SUPPLEMENTAL MATERIAL

Systemic inflammation is associated with incident stroke and heart disease in East Asians

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Table S1: Definitions of Case/Control and exclusions used with corresponding ICD:10codes (where appropriate)

Category	Definition/Disease (ICD-10 code)/Procedure
Study population (nested case- control study)	 No self-reported history of transient ischaemic attack, ischaemic heart disease, stroke, or cancer at baseline No statin use at baseline
	Clinical biochemistry measurements available
Controls	• No reported CVD event (ICD-10: I00-I09, I16- I25, I27-I88, I95-I99; I10-I15) up to 1 st Jan 2017.
Major Coronary Events (MCE)	 First CVD event: Ischaemic heart disease (ICD-10: I20-I25) (when fatal) Acute myocardial infarction (ICD-10: I21) PCI/CABG/stent procedure
Ischemic stroke (IS)	 First CVD event: Cerebral infarction, including sequelae (ICD-10: I63, I69.3)
Intracerebral haemorrhage (ICH)	 First CVD event: Non-traumatic intracerebral haemorrhage , including sequelae (ICD-10: I61, I69.1)
Case Exclusions	 First CVD event (ICD-10: I00-I09, I16-I19, I27-I88 [except I61, I63, I69.1, I69.3], I95-I99; I10-I15) is not a case More than one case event on the same day*

* Note: we used an individuals' first event to define their CVD status, i.e. if an individual had an MCE as their first CVD and subsequently had an IS, they contributed to the MCE analysis only (as a case). When an individual experienced more than one discrete CVD event on the same day, they were excluded from the analyses. Of the 12,886 total CVD cases, this affected only 404 cases (~3% of total).

Table S2: Geometric mean and 95% confidence interval (CI) of C-reactive protein (CRP) and Fibrinogen by key baseline characteristics

Baseline traits	Ν	CRP, mg/l ^a	P †	Ν	Fibrinogen, g/l ^a	P †
Age Categories, years ^b						
30-49	4024	0.76 (0.73-0.78)	1.16 x 10 ⁻¹²⁶	3279	2.70 (2.68-2.72)	5.42 x 10 ⁻³⁰⁷
50-59	5387	1.01 (0.98-1.04)		2518	3.06 (3.03-3.08)	
60 and over	7275	1.26 (1.23-1.29)		2801	3.31 (3.29-3.34)	
Gender ^c						
Male	8463	1.06 (1.03-1.09)	0.30	4426	2.93 (2.90-2.95)	8.00 x 10 ⁻⁵⁶
Female	8224	1.04 (1.01-1.07)		4173	3.15 (3.12-3.17)	
Region ^d						
Urban	4987	1.18 (1.14-1.23)	5.32 x 10 ⁻¹⁸	2486	3.01 (2.98-3.04)	5.03 x 10 ⁻⁰²
Rural	11700	0.99 (0.97-1.02)		6113	3.04 (3.02-3.06)	
Education		()			()	
Below Middle School	10192	1.06 (1.03-1.09)	0.52	4774	3.04 (3.02-3.06)	0.25
Middle school and above	6495	1.04 (1.00-1.08)		3825	3.02 (2.99-3.05)	
Income (annual)	0.70	1.0.1 (1.000 1.000)		0020	2.02 (2.55 2.00)	
<10,000 yuan	6480	1.03 (1.00-1.07)	0.25	3227	3.03 (3.01-3.06)	0.81
$\geq 10,000$ yuan	10207	1.06 (1.03-1.09)	0.25	5372	3.03 (3.01-3.05)	0.01
Occupation	10207	1.00 (1.05-1.07)		5512	5.05 (5.01-5.05)	
Non/Semi-manual*	6904	1.18 (1.14-1.23)	9.02 x 10 ⁻¹⁹	3198	3.08 (3.05-3.11)	2.49 x 10 ⁻⁰⁵
Mon/Semi-manual [*] Manual**	6904 9783	0.97(0.94-1.00)	9.02 X 10	5401	3.08 (3.05-3.11) 3.01 (2.98-3.03)	2.49 X 10
	9/85	0.97 (0.94-1.00)		3401	5.01 (2.98-5.05)	
Drinking (Males)	5000	1.02 (0.09.1.04)	0.68	2044	2 08 (2 05 2 02)	1 51 - 10 16
Less than weekly	5898 2565	1.02 (0.98-1.06)	0.68	3044	2.98 (2.95-3.02)	1.51 x 10- ¹⁶
Weekly	2565	1.04 (0.98-1.09)		1382	2.80 (2.76-2.84)	
Smoking (Males)		0.04 (0.05.4.04)	0.55 1.0-03			5.00 1.0-02
Never smokers	1100	0.94 (0.87-1.01)	8.77 x 10 ⁻⁰³	560	2.97 (2.92-3.03)	5.33 x 10 ⁻⁰²
Ever smokers	7363	1.04 (1.00-1.08)		3866	2.92 (2.89-2.95)	
Diabetes						
No	15238	1.00 (0.98-1.03)	6.12 x 10 ⁻⁴⁶	7947	3.02 (3.00-3.04)	1.26 x 10 ⁻¹²
Yes	1449	1.58 (1.49-1.68)		652	3.21 (3.15-3.26)	
BMI (kg/m ²)						
<22.0	5849	0.78 (0.75-0.80)	9.45 x 10 ⁻²¹⁸	2946	3.01 (2.99-3.04)	5.86 x 10 ⁻⁰⁶
22.0 - 24.9	5313	0.97 (0.94-1.00)		2748	3.00 (2.97-3.03)	
<u>>25.0</u>	5525	1.50 (1.45-1.55)		2905	3.07 (3.05-3.10)	
SBP (mmHg) [°]						
<120.0	3125	0.85 (0.81-0.89)	9.34 x 10 ⁻³⁴	1845	2.99 (2.95-3.02)	2.09 x 10 ⁻⁰⁷
120.0 - 139.9	5496	1.01 (0.98-1.05)		2922	3.02 (2.99-3.05)	
<u>>140.0</u>	8066	1.15 (1.12-1.19)		3832	3.06 (3.04-3.09)	
LDL-cholesterol [†] (mg/dL) ^f						
< 80.0	5942	0.92 (0.89-0.96)	3.12 x 10 ⁻⁴⁰	3281	2.92 (2.90-2.95)	1.60 x 10 ⁻⁵¹
80 - 99.9	5020	1.01 (0.97-1.05)		2632	3.02 (3.00-3.05)	-
>100	5725	1.22 (1.18-1.26)		2686	3.16 (3.13-3.19)	
$TG (mg/dL)^{f}$					(
<110.0	5640	0.90 (0.87-0.93)	6.05 x 10 ⁻⁴⁷	2882	3.02 (2.99-3.05)	9.02 x 10 ⁻⁰²
110 – 179.9	5360	1.02 (0.98-1.05)	0.00 A 10	2753	3.05 (3.02-3.08)	2.02 A 10
>180.0	5687	1.24 (1.20-1.28)		2755	3.03 (3.00-3.05)	
<u>Physical activity (MET hours/day)</u>	2007	1.27 (1.20-1.20)		2704	5.05 (5.00-5.05)	
<10.0	5218	1.22 (1.17-1.26)	1.42 x 10 ⁻²⁷	2363	3.11 (3.08-3.14)	1.45 x 10 ⁻⁰⁷
10.0 – 14.9		1.22(1.17-1.26) 1.12(1.07-1.17)	1.42 A 10			1.45 X 10
	3366	()		1632	3.05(3.01-3.08)	
<u>>15.0</u>	8103	0.95 (0.92-0.98)		4604	3 (2.97-3.02)	
Standing height of males (m)	2255	1.04 (0.00.1.10)	0.02	1000		0.05
<1.60	2255	1.04 (0.98-1.10)	0.93	1026	2.92 (2.87-2.97)	0.85
1.60 - 1.64	2508	1.02 (0.97-1.07)		1260	2.93 (2.89-2.97)	
1.65 – 1.69	2107	1.02 (0.97-1.08)		1137	2.91 (2.87-2.95)	
>1.70	1593	1.04 (0.97-1.11)		1003	2.93 (2.89-2.98)	
Standing height of females (m)						
<1.50	2495	1.06 (1.01-1.12)	4.41 x 10 ⁻⁰²	1154	3.15 (3.10-3.19)	2.13 x 10 ⁻⁰²
1.50 - 1.54	2656	1.08 (1.03-1.14)		1321	3.17 (3.13-3.21)	
1.55 – 1.59	2044	1.09 (1.03-1.15)		1098	3.13 (3.09-3.18)	
>1.60	1029	0.96 (0.89-1.03)		600	3.09 (3.03-3.14)	

BMI: Body mass index; SBP: Systolic Blood Pressure; LDL: Low-density lipoprotein; TG: Triglycerides

^aValues are geometric mean (95% CI) standardised for age, sex, study area and case status unless otherwise stated

^bStandardised for sex, study area and case status only

⁶Standardised for age, study area and case status only ^dStandardised for age, sex and case status only ^eCategorised based on global standard criterion for hypertension ^fTo convert LDL-C (TG) from mg/dL to mmol/L, divide by 38.67 (88.57).

†P value here represents the association of the traits (in their continuous form, where possible) with CRP, adjusted for age, sex, study area and case status unless otherwise stated.

*Includes white collar jobs, retired, housewife/husband, self-employed, un-employed or others/not stated

**Includes farmers and factory workers

[†]Low-density lipoprotein (LDL) cholesterol was directly measured (and not estimated using the Friedewald equation).

Vascular endpoint Area under the Receiver Operating Characteristic LRT** P-value **curve** (95%CI) Model 1 (age, sex, Model 2 (Model 1 + P-value* region, smoking, CRP) diabetes, BMI, SBP, LDL, HDL, TG) 1.82x10⁻³ 1.21x10⁻¹³ **Major Coronary Events** 0.7181 0.7251 (0.7028, 0.7334)(0.7101, 0.7402) **Ischemic stroke** 1.75x10⁻⁴ 0.7816 0.7822 0.095 (0.773, 0.7902) (0.7736, 0.7908) Intracerebral 0.7391 0.7379 0.075 9.54x10⁻⁷ (0.728-0.7477) (0.7293 - 0.7489)hemorrhage

Table S3: Discriminatory performance

*P-value from DeLong's test for two correlated ROC curves

**Likelihood ratio test

A) MCE

	Rec	assified pred	icted risk (with	CRP)	N recla	ssified as			
Predicted risk (without CRP)	< 5%	5 to < 10%	10 to < 20%	<u>></u> 20%	increased risk	reduced risk	Net correctly reclassified: N (Prop.)		
MCE (n = 1508)									
< 5%	5	2	0	0	85	94	-9 (-0.0060ª)		
5 to < 10%	4	63	19	0					
10 to < 20%	0	31	302	64					
<u>></u> 20%	0	0	59	959					
Controls (n = 5285)									
< 5%	75	10	1	0	385	600	215 (0.041 ^b)		
5 to < 10%	62	621	114	3					
10 to < 20%	0	267	1910	257					
<u>></u> 20%	0	0	271	1694					
Total correctly reclassified							206 (0.035°)		
Net							0.035 (0.014 -		
reclassification							0.056])		
improvement							p-value = 0.0011		
(95% CI)									

^bNRI_{non-event} = P(down|nonevent) -P(up|nonevent)

^cNRI = NRI_{event} + NRI_{non-event}

B) IS	;
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% 10 to < 20%				
	<u>></u> 20%	increased risk	reduced risk	Net correctly reclassified (Prop.)
				i de la companya de l
0 0	0	25	22	3 (0.00055ª)
.1 2	0			
1 141	23			
0 21	5219			
0 0	0	55	109	54 (0.010 ^b)
13	0			
.4 755	42			
0 94	4264			
				57 (0.011°)
				0.011 (0.0054 - 0.016) p-value = 8.0 x 10 ⁻¹

^bNRI_{non-event} = P(down|nonevent) -P(up|nonevent)

^cNRI = NRI_{event} + NRI_{non-event}

C)	ICH
-,	

		Reclassified	I predicted risk		N recla	ssified as			
Predicted risk (without CRP)	< 5%	5 to < 10%	10 to < 20%	<u>></u> 20%	increased risk	reduced risk	Net correctly reclassified (Prop.)		
ICH (n = 4476)									
< 5%	0	0	0	0	18	25	-7 (-0.0016 ^a)		
5 to < 10%	0	1	1	0					
10 to < 20%	0	0	103	17					
<u>></u> 20%	0	0	25	4329					
Controls									
(n = 5285) < 5%	0	0	0	0	52	94	42 (0.0080 ^b)		
5 to < 10%	0	25	2	0					
10 to < 20%	0	4	590	50					
<u>></u> 20%	0	0	90	4524					
Total correctly reclassified (%)							35 (0.0064 ^c)		
Teclassified (%)							0.0004/0.0044		

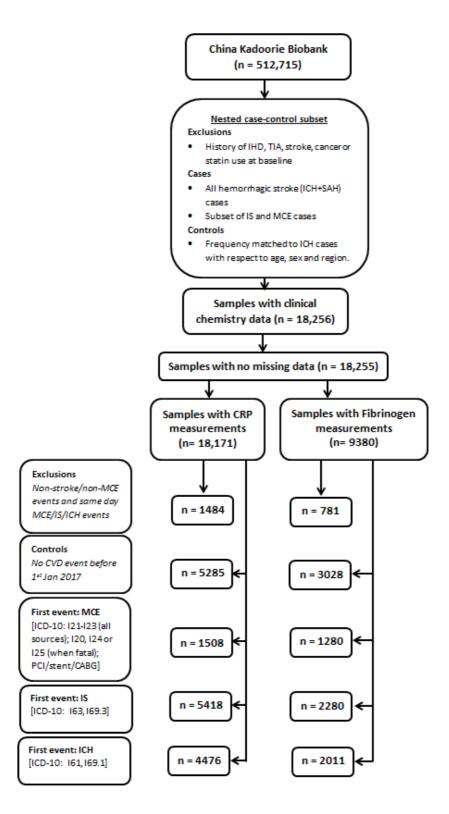
reclassified (%)	
Net	0.0064 (0.0011 -
reclassification	0.012)
improvement	p-value = 0.019
(95% CI)	

^aNRI_{event} = P(up|event) - P(down|event)

^bNRI_{non-event} = P(down|nonevent) -P(up|nonevent)

^cNRI = NRI_{event} + NRI_{non-event}

Figure S1: Flowchart of participant selection



CRP: C-reactive protein; CVD: Cardiovascular disease; ICD: International Classification of Diseases; ICH: Intracerebral haemorrhage; IHD: Ischaemic heart disease; IS: Ischaemic stroke; MCE: Major Coronary Event; TIA: transient ischaemic attack;

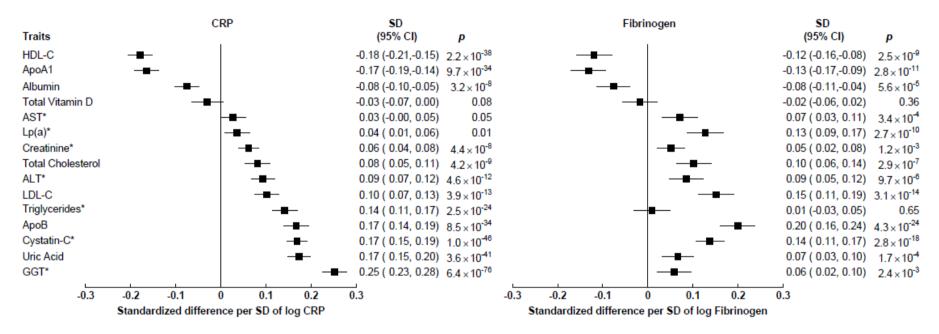


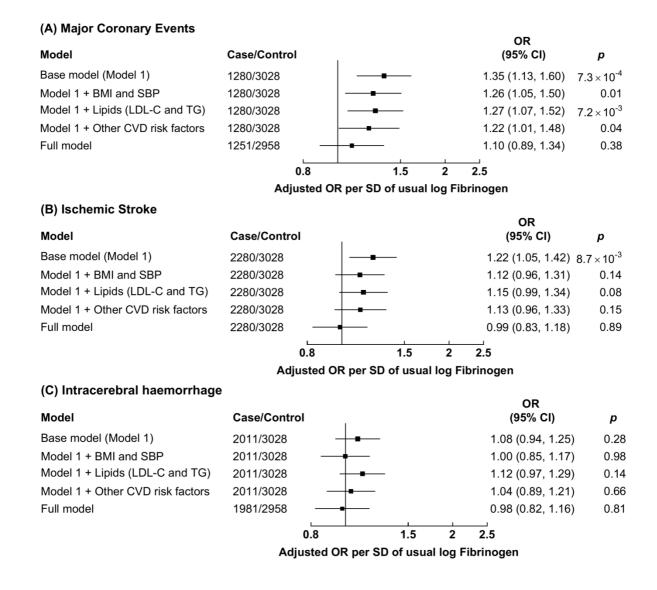
Figure S2: Cross-sectional associations of CRP and Fibrinogen in controls with selected biomarkers

CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; ApoA1: Apolipoprotein A1; AST: Aspartate transaminase; Lp(a): Lipoprotein(a); ALT: Alanine transaminase; LDL-C: Low-density lipoprotein cholesterol; ApoB: Apolipoprotein B; GGT: Gamma-glutamyl transferase

Note: All biomarkers standardized prior to analysis

*Biomarkers which were also log-transformed before standardization

Figure S3: Risk of (A) Major Coronary Events, (B) Ischemic Stroke and (C) Intracerebral Hemorrhage per standard deviation (SD) of usual log-transformed Fibrinogen levels



Base model includes age, age^2 and sex.

Other CVD Risk Factors: income, occupation, education, diabetes, physical activity, standing height, smoking, and alcohol

Full model includes base model, body-mass index (BMI), systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and other CVD risk factors;

Note: For each Model, models were fitted separately for each of the 10 study areas and estimates were meta-analyzed; study areas were excluded when models failed to converge (2 models out of 150 models)

Figure S4: Progressive adjustment of (A) CRP and (B) Fibrinogen for Major Coronary Events, Ischemic Stroke and Intracerebral hemorrhage

(B)

(A)

Мај	or Coronary even (1508 events)	ts OR				Major Coronary ever (1251 events)	nts OR		
Baseline Traits	(,	(95% CI)	p	X²	Baseline Traits		(95% CI)	p	X²
Age, Age ² and Sex	_	2.05 (1.80, 2.33)	-	115.6	Age, Age ² and Sex		1.35 (1.13, 1.60)	7 3 × 10 ⁻⁴	11.4
+SBP	_•	1.88 (1.64, 2.15)		85.3	+SBP	_ _	1.27 (1.06, 1.52)		6.9
+Diabetes	_•-	1.80 (1.58, 2.07)		72.8	+Diabetes	_ . _	1.21 (1.01, 1.45)	0.04	4.2
+Smoking		1.76 (1.54, 2.02)		65.6	+Alcohol	_ _	1.17 (0.98, 1.41)	0.09	2.9
+Occupation		1.73 (1.51, 2.00)		59.5	+LDL cholesterol		1.14 (0.95, 1.38)	0.17	1.9
+LDL cholesterol		1.70 (1.48, 1.96)		54.2	+Occupation		1.11 (0.92, 1.35)	0.28	1.2
+Triglycerides		1.67 (1.45, 1.93)		50.4	+Standing height	_ _ _	1.12 (0.92, 1.35)	0.26	1.3
+Alcohol	_•	1.65 (1.43, 1.90)		46.6	+Smoking	_ _ _	1.11 (0.91, 1.35)	0.28	1.1
+Physical activity	_•	1.63 (1.42, 1.89)	2.5×10^{-11}	44.6	+BMI	_ _ _	1.10 (0.91, 1.35)	0.32	1.0
+Income		1.64 (1.42, 1.89)	3.1×10^{-11}	44.1	+Income		1.10 (0.90, 1.34)	0.37	0.8
+Standing height		1.64 (1.42, 1.90)	2.5 × 10 ⁻¹¹	44.5	+Physical activity		1.10 (0.90, 1.34)	0.36	0.8
+BMI	_ 	1.66 (1.43, 1.93)	2.0×10^{-11}	45	+Triglycerides	_ _ _	1.09 (0.89, 1.34)	0.39	0.7
+Education	_•	1.67 (1.44, 1.94)	1.6×10^{-11}	45.4	+Education		1.10 (0.89, 1.35)	0.37	0.8
0.8 1	1.5 2	-					-	0.07	0.0
	R per SD of usual I	log CRP				.8 1 1.5 2			
	Ischemic Stroke	-			Adjusted O	R per SD of usual log			
	(5418 events)	OR				Ischemic Stroke (2280 events)	, OR		
Baseline Traits		(95% CI)	p	X²	Baseline Traits		(95% CI)	р	X²
Age, Age ² and Sex		1.57 (1.43, 1.73)	1.1×10 ⁻²¹	91.6	Age, Age ² and Sex	_ _	1.22 (1.05, 1.42)	8.7 × 10 ⁻³	6.9
+BMI		1.41 (1.28, 1.56)	2.1×10 ⁻¹²	49.3	+SBP		1.14 (0.97, 1.33)	0.10	2.6
+SBP		1.35 (1.22, 1.49)	2.7×10 ⁻⁹	35.4	+LDL cholesterol	+ • -	1.09 (0.93, 1.27)	0.30	1.1
+Diabetes		1.30 (1.18, 1.43)	2.8×10^{-7}	26.4	+Alcohol	_ -	1.06 (0.90, 1.25)	0.46	0.5
+Smoking		1.28 (1.16, 1.41)	1.7×10 ^{-€}	22.9	+Diabetes	_ - _	1.04 (0.88, 1.22)	0.65	0.2
+LDL cholesterol		1.26 (1.14, 1.39)	9.3×10 ⁻⁴	ⁱ 19.6	+Smoking	_ _	1.03 (0.87, 1.21)	0.73	0.1
+Physical activity		1.24 (1.12, 1.37)	3.6×10 ^{-€}	17.1	+Standing height	_ - _	1.03 (0.88, 1.22)	0.69	0.2
+Income		1.23 (1.11, 1.36)	7.2×10 ⁻⁵	15.8	+BMI	_ - _	1.03 (0.87, 1.21)	0.73	0.1
+Standing height		1.23 (1.11, 1.36)	8.0×10 ⁻⁵	15.6	+Physical activity	_ - _	1.02 (0.87, 1.21)	0.79	0.1
+Alcohol		1.22 (1.10, 1.36)	1.2×10 ⁻⁴	14.8	+Education	_ _	1.02 (0.86, 1.21)	0.81	0.1
+Education		1.22 (1.10, 1.35)	1.8×10⁻	14.1	+Income	_ -	1.00 (0.84, 1.18)	0.99	<0.01
+Occupation		1.22 (1.10, 1.36)	1.7×10 ⁻⁴	14.1	+Occupation	<u> </u>	1.00 (0.84, 1.19)	0.97	<0.01
+Triglycerides		1.22 (1.10, 1.36)	1.5×10⁻	14.4	+Triglycerides	<u> </u>	0.99 (0.83, 1.18)	0.89	<0.01
0.8	1 1.5 2	-			0.	8 1 1.5 2	-		
Adjusted OF	R per SD of usual	log CRP				R per SD of usual log	Fibrinogen		
	erebral hemorrha	ge				ntracerebral hemorrha			
	(4476 events)	OR				(1981 events)	OR		
Baseline Traits		(95% CI)	p	X²	Baseline Traits	L	(95% CI)	р	X²
Age, Age ² and Sex	-•-	1.43 (1.30, 1.56)			Age, Age ² and Sex	+•	1.08 (0.94, 1.25)	0.28	1.2
+SBP		1.26 (1.14, 1.38)	3.6×10 ^{-€}		+Standing height	+	1.08 (0.93, 1.24)	0.31	1.0
+Diabetes	-•-	1.23 (1.12, 1.35)			+SBP	-	0.98 (0.84, 1.15)	0.82	0.1
+Physical activity		1.21 (1.09, 1.33)	1.6×10 ⁻⁴		+Smoking	-+-	0.99 (0.85, 1.16)	0.90 <	<0.01
+Alcohol		1.19 (1.08, 1.31)			+BMI	-	1.00 (0.86, 1.17)	0.98 •	<0.01
+Education		1.18 (1.07, 1.31)			+Diabetes	-	0.98 (0.84, 1.15)	0.85 <	<0.01
+Income		1.18 (1.07, 1.30)			+Physical activity	-	0.98 (0.83, 1.15)	0.78	0.1
+Occupation	-	1.17 (1.06, 1.29)			+Alcohol		0.97 (0.82, 1.14)	0.71	0.1
+Standing height		1.17 (1.05, 1.29)			+Income		0.97 (0.82, 1.14)	0.72	0.1
+Smoking		1.16 (1.05, 1.29)			+LDL cholesterol	—• —	1.02 (0.87, 1.21)	0.78	0.1
+LDL cholesterol		1.18 (1.07, 1.31)			+Education	—	1.01 (0.85, 1.20)	0.91 •	<0.01
+Triglycerides		1.20 (1.09, 1.34)	3.9×10 ⁻¹		+Occupation	-+-	0.99 (0.83, 1.17)	0.88 <	<0.01
+BMI	- -	1.22 (1.10, 1.36)	1.8×10 ⁻⁴	14.0	+Triglycerides	_ -	0.98 (0.83, 1.17)	0.84 <	<0.01
0.8	1 1.5 2	-			0	.8 1 1.5 2	-		

Adjusted OR per SD of usual log CRP

Adjusted OR per SD of usual log Fibrinogen

Note: Models were fitted separately for each of the 10 study areas for each covariate and estimates were meta-analyzed; for each covariate, study areas were excluded when models failed to converge (2 models out of 780 models). Progressive adjustment used at each step the covariate giving the largest change in x².

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Figure S5: Risk of Major Coronary Events, Ischemic Stroke and Intracerebral Hemorrhage per standard deviation (SD) of usual Fibrinogen levels by subgroups

Major Coronary Events Subgroup Cases/Controls	Adjusted OR (95% CI)	Subgroup	Cases/Controls	Ischemic Stroke	Adjusted OR (95% CI)	Subgroup	Cases/Controls	Intracerebral hemorrhage	Adjusted OR (95% CI)
Sex Men 757/1499	1.07 (0.81, 1.40) 1.07 (0.77, 1.48) <i>p-het=1.00</i>	Sex Men Women	1063/1558 1179/1433		1.15 (0.89, 1.49) 0.78 (0.61, 1.01) <i>p-het=0.04</i>	Sex Men Women	1010/1525 950/1404		1.25 (0.98, 1.60) 0.71 (0.55, 0.92) p-het=0.002
Age, years 320/1154 30-49 320/1154 50-59 558/746 60 and over 302/875	→ 2.07 (1.41, 3.06) 0.66 (0.46, 0.94) 1.12 (0.75, 1.66) <i>p-trend</i> =0.03	Age, years 30-49 50-59 60 and over	1073/1231 598/790 554/946	- -	0.76 (0.59, 0.97) 0.96 (0.68, 1.37) 1.01 (0.71, 1.43) <i>p-trend=0.16</i>	Age, years 30-49 50-59 60 and over	787/1205 414/693 689/922	<u> </u>	0.97 (0.73, 1.27) 1.09 (0.74, 1.59) 1.06 (0.80, 1.42) p-trend=0.63
Region Rural 855/2399 Urban 425/629	0.98 (0.79, 1.23) – 1.69 (1.07, 2.68) <i>p-het=0.04</i>	Region Rural Urban	1295/2399 985/629	—	0.95 (0.78, 1.17) 1.09 (0.79, 1.50) <i>p-het=0.49</i>	Region Rural Urban	1564/2399 447/629		1.01 (0.84, 1.22) 0.96 (0.63, 1.47) p-het=0.83
Education Below Middle School 708/1805 Middle School and above 558/1174	0.93 (0.72, 1.21) 1.35 (0.95, 1.91) <i>p-het=0.10</i>	Education Below Middle School Middle School and above	999/1835 1240/1113		0.99 (0.78, 1.27) 0.94 (0.72, 1.21) <i>p-het=</i> 0.73	Education Below Middle School Middle School and above	1207/1779 759/1174	- _	1.05 (0.85, 1.30) 0.93 (0.69, 1.25) p-het=0.52
Smoking Never smokers 528/1509 Ever smokers 734/1414	1.09 (0.79, 1.49) 1.08 (0.82, 1.42) <i>p-het=0.97</i>	Smoking Never smokers Ever smokers	1278/1614 983/1387		0.74 (0.58, 0.93) 1.30 (0.99, 1.70) <i>p</i> -het=0.0021	Smoking Never smokers Ever smokers	1044/1614 955/1387	_ 	0.76 (0.59, 0.97) 1.21 (0.94, 1.55) p-het=0.01
Alcohol intake Non-regular drinkers 1057/2534 Regular drinkers 143/306	1.16 (0.94, 1.43) - 1.08 (0.47, 2.48) <i>p-het=0.87</i>	Alcohol intake Non-regular drinkers Regular drinkers	1885/2534 312/270	-	0.95 (0.79, 1.14) 1.58 (0.92, 2.71) <i>p</i> -het=0.08	Alcohol intake Non-regular drinkers Regular drinkers	1658/2534 292/381		0.99 (0.82, 1.19) 1.23 (0.71, 2.14) p-het=0.46
Physical activity, MET h/day 336/503 <10.0	→ 2.27 (1.44, 3.59) 0.63 (0.31, 1.31) 0.87 (0.65, 1.15) <i>p-het=0.00067</i>	Physical activity, MET h/day <10.0 10.0-14.9 ≥15.0	586/542 424/499 1138/1755		1.21 (0.79, 1.84) 1.03 (0.65, 1.62) 0.86 (0.68, 1.10) <i>p</i> -het=0.37	Physical activity, MET h/day <10.0 10.0-14.9 ≥15.0	568/607 326/499 1028/1780		1.11 (0.76, 1.64) 0.94 (0.58, 1.53) 0.85 (0.67, 1.07) p-het=0.49
SBP, mmHg 426/1447 <130	1.10 (0.78, 1.56) 0.92 (0.60, 1.40) 0.76 (0.47, 1.21) p-trend=0.20	SBP, mmHg <130 130-149 ≥150	885/1552 644/915 595/466		0.77 (0.59, 1.02) 1.36 (0.97, 1.92) 1.01 (0.66, 1.56) <i>p-trend=0.11</i>	SBP, mmHg <130 130-149 ≥150	464/1503 544/915 925/507		0.88 (0.64, 1.22) 1.08 (0.79, 1.49) 1.16 (0.82, 1.63) p-trend=0.26
BMI, kg/m2 <22.0 385/1087 22.0-24.9 330/959 225.0 417/668	1.00 (0.70, 1.42) 1.02 (0.67, 1.54) 1.35 (0.87, 2.09) p-trend=0.32	BMI, kg/m2 <22.0 22.0-24.9 ≥25.0	564/1153 649/1009 979/757 ←		1.05 (0.75, 1.45) 1.17 (0.84, 1.64) 0.65 (0.47, 0.91) <i>p</i> -trend=0.05	BMI, kg/m2 <22.0 22.0-24.9 ≥25.0	684/1128 595/1009 647/757		1.13 (0.84, 1.52) 0.88 (0.62, 1.23) 0.84 (0.57, 1.23) p-trend=0.19
LDL-cholesterol, mg/dL <80.0 387/1191 60.0 - 99.9 311/004 2100 485/778	0.82 (0.58, 1.15) 1.28 (0.83, 1.96) 1.24 (0.81, 1.88) p-trend=0.11	LDL-cholesterol, mg/dL <80.0 80.0 - 99.9 ≥100	697/1259 681/897 850/805		0.78 (0.57, 1.05) 1.17 (0.82, 1.66) 1.08 (0.77, 1.52) <i>p-trend=0.13</i>	LDL-cholesterol, mg/dL <80.0 80.0 - 99.9 ≥100	849/1259 557/853 537/805	<u> </u>	0.87 (0.66, 1.14) 1.03 (0.73, 1.47) 1.19 (0.80, 1.75) p-trend=0.18
Overall 1251/2958	1.10 (0.89, 1.34)	Overall	2280/3028	÷ .	0.99 (0.83, 1.18)	Overall	1981/2958		0.98 (0.82, 1.16)
0.5 1 2 Adjusted OR per SD of usual log F	3 ïbrinogen		0.5 Adjusted	1 2 : d OR per SD of usual log Fibri	•		0. Adjust	5 1 2 ed OR per SD of usual log Fibr	•

Note: Models were adjusted (where appropriate) for age, age² and sex (base model) and additionally for income, occupation, education, SBP, BMI, diabetes, physical activity, standing height, smoking, alcohol, LDL-C and TG. The models were fitted separately for each of the 10 study areas in each subgroup strata and estimates were meta-analyzed; in each subgroup strata, study areas were excluded when models failed to converge (141 models out of 750 models). Error bars represent 95% confidence intervals (CI). The sizes of the boxes are proportional to the inverse of the variance of the log ORs. The dotted line represents the overall adjusted OR. The open diamond represents the overall adjusted OR and its 95% CI. MET, metabolic equivalent of task; *p-het*, p-value for heterogeneity; *p-trend*, p-value for trend.