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Associations between fibrinogen levels and the risk of cardiovascular disease and all-cause death: a cohort study from the Chin-Shan community in Taiwan

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ABSTRACT

Objectives Although several studies have investigated the association between fibrinogen level and the risk of cardiovascular disease (CVD), few studies have been conducted in Asia.

Setting We conducted a community-based prospective cohort study in the Chin-Shan community, Taiwan.

Participants A total of 2222 participants (54.6±11.9 years, 53.4% women, and 22.4 years of follow-up) who underwent plasma fibrinogen measurements and were without CVD at baseline were recruited, among which 735 participants with available C reactive protein (CRP) were included in the joint analysis of the association of fibrinogen and CRP levels with the risk of CVD.

Primary and secondary outcome measures Fibrinogen and CRP levels were measured by clotting and high-sensitivity immunoturbidimetric assays, respectively. The study outcomes were CVD events and all-cause death. Our definition of CVD included both coronary artery disease (CAD) and stroke cases. Cox proportional hazards regression models were used to estimate the HRs and 95% CIs.

Results Compared with the lowest quartile, participants with higher fibrinogen levels tended to have a higher risk of CAD (adjusted HR for the highest quartile=1.48 (95% CI 0.90 to 2.44); test for trend p=0.037) regardless of CRP level (adjusted HR=2.12 (95% CI 1.24 to 3.63) and 2.17 (95% CI 1.06 to 4.44) for high fibrinogen/low CRP and high fibrinogen/high CRP, respectively). The association was not observed for stroke (adjusted HR for the highest quartile=0.99 (95% CI 0.62 to 1.60); test for trend p=0.99) and was only observed for all-cause death among participants <65 years of age (adjusted HR for the highest quartile=1.47 (95% CI 1.11 to 1.95); test for trend p=0.004).

Conclusions Fibrinogen may be a potential risk factor for CAD but not for stroke. Further studies are necessary to clarify the differences in the role of fibrinogen levels on the risk of CVD between Asian and Western countries.

Strengths and limitations of this study

- ► The community-based prospective study design in the present study avoided the potential selection and information bias for data collection.
- ► Considered the role of C reactive protein for the association of fibrinogen level with the risk of coronary artery disease.
- ► Only a single measurement of fibrinogen levels was performed.

INTRODUCTION

Cardiovascular diseases (CVDs), including coronary artery diseases (CAD) and stroke, are the leading causes of mortality, morbidity and disability-adjusted life-years worldwide, accounting for approximately one-third of all deaths globally.[1 2] Although there are many causes of CVD, most cases are related to atherosclerosis, a condition that develops owing to the build-up of plaque on arterial walls. Previous studies have shown that the progression of atherosclerosis is associated with inflammation.[3–5]

Fibrinogen, the major coagulation protein, is the substrate of thrombin, which forms fibrin during clot formation.[6] Fibrinogen is a well-known marker of inflammation.[7] Fibrinogen, as an inflammatory marker, was associated with subclinical CVD[8–11] and CAD[4 5 11] in Western countries; however, evidence for the association between fibrinogen level and stroke was relatively limited and the results were still inconsistent.[4 12 13] Moreover, C reactive protein (CRP), also a reactant of inflammation synthesised by the liver,[14–16] has been proved to be a risk factor for CVD.[17–20] Like fibrinogen, CRP levels increases sharply in response to inflammation.[21] It is possible that the associations that were observed between fibrinogen levels and the risk of CVD in previous studies were due to high CRP levels. However, few studies have considered the roles of CRP when investigating the associations between fibrinogen levels and CVD risk.

Although several studies have investigated the associations between fibrinogen levels

and the risk of CVDs, most were conducted in the Western countries. However, the disease patterns in Asia differ from those in Western countries[22 23] and some studies have reported ethnic differences in fibrinogen levels.[24 25] We found only one study investigating the association between fibrinogen levels and the risk of stroke in the general population in Asian countries[26] and no study has considered the roles of CRP in the association between fibrinogen level and CVD. Therefore, we conducted a community-based cohort study in the Chin-Shan community, Taiwan. The main purpose of this study was to investigate the associations of fibrinogen levels with the risk of CAD, stroke, and all-cause death. We also investigated the association of fibrinogen and CRP combined levels with the risk of CVD.

METHODS

Study design and participants

The details of the present cohort study have been described in previous publications.[27–30] Briefly, the Chin-Shan Community Cardiovascular Cohort study was a prospective cohort study that began in 1990–1992 and followed the participants until 2014. All participants resided in the Chin-Shan community (30 km north of metropolitan Taipei, Taiwan). First, we contacted 4349 individuals and 747 (17.2%) of whom did not respond. The 3602 (response rate 82.8%) respondents (1703 men and 1899 women) were all ≥35 years at the start of the study. The present study included 2222 individuals (61.68%) with available fibrinogen measurements. In 1994, CRP levels were measured during the follow-up examinations. Among the participants with available fibrinogen measurements, 735 also had available CRP data. The flow diagram was shown in online supplemental figure 1). We used the CRP measurements in 1994 and fibrinogen measurements in 1992 to divide the 735 participants into four groups (low fibrinogen/low CRP, high fibrinogen/low CRP, low fibrinogen/high CRP, high fibrinogen/high CRP) for further joint analysis.

Covariates

Baseline information such as demographic characteristics, lifestyle factors, dietary characteristics and personal and family histories of diseases and hospitalisation was collected by trained medical students using interview questionnaires in biennial follow-up cycles performed up to 2014. Laboratory tests were conducted by a physician and senior medical students with the consent of the participants. All blood samples were evaluated at the National Taiwan University Hospital. In the present study, we adjusted for sex, age group, body mass index (BMI), smoking status (yes or no (never or quit smoking)), drinking status (yes or no, defined as ≥1 drink per day), regular exercise (yes or no, defined as ≥30 min/day of moderate-intensity physical activity such as walking or cycling), hypertension status (yes or no, defined as a baseline systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg or using of hypertensive medication), diabetes status (yes or no, defined as a baseline fasting glucose level of ≥126 mg/dL or using of hypoglycaemic medications), triglyceride levels, total cholesterol levels, high-density lipoprotein (HDL) cholesterol levels, low-density lipoprotein (LDL) cholesterol levels, and fasting glucose levels.

Exposure and outcome measurements

Biochemical measurements were performed only once, at baseline (1992) for fibrinogen and at first follow-up (1994) for CRP. The blood samples were stored at −76°C in liquid nitrogen if not sent to the National Taiwan University Hospital clinical laboratory 8 hours after collection. The fibrinogen levels were evaluated in the hospital laboratory using a clotting assay (STA-Fibrinogen, Diagnostica Stago, France). The CRP levels were measured using a high-sensitivity immunoturbidimetric assay (Denka Seiken, Tokyo, Japan). The outcomes of this study were CVD and all-cause death. Both CAD and stroke cases were included in our definition of CVD. CAD cases were defined by nonfatal myocardial infarction, fatal coronary heart disease and hospitalisation due to percutaneous coronary intervention and coronary bypass surgery. Stroke included ischaemic, haemorrhagic and unclassified types.[28 30] Data on deaths were collected from the government vital registry.

Statistical analyses

The participants were categorised based on fibrinogen quartiles. Analysis of variance and χ^2 tests were used to compare the basic characteristics among the quartiles of fibrinogen levels.

The incidence rates of events were calculated as the number of cases divided by the number of follow-up person-years. Kaplan-Meier survival curves were plotted to compare the cumulative incidence of events between participants in different quartiles. Quartiles of fibrinogen were entered as dummy variables in the Cox proportional hazards regression model, and the HRs and 95% CIs were estimated, with the lowest quartile as the reference group. We built four models to investigate the associations. Model 1 was adjusted for sex and age groups (entered the Cox models as dummy variables: ≤45.0, 45.0–54.1, 54.1–63.2, and >63.2 years of age, grouped by quartiles) only. Model 2 included additional lifestyle covariates: adjusted for BMI (continuous variable), smoking status (yes or no), drinking status (yes or no) and regular exercise (yes or no). Model 3 was constructed from model 2 and included clinical covariates as follows: hypertension status (yes or no) and diabetes status (yes or no). Model 4 was constructed from model 3 and included biochemical covariates as follows: triglycerides levels (continuous variable), total cholesterol levels (continuous variable), HDL cholesterol levels (continuous variable), LDL cholesterol levels (continuous variable) and fasting glucose (continuous

variable). The tests for trends were derived from the regression models with a single term representative of the medians of each quartile.

Subgroup analyses were conducted to test for the effect modification. We stratified the participants by sex, age (using 65 years old as the cut-off point), and baseline smoking status. Tests for interaction were calculated by subtracting the −2log(likelihood) of the full model from the nested model and performing χ^2 tests.

In the sensitivity analysis, joint analyses were conducted to investigate the associations of fibrinogen and CRP levels with CAD risk in a total of 735 participants with available fibrinogen and CRP levels. We used 333.5 mg/dL (third quartile) as the cut-off point for low and high fibrinogen groups and 0.3 mg/dL as the cut-off point for low and high CRP groups. A total of four groups (low fibrinogen/low CRP, high fibrinogen/low CRP, low fibrinogen/high CRP, and high fibrinogen/high CRP) were created and entered as dummy variables in the Cox proportional hazards regression model, taking the low fibrinogen/low CRP group as the reference group.

All statistical tests were two-tailed and p values <0.05 were considered statistically significant. Analyses were performed using SAS V.9.4 (SAS Institute) and Stata V.14 (Stata).

Patient and public involvement

No patients were involved in the development of the research question, outcome measures and overall design of the study. We provided all study participants with medical consultation in the communities and further clinical examinations if an abnormal health-related issue was found during the study.

RESULTS

This study included a total of 2222 participants (54.6±11.9 years old, 53.4% women) with available fibrinogen measurements. All participants were free from CVD at baseline. During a median follow-up period of 22.4 years, 143 participants developed CAD events, 187 experienced stroke and 769 participants died from any cause. The baseline characteristics were comparable between participants and non-participants (online supplemental table 1).

The basic characteristics of the participants according to the fibrinogen quartiles are shown in table 1. Compared with those in the first quartile, participants in higher quartiles of fibrinogen tended to be older, to have higher systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, LDL cholesterol and fasting glucose. In addition, the participants in the

Table 1 Basic characteristics of the study participants, specified by fibrinogen concentration quartiles

	Q1		Q2		Q3		Q4		
Fibrinogen, mg/dL	≤261.8		261.8–294.0		294.0–333.5		>333.5		
n	556		578		545		543		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P value
Age, year	50.9	10.7	53.3	11.5	55.8	12.1	58.5	11.9	<0.001
BMI, kg/m^2	23.5	3.2	23.4	3.0	23.7	3.4	23.6	3.7	0.49
Systolic BP, mm Hg	122.0	19.4	123.3	18.2	126.4	21.2	128.4	21.9	<0.001
Diastolic BP, mm Hg	76.2	10.4	76.7	10.5	77.6	11.3	77.9	11.5	0.04
Triglycerides, mg/dL	117.8	90.7	121.5	89.4	128.1	89.6	141.8	109.9	<0.001
Total cholesterol, mg/dL	188.0	43.6	196.9	44.3	206.3	43.4	207.9	47.0	<0.001
HDL-cholesterol, mg/dL	47.9	12.1	48.0	12.8	46.5	11.8	46.4	13.0	0.05
LDL-cholesterol, mg/dL	127.5	41.1	136.7	43.1	146.9	41.8	148.4	46.5	<0.001
Fasting glucose, mg/dL	106.7	21.1	107.2	25.5	111.1	31.7	114.4	37.6	<0.001
	N	%	N	%	N	%	N	%	P value
Sex	556		578		545		543		<0.001
Men	291	52.3	250	43.3	220	40.4	275	50.6	
Women	265	47.7	328	56.8	325	59.6	268	49.4	
Smoking status	192	34.5	170	29.4	179	32.8	233	42.9	<0.001
Alcohol drinker	180	32.4	134	23.2	148	27.2	174	32.0	0.001
Regular exercise	79	14.2	86	14.9	93	17.1	92	16.9	0.45
Hypertension	139	25.2	146	25.4	182	33.5	184	34.0	<0.001
Diabetes mellitus	58	10.5	53	9.3	68	12.5	98	18.1	<0.001

.BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein.

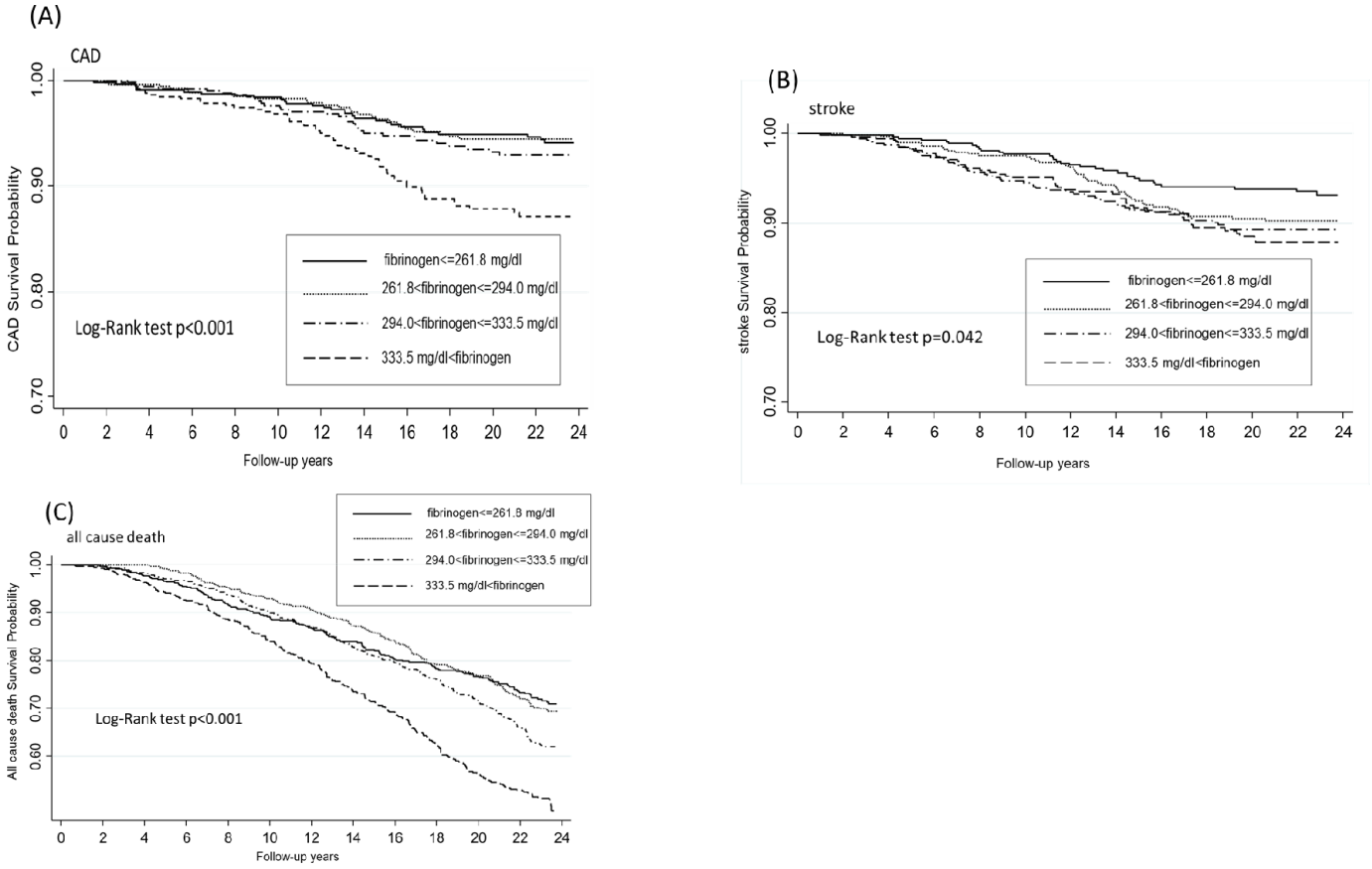

Figure 1 Kaplan-Meier survival curves for the risk of CAD (A), stroke (B), and all-cause death (C) in the study participants, according to quartiles. CAD, coronary artery disease.

highest quartile of fibrinogen level tended to be women, current smokers, drinkers and were more likely to have hypertension and diabetes mellitus.

The Kaplan-Meier curves for the probabilities of survival free from CAD, stroke and all-cause death are shown in figure 1. Compared with the lower quartiles, the fourth quartile of fibrinogen level showed the highest incidence rates for CAD, stroke and all-cause death (log-rank test p<0.001 for CAD, p=0.042 for stroke, p<0.001 for all-cause death).

The number of cases, follow-up period, incidences of event (CAD, stroke, and all-cause death), and HRs and 95% CIs for the associations between fibrinogen level and outcomes are shown in table 2. As the levels of fibrinogen increased, the incidences of CAD, stroke, and all-cause death increased progressively. Although the HRs were not significant for the association between fibrinogen and CAD (adjusted HR 0.86, 95% CI 0.50 to 1.49 for the second quartile group; adjusted HR 0.86, 95% CI 0.50 to 1.47 for the third quartile group; and adjusted HR 1.48, 95% CI 0.90 to 2.44 for the fourth quartile group), the *p*-value for the trend test was 0.037 after adjusting for age, sex, BMI, smoking, drinking and exercise status, hypertension and diabetes mellitus status, triglycerides, cholesterol, HDL cholesterol, LDL cholesterol and glucose (model 4), implying that a higher fibrinogen level may be associated with a higher risk of CAD. However, we observed no association between fibrinogen level and the risk of stroke, with adjusted HRs of 1.19 (95% CI 0.74 to 1.89), 1.06 (95% CI 0.66 to 1.70) and 0.99 (95% CI 0.62 to 1.60), respectively, from the second to the fourth quartile groups (p value for trend test=0.99). Regarding the risk of all-cause death, although the trend tests were significant in model 1 (p=0.025) and borderline in model 4 (p=0.06), the HRs of all-cause death were similar in the fourth and the first quartiles in model 4 (adjusted HR 1.09, 95% CI 0.88 to 1.35 for the fourth quartile).

In the subgroup analysis of the risk of CAD and all-cause death, we divided our participants according to age (<65 or ≥65 years), sex, and baseline smoking status (table 3). Although significant trend tests were observed for the associations between fibrinogen levels and the risk of CAD among participants>65 years and among smokers, the 95% CIs were wide and crossed one (adjusted HR was 2.85 (95% CI 0.82 to 9.88) for the fourth quartile of fibrinogen level among participants>65 years; adjusted HR was 2.21 (95% CI 0.98 to 4.97) for the fourth quartile of fibrinogen level among smokers). In addition, we did not observe any effect modifications based on the tests for interaction (p for interaction=0.75, for age and p for interaction=0.52 for smoking status), implying no interaction effects between fibrinogen level and age or smoking status regarding the risk of CAD. The subgroup analysis of the risk of all-cause death showed a higher risk of death from any cause among the participants <65 years

Table 2 The incidence, follow-up years, HRs and 95% CIs for the study participants in each quartile of fibrinogen concentration

	Q1	Q2	Q3	Q4	
Range, mg/dL	≤261.8	261.8–294.0	294.0–333.5	>333.5	
Median, mg/dL	240.8	280.0	314.2	370.4	
CAD					
Cases	26	31	32	54	
Person-years	10 644.5	11 302.5	10 311.9	9319.7	
Incidence*1000	2.44	2.74	3.10	5.79	
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	Trend test
Model 1	1	0.91 (0.53 to 1.55)	1.06 (0.63 to 1.79)	1.72 (1.06 to 2.79)	0.006
Model 2	1	0.93 (0.55 to 1.59)	1.02 (0.60 to 1.73)	1.63 (1.00 to 2.63)	0.015
Model 3	1	0.94 (0.55 to 1.60)	0.98 (0.58 to 1.65)	1.61 (0.99 to 2.61)	0.017
Model 4	1	0.86 (0.50 to 1.49)	0.86 (0.50 to 1.47)	1.48 (0.90 to 2.44)	0.037
Stroke					
Cases	33	50	52	52	
Person-years	10 656.7	11 266.9	10 258.6	9404.2	
Incidence*1000	3.10	4.44	5.07	5.53	
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	Trend test
Model 1	1	1.14 (0.73 to 1.79)	1.20 (0.77 to 1.87)	1.08 (0.69 to 1.70)	0.83
Model 2	1	1.18 (0.75 to 1.84)	1.18 (0.75 to 1.85)	1.07 (0.69 to 1.69)	0.92
Model 3	1	1.19 (0.76 to 1.87)	1.12 (0.72 to 1.76)	1.07 (0.68 to 1.69)	0.96
Model 4	1	1.19 (0.74 to 1.89)	1.06 (0.66 to 1.70)	0.99 (0.62 to 1.60)	0.99
All-cause death					
Cases	151	165	197	256	
Person-years	10 819.9	11 532.0	10 592.2	9588.4	
Incidence*1000	13.96	14.31	18.60	26.70	
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	Trend test
Model 1	1	0.75 (0.60 to 0.93)	0.90 (0.72 to 1.11)	1.10 (0.90 to 1.35)	0.025
Model 2	1	0.76 (0.61 to 0.95)	0.89 (0.72 to 1.11)	1.07 (0.87 to 1.31)	0.08
Model 3	1	0.79 (0.63 to 0.99)	0.85 (0.69 to 1.06)	1.09 (0.88 to 1.34)	0.08
Model 4	1	0.77 (0.61 to 0.97)	0.83 (0.67 to 1.04)	1.09 (0.88 to 1.35)	0.06

Model 1: adjusted for sex and age.
Model 2: adjusted for model 1 and BMI, smoking, drinking, regular exercise.
Model 3: adjusted for model 2 and hypertension, diabetes mellitus.
Model 4: adjusted for model 3 and triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, glucose.
BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio.

of age in the fourth as compared with the first quartile of fibrinogen (adjusted HR 1.47, 95% CI 1.11 to 1.95; p for trend=0.004). An effect of age modification on the association between fibrinogen level and the risk of all-cause death was also observed (p for interaction <0.001).

The sensitivity analysis included 735 participants with available fibrinogen and CRP measurements. We conducted joint analysis to estimate the associations of fibrinogen and CRP levels with the risk of CAD (table 4). The baseline characteristics of the participants with and without CRP measurements are shown in online supplemental table 2). All models, including the crude model, showed a higher risk of CAD in participants with high fibrinogen/low CRP levels or with high fibrinogen/high CRP levels compared with participants with low fibrinogen/low CRP levels (crude HR 1.90, 95% CI 1.13 to 3.18; adjusted HR (model 4)=2.12, 95% CI 1.24 to 3.63 for high fibrinogen/low CRP; crude HR 2.27, 95% CI 1.18 to 4.37; adjusted HR (model 4)=2.17, 95% CI 1.06 to 4.44 for high fibrinogen/high CRP). However, this association was not observed in the low fibrinogen/high CRP group (crude HR 1.12, 95% CI 0.52 to 2.40). These results implied that a high fibrinogen level (>333.5 mg/dL (Q3)) may be a risk factor for CAD, even in individuals with a low CRP level (≤0.3 mg/dL).

Table 3 Subgroup analysis and test for effect modification for the association between fibrinogen and the risk of coronary artery disease, according to age, sex and smoking status

	n	Q1 HR	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	Trend test	P for interaction
CAD							
Age							0.75
Age <65	1757	1	0.84 (0.45 to 1.56)	0.93 (0.51 to 1.69)	1.33 (0.75 to 2.34)	0.22	
Age ≥65	465	1	1.28 (0.34 to 4.86)	0.99 (0.25 to 3.87)	2.85 (0.82 to 9.88)	0.013	
Sex							0.46
Men	1036	1	0.99 (0.47 to 2.09)	1.21 (0.59 to 2.52)	1.69 (0.85 to 3.37)	0.059	
Women	1186	1	0.77 (0.34 to 1.74)	0.53 (0.23 to 1.23)	1.33 (0.64 to 2.77)	0.33	
Smoking							0.52
Smoking (–)	1448	1	0.81 (0.41 to 1.60)	0.71 (0.35 to 1.46)	1.08 (0.56 to 2.11)	0.74	
Smoking (+)	774	1	1.06 (0.42 to 2.68)	1.17 (0.48 to 2.83)	2.21 (0.98 to 4.97)	0.011	
All-cause death							
Age							<0.001
Age <65	1757	1	0.92 (0.68 to 1.23)	1.00 (0.74 to 1.34)	1.47 (1.11 to 1.95)	0.004	
Age ≥65	465	1	0.66 (0.46 to 0.95)	0.81 (0.57 to 1.15)	0.99 (0.70 to 1.39)	0.14	
Sex							0.61
Men	1036	1	0.83 (0.62 to 1.12)	0.80 (0.59 to 1.09)	1.07 (0.81 to 1.42)	0.29	
Women	1186	1	0.71 (0.49 to 1.03)	0.89 (0.64 to 1.26)	1.12 (0.80 to 1.58)	0.12	
Smoking							0.88
Smoking (–)	1448	1	0.79 (0.58 to 1.08)	0.91 (0.67 to 1.24)	1.16 (0.86 to 1.58)	0.09	
Smoking (+)	774	1	0.77 (0.55 to 1.07)	0.77 (0.56 to 1.07)	1.03 (0.76 to 1.40)	0.33	

*Adjusted for sex, age, body mass index, smoking, drinking, regular exercise, hypertension, diabetes mellitus, triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and glucose.
CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio.

DISCUSSION

The results of the present community-based cohort study showed that a higher fibrinogen level tended to be associated with a higher risk of CAD regardless of the CRP level. The association between fibrinogen level and the risk of all-cause death was only observed among participants <65 years at baseline. However, no association was observed for stroke.

Table 4 Joint analysis: the associations of fibrinogen and CRP levels with the risk of coronary artery disease

	*Low fibrinogen *Low CRP	High fibrinogen Low CRP	Low fibrinogen High CRP	High fibrinogen High CRP
n	418	157	89	71
Cases	38	25	8	12
Person-years	7221.4	2517.6	1430.3	1073.2
Incidence*1000	5.26	9.93	5.59	11.18
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)
Crude	1	1.90 (1.13 to 3.18)	1.12 (0.52 to 2.40)	2.27 (1.18 to 4.37)
Model 1	1	1.90 (1.12 to 3.22)	1.18 (0.55 to 2.56)	2.36 (1.22 to 4.57)
Model 2	1	1.88 (1.10 to 3.18)	1.08 (0.49 to 2.34)	2.14 (1.10 to 4.18)
Model 3	1	1.95 (1.15 to 3.32)	1.01 (0.46 to 2.21)	2.20 (1.13 to 4.31)
Model 4	1	2.12 (1.24 to 3.63)	1.06 (0.48 to 2.33)	2.17 (1.06 to 4.44)

Model 1: adjusted for sex and age.
Model 2: adjusted for model 1 and body mass index, smoking, drinking, regular exercise.
Model 3: adjusted for model 2 and hypertension, diabetes mellitus.
Model 4: adjusted for model 3 and triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, glucose.
*Low fibrinogen: ≤333.5 mg/dL; high fibrinogen: >333.5 mg/dL; low CRP: ≤0.3 mg/dL; high CRP: >0.3 mg/dL.
.CRP, C reactive protein.;

Several studies have reported results similar to those of our study regarding the association between fibrinogen level and CAD risk; however, most of them observed a stronger relationship than that observed in the present study. Wilhelmsen *et al* reported fibrinogen as a predictor of myocardial infarction, although the results were not significant after adjusting for potential confounding factors.[4] Kannel *et al* observed a positive association using data from the Framingham study.[31] A study in Italy also demonstrated increasing CAD prevalence with increased fibrinogen level, especially at extremely high levels (80th percentile OR 1.34; 95% CI 1.03 to 1.76).[11] A meta-analysis of 31 prospective cohort studies observed a linear trend for the association, with an HR of 2.42 (95% CI 2.24 to 2.60) per 1 g/L fibrinogen level increase.[32] Another meta-analysis reported that the association between fibrinogen level and CVD risk remained unchanged after adjusting for CRP level in the model.[33] However, some studies only observed an association among men. Stone and Thorp built a study that included 297 men (40–69 years old) who were initially free from CAD.[5] They observed a higher incidence of heart attacks in the high-level fibrinogen group (31%) compared with the low-level fibrinogen group (5%). In 2006, a study that only recruited men conducted in the UK also reported that the risk of CAD increased by 52% as the log fibrinogen level increased by one SD.[34] In addition, in their cohort study including both men and women in the USA, Tracy *et al* observed a significant association between fibrinogen level and the risk of CAD among men but not women.[35] In our main analysis that included both men and women, we did not find significant results in the adjusted HR, but the over-than-one-HR in the fourth quartile and the significant trend test still showed a potential association between fibrinogen level and the risk of CAD. However, in our subgroup analysis, the trend disappeared for women. We did note that the adjusted HR for the highest quartile was larger than one, which implied the potential risk for high fibrinogen levels. The non-significant result for women may be due to the limited number of CAD cases in women (n=56). Further studies including more CAD cases in women are needed to clarify the association between fibrinogen levels and CAD risk.

Previous studies have reported inconsistent results for the association between fibrinogen level and the risk of stroke. Similar to our results, some studies concluded that fibrinogen was not associated with stroke[36–38]; however, other studies showed a positive association among men[31 34 35] or both sexes.[12 26 33] In their cohort study in Taiwan of 3281 adults, Chuang *et al* observed a significant association between fibrinogen level and the risk of ischaemic stroke. The HR for the highest fibrinogen group compared with the lowest group was 1.72 (95% CI 1.02 to 2.90) after adjusting for potential confounding factors.[26] Both the study from Chuang and our study were based on the Taiwanese population; the different conclusions regarding stroke may be due to the age of the population and the methods of identifying stroke cases. In Chuang's study, the mean age of the population was approximately 45 years and they included participants >20 years at baseline, while the mean age of our population was approximately 55 years and we included a population ≥35 years at baseline. In addition, in our study, stroke cases were identified by cardiologists in the follow-up visits. In Chuang's study, they determine stroke cases by death certificate data, insurance claim records of the National Health Insurance database, and participants' self-reported disease history. Differential misclassification of outcome may happen due to the use of medical records without identifying by physicians, which may lead to either overestimate or underestimate of the effects. Further studies are needed to evaluate whether fibrinogen is a risk factor of stroke among young Asian adults.

Several studies have indicated the biological effects of fibrinogen levels on CVD risk.[10 39–43] Fibrinogen is the first clotting factor and an acute-phase protein synthesised in the liver. Fibrinogen influences platelet aggregation, blood viscosity, fibrin formation, and modulates subsequent coagulation activation and fibrinolysis. Kim *et al* maintained that as the level of fibrinogen increased, especially above physiological levels, the balance between clotting and fibrinolysis tends to favour clotting.[44] As blood clotting is associated with CAD, increasing fibrinogen levels may increase the risk of CAD.

According to the Ministry of Health and Welfare in Taiwan, heart disease has ranked second among the top ten major causes of death for several years. Therefore, one of the urgent issues is to prevent CAD more effectively. Based on our research, we found that a high fibrinogen level may be a risk factor for CAD. Several studies have reported that lifestyle changes such as quitting smoking and maintaining exercise can reduce the fibrinogen level[7 45 46]; therefore, monitoring fibrinogen levels may provide further hints for CAD prevention in clinical practice. Further studies that include more cases of CAD or stroke in Asia are required to provide more evidence of these associations.

In this study, we have several strengths. The prospective cohort design avoided information bias in the baseline measurements of the participants. Due to the community-based population, the data were less likely to be affected by selection bias. In addition, we also considered the role of CRP, a factor known as a marker of atherosclerosis,[15 21] for the association of fibrinogen level with the risk of CAD. We found that higher level of fibrinogen was associated with a higher risk of CAD regardless of CRP level.

Our study has several limitations. First, because the fibrinogen levels were only measured once, we could not assess their changes in our patients and whether these changes modified the observed associations. However, fibrinogen levels tend to be positively associated with age.[47] Our one-time measurement at baseline provided evidence that a high fibrinogen level may be a potential risk factor for CAD; thus, we believe that the results of the present study should be towards the null. Second, although we believe that including the CRP

level in our analysis has made our study more complete, only one-third of our participants had available CRP measurements. Further studies including more data on fibrinogen and CRP measurements are necessary. Third, CRP in the present study was measured in 1994 while fibrinogen levels were measured in 1992. Because CRP level tend to be positively associated with age,[48] the 2-year later measurements of CRP may lead to non-differential misclassification of CRP groups. Forth, this study was based on the Taiwanese population and the results may not be similar to those of other races. Our observed association between fibrinogen level and CAD risk was not as strong as that observed in Western countries. This finding may imply a racial difference in the association between fibrinogen levels and CAD risk.

This community-based cohort study indicated that a high level of fibrinogen may be a risk factor for CAD but not for stroke in Taiwanese population. In addition, fibrinogen level may also be positively associated with the risk of all-cause death among people aged <65 years. These findings highlight the potential benefits of monitoring blood fibrinogen concentrations in clinical practice. Further studies are required to evaluate the differences in the role of fibrinogen levels in the risk of CVD between Asian and Western countries.

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