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Lipoprotein (a) level in the population in Taiwan: relationship to sociodemographic and atherosclerotic risk factors

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Abstract

To examine the lipoprotein(a) (Lp(a)) level in the Taiwanese population and its association with cardiovascular risk factors, 1703 men and 1899 women aged 35 years and above were enrolled in a community-based study cohort established between 1990 and 1991. The distributions of Lp(a) levels were skewed to the right, and females were more likely than males to have Lp(a) levels greater than 30 mg/dl (14.3% versus 11.6%, $P < 0.05$). The Lp(a) level increased with age. Socioeconomic status did not seem to have consistent influence on the level of Lp(a). Smoking and alcohol use also had no effect on Lp(a) levels. Multivariate analysis indicated that older age and high level of low-density-lipoprotein cholesterol corresponded to an elevated Lp(a) level, while hypertriglyceridemia, low high-density-lipoprotein cholesterol level, obesity and high insulin resistance corresponded to a lower Lp(a) level. In univariate analysis, hyperinsulinemia was negatively associated with Lp(a) level (-0.107, $P < 0.01$) only in males. In females, use of oral contraceptive lowered Lp(a) levels, but menopause did not change Lp(a) levels. We also found that different correlation patterns existed for selected coagulation profiles between sexes. There was a significant correlation between Lp(a) and fibrinogen levels in males (0.154, $P < 0.001$) but not in females (0.007, $P > 0.05$). These data provided clues for investigating atherosclerotic risk factors and coagulation parameters for the Taiwanese population.

Keywords: Lipoprotein(a); Atherosclerosis; Taiwanese; Population-based

1. Introduction

Lipoprotein(a) (Lp(a)), consisting of low density lipoprotein and apolipoprotein(a) with disulfide binding, has been well established as a cardiovascular risk factor [1,2]. Apolipoprotein(a) is a glycoprotein with its DNA locus on the sixth chromosome, near the plasminogen loci that has size polymorphism [3]. The structure of apolipoprotein(a) is similar to plasminogen; it can interfere with hemolytic functions and increase the time required for clot hemolysis by competing with the plasminogen receptor[4]. Found in the arterial walls of patients with coronary artery disease, according to experimental studies, Lp(a) can penetrate the intimal layers of vessel walls to stimulate foamy-cell production and is considered a risk factor in atherogenesis and thrombosis. Along with excess serum low-density lipoprotein cholesterol (LDL-C) or other risk factors, Lp(a) may synergistically contribute to the incidence of cardiovascular disease[5].

Although Lp(a) levels have strong genetic links and are neither affected by life style nor altered by medication[6], factors associated with Lp(a) concentrations and other atherosclerotic risk factors remain elusive. The Framingham offspring study demonstrated that serum Lp(a) concentration increased with age, only in

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women [7]. Correlations with other atherosclerotic risk factors, such as sex, smoking, waist-to-hip ratio, impaired glucose tolerance, selected medications, fibrinogen levels, and blood pressure, have also been demonstrated [8–10]. However, most studies are hospital-based or employee-based [11] and limited data are available for Asian populations. Only a few studies on Chinese ethnic groups are available and have provided inconsistent data on Lp(a) due to small sample size [12,13].

The Chin-Shan Community Cardiovascular Cohort (CCCC) study is a population-based prospective investigation on the impact of atherosclerotic risk factors in the development of cardiovascular diseases in adults 35 years of age and older. This report attempted to determine the Lp(a) distribution for this cohort in which a large number of demographic, cardiovascular, lipid profiles and other hemostatic parameters were available. Evaluations emphasize the correlations between these variables.

2. Materials and methods

2.1. Study design and population

The study cohort, consisting of 1703 men and 1899 women, 35 years old and above, was established in 1990 and 1991. All were recruited based on 1990 residential registration files ($N = 4399$) in the Chin-Shan community, a suburban community 20 miles outside of metropolitan Taipei. The response rate was 82.8%. Among the non-respondents, 95 were refusals and 652 could not be reached, based on the registration, and were somewhat younger than respondents. The current report uses baseline data collected in 1990–1991, and ultrasound results and coagulation profiles collected in 1992–1993. The leading causes of deaths, mainly from cardiovascular disease and cancer in this community, mirror national mortality patterns in Taiwan between 1990 and 1994 [14].

2.2. Data collection and interpretation

A clinic was set up at the Chin-Shan Community Health Center by a study team consisting of 20 senior medical students, two assistant nurses and 10 cardiologists and local practitioners. Trained medical students canvassed door-to-door with the assistance of community leaders to extend invitations for the baseline survey. Information collected included sociodemographic characteristics, lifestyle, dietary characteristics, personal and family histories of diseases and hospitalizations, etc. With the consent of participants, the team of physicians and students conducted physical examinations and laboratory tests on those participants invited to the clinic. A 12-lead electrocardiography was also performed for each participant, and the result was evaluated by a cardiologist.

2.3. Blood sampling and analytical methods

All venous blood samples were drawn after a 12-h overnight fast, immediately refrigerated and transported to National Taiwan University Hospital within 6 h. Serum samples were then stored at -70°C prior to batch assay of the concentrations of total cholesterol, triglyceride, LDL-C, high density lipoprotein cholesterol (HDL-C), and Lp(a) [15]. Standard enzymatic tests for serum cholesterol and triglyceride were used (Merck 14354 and 14366, respectively). HDL-C levels were measured in supernatants after precipitation with magnesium chloride phosphotungstate reagents (Merck 14993). LDL-C concentrations were calculated as 'total cholesterol minus cholesterol in the supernatant' by the precipitation method [16], since the HDL-C was precipitated using heparin/citrate reagent (Merck 14992). Apolipoprotein A1 (apo A1) and apolipoprotein B (apo B) concentrations were measured by turbidimetric immunoassay using commercial kits (Sigma). Lp(a) was determined by enzyme-linked immunosorbent assay (ELISA) (Organon) regardless of isoforms. The plasma insulin level was determined using the ELISA method in which a reagent kit supplied by Dako is employed. The plate antibody binds A-chains somewhere near the intra-chain disulphide. The conjugate antibody binds very close to the cleavage site in proinsulin and its epitope is partially composed of lysine residue at position 30 on the B-chain. Thus, the assay will not measure intact proinsulin, but provides specificity of the insulin assay [17].

2.4. Coagulation profile measurement

The measurements of coagulation profiles were made in the following manner: Tissue plasminogen activator (TPA) was analyzed using enzyme immunoassay (Asserachrom tPA, Diagnostica Stago, France), and plasminogen activator inhibitor (PAI-1), Factor VII antigen, and fibrinogen were measured using commercial kits. PAI-1 was measured using enzyme immunoassay (Asserachrom PAI-1, Diagnostica Stago, France). Factor VII antigen was measured using enzyme immunoassay (Asserachrom VII: Ag, Diagnostica Stago, France). Fibrinogen was measured using clotting assay (STA-Fibrinogen, Diagnostica Stago, France). Factor VIII concentration was measured using single-stage assay [18].

2.5. Diagnostic criteria

Hypertension was defined according to the criteria established by the Fifth Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure [19]. We adapted the following criteria: systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg, and/or receiving anti-hypertensive medication. The presence of coronary heart disease was defined as the presence of abnormal Q or QS patterns on electrocardiograms, or clinical histories of myocardial infarction or angina pectoris, based on medical records. Stroke was defined as hemiparesis or hemiplegia histories, and confirmed by a neurologist. Diabetes mellitus was defined as fasting blood sugar levels higher than 140 mg/dl or use of oral hypoglycemic agents or insulin injections. The 90th percentile values of body-mass indices (BMI) and waist-to-hip ratios (WHR) were considered normal for the study population. Hyperinsulinemia was defined as fasting insulin levels greater than the 90th percentile values for each gender. Mathew's homeostasis modeling formula for insulin resistance were calculated [20]. Women older than 45 years with secondary amenorrhea for longer than 1 year were defined as in menopausal status.

2.6. Statistical analysis

We first compared the distribution pattern of serum Lp(a) concentrations by age and gender. Because of the highly right-skewed distribution of Lp(a) values, the natural logarithm of Lp(a) was used to normalize its distribution to satisfy analysis of covariance assumption. Gender- and age-specific quartiles of Lp(a) values were generated from logarithmically transformed Lp(a). Age-adjusted geometric means of Lp(a) by gender were also calculated to measure the effects of lipid level, BMI, WHR and hyperinsulinemia. The total cholesterol and LDL cholesterol cut-off points were according to NCEP guidelines. Both the 75th and 90th percentile cut-off points were used for the rest of the variables (Table 2). A Spearman correlation analysis was performed to measure the linear relationship between covariates and L(a) values. One-way analysis of covariance with adjustment for age was employed for comparison of the mean values. When using parametric procedures, triglyceride and Lp(a) levels were transformed into natural logarithms. A significant difference was defined at $P < 0.05$. Several optional multivariate analysis models were further developed using either stepwise regression or Mallows' C(p) method to summarize factors contributing to the Lp(a) level [21]. Data analysis was performed using the SAS 6.11 version [22].

3. Results

The empirical distribution of serum Lp(a) levels for the study population clearly demonstrated a right skewed shape, ranging widely from 0.11 to 116.9 mg/dl in men, and from 0.11 to 129.4 mg/dl in women (data not shown). The Lp(a) values were undetectable in 1.0% of the males and 0.8% of the females. Table 1 details the gender- and age-specific distributions and the proportions of Lp(a) greater than 30 mg/dl. As age increased, the Lp(a) levels increased in both genders, peaking at 65–74 years of age for men (geometric mean

Table 1
The distribution of lipoprotein(a) levels (mg/dl) in the study population by sex and age: the Chin-Shan Community Cardiovascular Cohort Study, 1990–1991

Sex, age	Number	Geometric mean (S.D.)	Percentile					≧30 mg/dl (%)
			10	25	50	75	90	
Male								
35–44	381	12.0 (12.9)	1.3	3.3	7.1	16.3	28.8	8.9
45–54	376	12.7 (16.1)*	1.0	2.6	7.1	16.0	30.6	10.1
55–64	473	14.4 (16.1)	1.4	3.8	9.6	18.9	35.2	12.5
65–74	292	16.0 (15.3)	2.3	5.1	11.2	21.2	37.9	15.1
≧75	102	15.9 (15.9)	1.9	5.4	10.3	22.1	34.3	12.8
All	1624	13.8 (15.3)	1.3	3.7	8.6	18.4	32.3	11.6[a]
Female								
35–44	527	13.3 (15.5)	1.5	3.7	8.3	17.0	33.7	12.9
45–54	498	14.1 (15.4)*	1.4	3.8	8.6	17.8	36.9	13.9
55–64	439	14.5 (15.5)	1.1	3.5	9.5	19.9	37.3	15.5
65–74	286	15.3 (16.0)	1.9	4.4	10.6	20.7	36.8	13.6
≧75	109	18.1 (17.6)	2.8	6.1	12.3	24.4	43.0	19.3
All	1859	14.4 (15.4)	1.5	4.0	9.1	19.1	36.2	14.3[a]

* $P < 0.05$ by the unpaired t-test for males versus females in the 45–54 years age group.
[a] Difference between each sex: 2.7%, 95% confidence interval: (0.6%, 4.9%).

Table 2
Age-adjusted geometric mean of lipoprotein(a) (mg/dl) by atherosclerotic risk factor in the study population: the Chin-Shan Community Cardiovascular Cohort Study, 1990–1991

Risk factor	Men			Women		
	Number	Mean[a]	S.E.M.[b]	Number	Mean	S.E.M.
Cholesterol level						
<200 mg/dl	993	6.80	1.04	968	7.11	1.04
200–240 mg/dl	405	7.96*	1.07	524	8.35*	1.06
≥240 mg/dl	223	8.52*	1.09	365	9.29***	1.07
LDL-C level						
<130 mg/dl	851	6.39	1.05	806	7.22	1.05
130–160mg/dl	379	8.00**	1.07	475	7.74	1.06
≥160 mg/dl	394	8.84***	1.07	578	8.92**	1.06
Body-mass index[c]						
<75th%	674	7.85	1.05	854	8.26	1.04
≥75th%	223	5.77**	1.09	273	6.87*	1.08
<90th%	806	7.69	1.04	1015	8.08	1.04
≥90th%	91	4.41***	1.15	112	6.37	1.13
Waist–hip ratio[c]						
<75th%	734	7.89	1.05	924	7.95	1.04
≥75th%	251	6.06**	1.09	318	7.53	1.08
<90th%	893	7.61	1.04	1136	7.85	1.04
≥90th%	92	5.43*	1.14	106	7.73	1.14
Fasting insulin level[c]						
<75th%	693	7.83	1.05	895	8.13	1.04
≥75th%	232	5.26***	1.09	299	7.19	1.08
<90th%	832	7.33	1.05	1074	8.11	1.04
≥90th%	93	5.20*	1.15	120	6.10*	1.12
Insulin resistance by HOMA[c]						
<75th%	693	7.76	1.05	895	8.26	1.04
≥75th%	232	5.40***	1.09	298	6.81*	1.08
<90th%	832	7.37	1.05	1072	8.06	1.04
≥90th%	93	4.94**	1.15	121	6.44	1.12

[a] Geometric mean.
[b] S.E.M., standard error of mean.
* $P<0.05$, compared for counterpart stratum by genders.
** $P<0.01$, compared for counterpart stratum by genders.
*** $P<0.001$, compared for counterpart stratum by genders.
[c] Sex-specific 75th or 90th percentile value.

16.0 mg/dl) and 75 years of age or above for women (geometric mean 18.1 mg/dl). Generally, geometric means of Lp(a) levels were higher in females than in males, and the difference was statistically significant for the 45–54 age group. The proportion of individuals with 30 mg/dl Lp(a) or greater also increased as age increased and was greater in females than in males (14.3% versus 11.6%, $P<0.05$), with the greatest difference in the oldest group(19.3% in women and 12.8% in men, $P<0.05$).

Analyses also attempted to distinguish age-adjusted Lp(a) levels by smoking, drinking, educational attainment, marital status and occupation. Decreased levels were found for male government employees, teachers and businessmen (5.80 mg/dl for white-collar workers versus 7.92 mg/dl for blue collar workers, $P<0.01$; data not shown).

Table 2 shows age-adjusted Lp(a) concentration distributions by gender and selected atherosclerotic risk factors. The geometric means of Lp(a) were significantly elevated for both men and women with higher levels of cholesterol, LDL-C and triglyceride or lower HDL-C level. The obese group (BMI 90th percentile) exhibited a significant lower Lp(a) level than the non-obese group, regardless of sex. This association was significant for males only when the central-obesity group was defined as having a waist-to-hip ratio at the 90th percentile or greater that had lower Lp(a) levels (5.43 mg/dl versus 7.61 mg/dl, $P<0.05$).

Table 2 also shows that individuals with hyperinsulinemia had much lower Lp(a) levels than non-hyperinsulinemics, significant for both men (5.20 mg/dl versus 7.33 mg/dl, $P<0.05$) and women (6.10 mg/dl versus 8.11 mg/dl). The distribution of Lp(a) was relatively unaffected by menopause and cardiovascular disorders, including hypertension, diabetes mellitus, coronary heart disease and stroke. However, women taking oral contraceptives had significantly lower age-adjusted

Table 3
Spearman correlation coefficients, γ, between lipoprotein(a) levels and various lipid and obesity profiles in the study population: the Chin-Shan Community Cardiovascular Cohort study, 1990–1991

Covariates	Male		Female	
	Number	γ	Number	γ
Age	1624	0.122**	1859	0.078**
BMI	897	−0.122**	1127	−0.065*
WHR	985	−0.063*	1224	0.014
Systolic blood pressure	1617	0.018	1849	0.007
Diastolic blood pressure	1617	−0.045	1849	−0.034
Cholesterol	1621	0.104**	1857	0.131**
Triglyceride	1620	−0.120**	1857	−0.090**
HDL-C	1599	0.038	1844	0.045
LDL-C	1596	0.117**	1837	0.123**
Apo A1	1064	−0.049	1350	0.025
Apo B	1063	−0.014	1350	−0.002

* $P<0.05$.
** $P<0.001$.

Lp(a) levels than women who did not take them (4.55 mg/dl versus 7.78 mg/dl, $P<0.05$).

The Spearman correlations between Lp(a) and lipid profiles and other atherosclerotic risk factors are presented by gender in Tables 3 and 4. For both sexes, Lp(a) had significant positive correlations with age, total cholesterol and low-density cholesterol, and significant negative correlations with body-mass index, triglycerides and plasminogen activator inhibitors (Table 3). Lp(a) was negatively associated with apo A1 and apo B levels, but was not significant. We also found significant negative relationships between Lp(a) and serum insulin profiles, fasting glucose, TPA and PAI-1 for men, and PAI-1 for women (Table 4). The Lp(a) level was significantly correlated with fibrinogen (0.154, $P<0.001$) among males only.

Table 4
Spearman correlation coefficients between lipoprotein(a) levels and various atherosclerotic risk-factor profiles in the study population: the Chin-Shan Community Cardiovascular Cohort study in Taiwan, 1990–1991

Covariates[a]	Male		Female	
	Number	γ	Number	γ
AC insulin	925	−0.140***	1194	−0.047
PC insulin	897	−0.099**	1154	−0.037
AC glucose (mg/dl)	933	−0.107**	1195	−0.019
FVII antigen	1004	−0.000	1171	−0.009
FVIII	1006	0.033	1169	0.004
TPA	1006	−0.065*	1171	−0.043
PAI	1006	−0.093**	1171	−0.075**
Fibrinogen	1006	0.154***	1171	0.007

[a] AC, fasting; PC, 2 h post 75 g glucose intake; FVII, factor VII; FVIII, factor VIII; TPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor.
* $P<0.05$.
** $P<0.01$.
*** $P<0.001$.

Table 5
Multivariate model by Mallows' C(p) criteria of variable selection

Covariate[a]	β	S.E.	P value
Intercept	2.071	0.042	0.0001
Age (65–74 vs. 35–44)	0.164	0.081	0.0427
TG ($\geqq$200 mg/dl vs. <200 mg/dl)	−0.349	0.092	0.0002
HDL (<35 mg/dl vs. $\geqq$35 mg/dl)	−0.166	0.081	0.0403
LDL ($\geqq$160 mg/dl vs. <160 mg/dl)	0.310	0.066	0.0001
BMI ($\geqq$75th percentile vs. < 75th percentile)	−0.162	0.074	0.029
HOMA ($\geqq$75th percentile vs. < 75th percentile)	−0.182	0.074	0.0141
Intercept	2.039	0.040	0.0001
Age (65–74 vs. 35–44)	0.168	0.081	0.0373
TG ($\geqq$200 mg/dl vs. <200 mg/dl)	−0.365	0.092	0.0001
HDL (<35 mg/dl vs. $\geqq$35 mg/dl)	−0.188	0.080	0.0194
LDL ($\geqq$160 mg/dl vs. <160 mg/dl)	0.300	0.066	0.0001
BMI ($\geqq$90th percentile vs. < 90th percentile)	−0.296	0.100	0.0032
HOM ($\geqq$90th percentile vs. < 90th percentile)	−0.152	0.101	0.1311

[a] Covariates are: sex, age (45–54 years old versus 35–44 years old), age (55–64 years old versus 35–44 years old), age (64–74 years old versus 35–44 years old), age ($\geqq$75 years old versus 35–44 years old), hypercholesterolemia, hypertriglyceridemia, low HDL-C, high LDL-C, obesity, high WHR, diabetes status, hypertension status, insulin resistance index by homeostatsis modelling HOMA.

The multivariate model obtained from Mallows' C(p) showed that factors significantly associated with the Lp(a) level included older age groups, triglyceride (200 mg/dl versus <200 mg/dl), HDL-C (<35 mg/dl versus 35 mg/dl), LDL(160 mg/dl versus <160 mg/dl) and high BMI (Table 5). Triglyceride and LDL were the most significant influential factors. Hyperinsulinemia influence would become significant if the cut-off for this variable was set at the 75th percentile in this model.

4. Discussion

The Lp(a) and other blood-chemistry measured for 3602 native Taiwanese men and women in the population-based study provided a unique opportunity to observe how Lp(a) is associated with other atheroscle-

rotic risk factors in this Chinese population. The distribution of Lp(a) was skewed to the right, similar to that found for Caucasians [1,7], higher in females than in males, and positively correlated with age. The range of Lp(a) levels for this study population seemed similar to that for the Framingham offspring [7], and significantly lower than that for Japanese and black populations [23,24].

A limited number of studies have reported the median values of Lp(a) for other Chinese ethnic groups, ranging from 7.0 mg/dl for Chinese in Singapore to 25.0 mg/dl for Chinese in Hong Kong [3,12]. However, those measures were based on small sample sizes between 30 and 304. To our knowledge, this study was the largest study based on a healthy Chinese community, and based on a large-scale population.

The relationships between Lp(a) and other atherosclerotic risk factors vary among studies [7,8,23–27]. Studies based on the Japanese population have demonstrated significant correlations between Lp(a) and cholesterol and LDL-C levels[23,25]. We did observe striking differences in Lp(a) distributions by lipid profiles; the average Lp(a) levels were elevated for individuals with hypercholesterolemia and high LDL-C levels in both genders. However, several studies report a negative correlation between levels of Lp(a) and triglyceride [7,23,28–30]. Since hypercholesterolemia, high LDL-C, low HDL-C and/or hypertriglyceridemia have been considered important atherosclerotic risk factors, much of the relationship between Lp(a) and these lipid profiles remains to be understood, particularly concerning the control of Lp(a) metabolism and its role in atherosclerosis. The negative correlation between Lp(a) and triglyceride levels and the positive correlation between Lp(a) and LDL-C levels are puzzling and deserve further investigation.

Because of common metabolic pathways for insulin resistance syndrome, including hypertriglyceridemia, low HDL-C, and obesity, we observed a strong negative correlation between Lp(a) and insulin, glucose and insulin-related metabolic factors. Regardless of whether hyperinsulinemia was defined as above the 75th percentile or the 90th percentile of fasting insulin levels for the population, the average Lp(a) was significantly lower in hyperinsulinemic males than in non-hyperinsulinemic males. A similar pattern was observed for females, but not as significantly as that for males. The Lp(a) level and obesity also exhibited a similar gender-specific pattern. This finding may explain the gender difference in the pathogenesis of atherogenesis as noted in other studies [31,32] and may imply that some complex mechanisms associating Lp(a) with insulin resistance syndrome deserve further investigation.

In our studies, blood pressure levels and the presence of hypertension, diabetes mellitus, coronary heart disease and stroke status did not have significant correlations with Lp(a) levels. Other studies suggest coronary artery disease events are related to excess Lp(a) levels [33–35], but definitive causation is unproved, and may be due to population-specific characteristics.

The Lp(a) level may be elevated for women in the menopause and lowered for those with oral estrogen. The menopausal association was not as significant in the Framingham Offspring study and the Japanese study [7,23], but was significant in the Northern Sweden MONICA study [8]. In our study, menopausal status had no influence on Lp(a) levels. However, women who took oral contraceptives may have been younger and, therefore, had significantly lowered age-adjusted Lp(a) levels than women who did not use oral contraceptives. Similar results were also reported by Lobo et al. [36].

In the coagulation profiles study, we found that in males, the Lp(a) level was closely correlated with fibrinogen levels, but inversely correlated with TPA and PAI-1. In females, only PAI-1 levels were inversely significantly correlated with Lp(a) levels. Lp(a) is presumed to be a dual risk factor for both atherogenesis and thrombosis, and may play different roles in males and females. Other studies reported significant associations between Lp(a) levels and fibrinogen levels in females rather than in males [23,37,38]. In this study, a significant association between Lp(a) and fibrinogen level was found for males only. This gender discrepancy may underscore the pathogenesis of Lp(a) thrombosis in different sexes.

In conclusion, this community-based population study showed that Lp(a) levels were: (i) higher in women than in men; (ii) positively associated with atherosclerotic risk factors such as LDL-C, and negatively associated with HDL-C and triglyceride; and (iii) positively associated with selected coagulation profiles such as fibrinogen, and negatively associated with TPA and PAI. Lp(a) levels had no strong association with coronary heart disease, stroke, hypertension, and diabetes mellitus. However, individuals with the insulin resistance syndrome, including those with high triglyceride, low HDL-C, obesity and high insulin levels, levels tended to have lowered Lp(a) level. These relationships in Lp(a) atherosclerosis and thrombosis pathogenesis should be explored further, using longitudinal data that will be available from our Chin-Shan cohort in the next few years.

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