including 184 nonhemorrhagic stroke and 26 hemorrhagic stroke), 122 cases of coronary heart disease, and 781 cases of death (including 165 cardiovascular deaths). The incidence rates for each event increased appreciably for stroke and all-cause death as the Lp(a) lipoprotein quartiles increased, and the rates were approximately the same for coronary heart disease across quartiles (Table 2). The relative risks (RRs) comparing individuals in the highest quartile with those in the lowest quartile of Lp(a) lipoprotein 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 the multivariate analyses with adjusting for potential confounders, baseline Lp(a) lipoprotein by quartile values were not significantly associated with stroke, all-cause death, and coronary heart disease. However, we evaluated the risks of Lp(a) lipoprotein levels greater than or equal to the 90<sup>th</sup>, 95<sup>th</sup> and 99<sup>th</sup> percentiles (the cutoff levels of the study participant were 34.43 mg/dL, 47.08 mg/dL and 69.30 mg/dL, respectively) and we found the multivariate RRs increased with the cutoff selected and was significant for stroke at the 90<sup>th</sup> and 95<sup>th</sup> percentiles, and for total death at the 95<sup>th</sup> and 99<sup>th</sup> percentile (Table 3). However, the RRs for CHD showed a non-significantly increased trend,

with little power.

To address the possibility that risk of Lp(a) lipoprotein may have varied by different gender and age groups, we performed stratified analyses according to gender and age. The relationship between Lp(a) lipoprotein and stroke were not modified as a result of age and genders (all interaction *P* values >0.1)(Table 4). Among participants with age more than 65 years, the association between Lp(a) lipoprotein and stroke remained marginally significant after adjusting for multivariate risk factors, showing increasing risks of each quartile of Lp(a) lipoprotein, from the second (RR, 1.05), third (RR, 1.24) and fourth quartile (RR, 1.59, *P* for trend=0.055). However, we cannot find these patterns among participants younger than 65 years old.

## **Discussion**

We have previously reported on an association between cardiovascular risk factors and Lp(a) lipoprotein in the same participants cross-sectionally, and showed that Lp(a) lipoprotein was positively associated with low density lipoprotein and inversely associated with triglyceride and insulin resistance(13). In the present longitudinal study, Our data suggested that a threshold relationship with little gradient of risk across Lp(a) lipoprotein values for stroke and all-cause death among Chinese. We found marginally significant association between Lp(a) lipoprotein and stroke only in men of age 65 years and older. Moreover, the strength of association of Lp(a) and stroke was attributable to the ischemic subtype of stroke.

Different observational studies have provided the controversial evidence about the role of Lp(a) lipoprotein on stroke. Rigal and colleagues conducted a case-control study based on 100 cases of ischemic stroke and 100 matched controls on young adults (18-55 years old) and found that the relationship of Lp(a) lipoprotein to stroke remained significant only in men (odds ratio, 3.55, 95% CI, 1.33-9.48 for comparison of the highest and lowest tertile), but not in women (odds ratio, 0.42, 95% CI, 0.14-1.26)(20). In another case-control study based on Japanese, a high Lp(a) was related to ischemic stroke(21). However, the weakness of these studies due to small sample sizes and little confounding adjustments may invalidate the results. Nested case-control studies, measuring retrospectively stored Lp(a) lipoprotein concentrations which may be unstable, still did not prove significant association for further stroke(8, 22). Among the 198 incident stroke and 198 controls from a 7.5 years' follow-up cohort in the nearly 15000 healthy male physicians, Ridker and colleagues found no association between Lp(a) lipoprotein and incidence of stroke(8).

Results based on prospective cohort studies are still inconsistent about the risk of Lp(a) lipoprotein on cardiovascular events. Ariyo and colleagues traced the cardiovascular and death events of 3972 older adults, who were 65 years of age and older and Caucasian, for 7.4 years' follow up and found that the relationship of Lp(a) lipoprotein remained a significant predictor for stroke in men, but not for coronary heart disease(9). Also, they did not find significant association between Lp(a) lipoprotein and cardiovascular outcomes among older women. In addition, using a 3.2 years' follow-up cohort based on 5732 elder Caucasians who had received statin treatment, Gaw and colleagues did not find a statistical association between logarithm-transformed Lp(a) lipoprotein and stroke and coronary events in univariate analysis in

elderly men and women(10). Short durations of follow up may contribute to the cause of insignificant results. Among 27791 healthy women in the Women's Health Study who were most Caucasian and were followed for 10 years, a clear threshold effect by Lp(a) lipoprotein was seen(7): the association of Lp(a) lipoprotein and total cardiovascular events remained significant only in the extremely high levels of Lp(a) lipoprotein (the relative risk, 1.66, 95% CI, 1.38-1.99, comparing the participants above the 90th percentile with those below the percentile). Nearly no risk gradient at the lower Lp(a) lipoprotein quintiles was seen among these women. Inclusions of both coronary heart disease and stroke in the Women's Health Study may limit the biological plausibility for Lp(a) lipoprotein pathogenesis. Ohira and colleagues examined the association between Lp(a) lipoprotein and ischemic stroke among a biracial population of 14221 middle-age adults for 13.5-year follow-up period(11), and they found appreciable association only in African Americans and Caucasian women, but not in Caucasian men. Our data suggested a threshold effect for stroke: the risks above the 90<sup>th</sup> and 95<sup>th</sup> percentiles of Lp(a) lipoprotein had significant risk on stroke, implying that atherosclerotic burdens increased appreciably among individuals with extreme high Lp(a) levels.

Our negative results on Lp(a) lipoprotein in relation to coronary heart disease are comparable with previous cohort studies among the Caucasian and African American population(9, 10) but are not consistent to the positive association reported in the nested case-control study(23). Rifai and colleagues conducted a nested case-control study and collected Lp(a) lipoprotein and apolipoprotein(a) information from 195 men who developed severe coronary atherosclerosis during a 5-years' follow up and 195 matched control from the Physicians' Heart Study(23). Although two metaanalyses indicated significant association of Lp(a) lipoprotein and coronary heart disease risk, the results may not be valid for different populations because of heterogeneity of different participant characteristics and study(24, 25).

The inconsistency of findings among different studies is troublesome and begs explanation(26). One proposed explanation has been that Lp(a) lipoprotein has an interaction between other risk factors for further cardiovascular events. Different genders, young or older ages, and presence of high low density lipoprotein cholesterol and triglyceride levels were reported to modify the association of Lp(a) lipoprotein and cardiovascular events(3, 7, 9, 11, 20, 23). Our subgroup analysis did not provide significant interaction of Lp(a) lipoprotein and age as well as gender for cardiovascular risk. Our data suggested a potential relationship among older male Chinese, which was compatible with the findings from the Cardiovascular Health Study data(9). However, our subgroup results should be considered exploratory and require further investigation in larger studies. Specific high-risk population, including type 2 diabetes and hypercholesterolemia, may provide new evidence for the role of Lp(a) lipoprotein on cardiovascular disease(27).

Another possible explanation for the controversial results has been that Lp(a) lipoprotein may be only an indicator, not a hazard, for progressive atherosclerotic burden status. Researchers have demonstrated the presence of Lp(a) lipoprotein within the early atherosclerotic plaques in aorta and cerebral arteries(28). Blood levels of Lp(a) lipoprotein also correlated with subclinical atherosclerosis(29, 30), and thus reflected early pathophysiologic process that related

to vascular events.

To our knowledge, this is the first extensive investigation of Lp(a) lipoprotein and the risks of stroke, coronary heart disease and all-cause death among ethnic Chinese. Because of the prospective cohort design, the baseline measurements of all cohort members were unlikely to be affected by storage and laboratory issues that might be raised in some nested case-control studies. The use of a homogeneous community-based population could reduce the possibility of selection bias. We also included important socioeconomic status and lifestyle factors in the models to control the potential confounding factors. Finally, because few 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 coronary heart disease were relatively few, even with median 13.8-years' follow-up, which would reduce the power to detect the subtle effects between Lp(a) lipoprotein levels and make the relative risk estimation unstable. Second, because Lp(a) lipoprotein concentrations were measured only once, our results might be attenuated by intraindividual variations.

In conclusion, our data did not support the hypothesis that an increase in Lp(a) lipoprotein, over most of its range, was significantly associated with stroke, coronary heart disease and all-cause death among ethnic Chinese adults. At the same time, a small proportion of people with extremely high Lp(a) lipoprotein were at excess risk. These findings limit the use of Lp(a) lipoprotein as a biomarker in comprehensive evaluation of risk of cardiovascular disease in Chinese. However, a single measure of Lp(a) lipoprotein to identify the small subgroup with extreme values may have some utility.

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#### 計畫成果自評

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

可供推廣之研發成果資料表

**Table 1. Distribution of Various Baseline Demographic, Lifestyle, and Socioeconomic Factors in the Study Population in the CCCC cohort (1990-91), specified by Lp(a) lipoprotein quartiles**

Quartiles	1		2		3		4		P
	N=871	(%)	N=871	(%)	N=871	(%)	N=871	(%)	
Gender									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
Married status									0.10
Single	2.8		3.6		2.4		2.4		
Lived with spouse	88.0		85.5		85.8		84.1		
Divorced or separate	9.2		10.9		11.8		13.5		
Education level									0.14
<9 yr	93.3		93.2		95.2		95.1		
>=9 yr	6.7		6.8		4.8		4.9		
Job status									<.0001
No job	46.2		49.6		51.9		53.3		
Manual	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
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (yr)	53.2	11.5	54.2	12.5	55.6	12.2	56.6	12.8	<.0001
Body mass index	24.0	3.6	23.5	3.4	23.2	3.3	23.2	3.3	<.0001
TC	191.3	42.8	195.0	44.8	199.2	45.7	205.8	46.7	<.0001
Triglycerides	146.1	116.5	129.4	101.3	116.5	82.5	113.0	71.0	<.0001
HDL-Cholesterol	47.1	13.9	47.1	12.5	47.6	12.1	48.1	12.1	0.3
LDL- Cholesterol	131.2	42.0	135.0	43.2	139.6	44.3	145.4	46.0	<.0001
Non-HDL-C	143.8	43.8	147.6	45.1	151.7	45.5	157.5	47.3	<.0001
TC/HDL-C	4.39	1.62	4.40	1.52	4.42	1.42	4.53	1.50	0.2
ApoA1	136.0	54.4	132.3	28.5	133.8	26.4	132.7	26.3	0.1
ApoB	95.3	46.5	94.1	31.6	97.8	45.4	96.9	66.5	0.4
ApoB/A1	0.73	0.40	0.73	0.25	0.75	0.34	0.75	0.52	0.6

Abbreviation: Apo: apolipoprotein; CHD: coronary heart disease; SD: standard deviation; TC: total cholesterol;

**Table 2. Incidence Cases, Person-year, Incidence Rates and Relative Risks (and 95% Confidence Intervals) of Stroke, CHD, and All-cause Death outcomes during median 13.6 Years of Follow-Up According to Quartiles of Baseline Lp(a) Lipoprotein Concentrations in 1990-91 in the CCCC Study**

	1	2		3		4		P, trend
Stroke								
Cases	47	42		48		68		
Person-Years	11044	10986		10852		10578		
Rates	4.3	3.8		4.4		6.4		
Model 1	1	0.92	( 0.60 - 1.40 )	1.04	( 0.69 - 1.57 )	1.56	( 1.07 - 2.28 )	0.003
Model 2	1	0.85	( 0.55 - 1.29 )	0.87	( 0.58 - 1.31 )	1.19	( 0.81 - 1.74 )	0.12
Model 3	1	0.85	( 0.55 - 1.30 )	0.89	( 0.58 - 1.34 )	1.23	( 0.84 - 1.81 )	0.09
Model 4	1	0.88	( 0.58 - 1.36 )	0.90	( 0.60 - 1.37 )	1.21	( 0.83 - 1.79 )	0.13
Model 5	1	0.87	( 0.56 - 1.34 )	0.90	( 0.59 - 1.37 )	1.20	( 0.81 - 1.78 )	0.14
Coronary artery disease								
Cases	33	25		30		31		
Person-Years	11086	11058		10865		10693		
Rates	3	2.3		2.8		2.9		
Model 1	1	0.76	( 0.45 - 1.28 )	0.93	( 0.57 - 1.52 )	0.98	( 0.60 - 1.60 )	0.74
Model 2	1	0.71	( 0.42 - 1.20 )	0.82	( 0.50 - 1.34 )	0.81	( 0.49 - 1.32 )	0.68
Model 3	1	0.76	( 0.45 - 1.27 )	0.84	( 0.51 - 1.40 )	0.89	( 0.54 - 1.47 )	0.95
Model 4	1	0.77	( 0.46 - 1.30 )	0.86	( 0.52 - 1.42 )	0.89	( 0.54 - 1.47 )	0.92
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	175	170		193		211		
Person-Years	11216	11151		10978		10764		
Rates	15.6	15.2		17.6		19.6		
Model 1	1	0.98	( 0.79 - 1.21 )	1.13	( 0.92 - 1.39 )	1.26	( 1.03 - 1.54 )	0.007
Model 2	1	0.88	( 0.71 - 1.09 )	0.91	( 0.74 - 1.12 )	0.93	( 0.76 - 1.13 )	0.78
Model 3	1	0.88	( 0.71 - 1.09 )	0.90	( 0.73 - 1.11 )	0.91	( 0.74 - 1.12 )	0.68
Model 4	1	0.89	( 0.72 - 1.11 )	0.91	( 0.74 - 1.12 )	0.91	( 0.74 - 1.12 )	0.61
Model 5	1	0.88	( 0.71 - 1.09 )	0.92	( 0.74 - 1.13 )	0.91	( 0.73 - 1.12 )	0.62

Incidence rates presented as per 1000 person yrs. Model 1: univariate; Model 2: adjusted for age groups (35-44, 45-54, 55-64, 65-74, >=75 years old) and gender, Model 3: Model 2 plus body mass index (<18, 18 to 20.9, 21 to 22.9, 23 to 24.9, or >=25 kg/m<sup>2</sup>), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status(single, married and living with spouse, or divorced and separate), education level (less than 9 years, at least 9 years), occupation (no work, labor, official or business), regular exercise habit (yes/no), and family history of coronary heart disease (yes/no), Model 4: plus hypertension(yes/no) and diabetes mellitus (yes/no), Model 5: plus HDL-C and LDL-C levels.

**Table 3. Multivariate relative risks and 95% confidence intervals of stroke, CHD, and all-cause death outcomes during median 13.6 Years of Follow-Up According to the 90<sup>th</sup>, 95<sup>th</sup> and 99<sup>th</sup> percentile values of Baseline Lp(a) Lipoprotein Concentrations in 1990-91 in the CCCC Study**

	Relative risk*	95% CI	P
<b>Stroke</b>			
>=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
<b>CHD</b>			
>=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
<b>All-cause death</b>			
>=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

\*Adjusted variables included age groups (35-44, 45-54, 55-64, 65-74, >=75 years old), gender, body mass index (<18, 18 to 20.9, 21 to 22.9, 23 to 24.9, or >=25 kg/m<sup>2</sup>), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status(single, married and living with spouse, or divorced and separate), education level (less than 9 years, at least 9 years), occupation (no work, labor, official or business), regular exercise habit (yes/no), family history of coronary heart disease (yes/no), hypertension(yes/no), diabetes mellitus (yes/no), HDL-C and LDL-C levels.

**Table 4. Stratified Analysis of Relative Risks for Stroke, CHD, and All-cause Death outcomes during median 13.6 Years of Follow-Up According to Quartiles of Baseline Lipoprotein(a) Concentrations, Stratified by Age groups (<65 years and ≥65 years) and Genders**

Quartiles	1	2	3	4	P for trend	P for interaction
<b>Stratified by age</b>						
Stroke						0.67
Age <65 years	1	0.78	0.70	1.02	0.71	
Age ≥65 years	1	1.05	1.24	1.59	0.055	
Coronary artery disease						0.25
Age <65 years	1	0.80	0.88	0.53	0.13	
Age ≥65 years	1	0.64	0.74	1.06	0.37	
All-cause death						0.32
Age <65 years	1	0.72	0.95	0.90	0.96	
Age ≥65 years	1	1.01	1.02	1.10	0.44	
<b>Stratified by gender</b>						
Stroke						0.94
Men	1	0.87	0.81	1.17	0.31	
Women	1	0.86	1.01	1.26	0.24	
Coronary artery disease						0.78
Men	1	0.70	0.92	0.80	0.75	
Women	1	0.88	0.67	0.83	0.72	
All-cause death						0.11
Men	1	0.89	0.82	0.81	0.19	
Women	1	0.87	1.15	1.15	0.20	

Adjusted variables included age groups (35-44, 45-54, 55-64, 65-74, ≥75 years old) [except stratified by age], gender [except stratified by gender], body mass index (<18, 18 to 20.9, 21 to 22.9, 23 to 24.9, or ≥25 kg/m<sup>2</sup>), smoking (yes/no or abstinence), current alcohol drinking (regular/no), marital status (single, married and living with spouse, or divorced and separate), education level (less than 9 years, at least 9 years), occupation (no work, labor, official or business), regular exercise habit (yes/no), family history of coronary heart disease (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), HDL-C and LDL-C levels.

## 附錄

### From *Clinical Chemistry* Editorial Office

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Chien, Kuo-Liong

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