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Relationship of pericardial fat with biomarkers of inflammation and hemostasis, and cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—Pericardial fat may increase the risk of cardiovascular disease (CVD) by increasing circulating levels of inflammation and hemostasis biomarkers. We investigated the associations of pericardial fat with inflammation and hemostasis biomarkers, as well as incident CVD events, and whether there are any ethnic differences in these associations.

Methods—We analyzed results from 6415 participants from the Multi-Ethnic Study of Atherosclerosis who had measurements of pericardial fat volume and circulating levels of C-reactive protein (CRP), fibrinogen, interleukin (IL)-6, factor VIII, D-dimer and plasmin-antiplasmin complex (PAP), and had a mean follow-up period of 9.5 years. Incident CVD event was defined as any adjudicated CVD event.

Results—After adjusting for confounding factors, pericardial fat volume was positively associated with natural log (ln) of IL-6 levels, but inversely associated with ln D-dimer and ln PAP levels (β=0.067, −0.032, and −0.105 respectively, all $P<0.05$). Although a larger pericardial fat volume was associated with a higher risk of incident CVD, the association was attenuated to borderline significance after adjusting for traditional cardiovascular risk factors ($P=0.050$). There

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was a borderline significant ethnicity interaction (P=0.080), whereby the association between pericardial fat volume and incident CVD was significant in Hispanic Americans, even after further adjusting for biomarkers of inflammation and hemostasis (hazard ratio=1.31 per SD increase, 95% confidence interval 1.09-1.57, P=0.004).

Conclusion—Pericardial fat was associated with several inflammation and hemostasis biomarkers. The association of pericardial fat with incident CVD events was independent of these biomarkers only among Hispanic Americans.

Keywords

biomarkers; cardiovascular disease; hemostasis; inflammation; pericardial fat

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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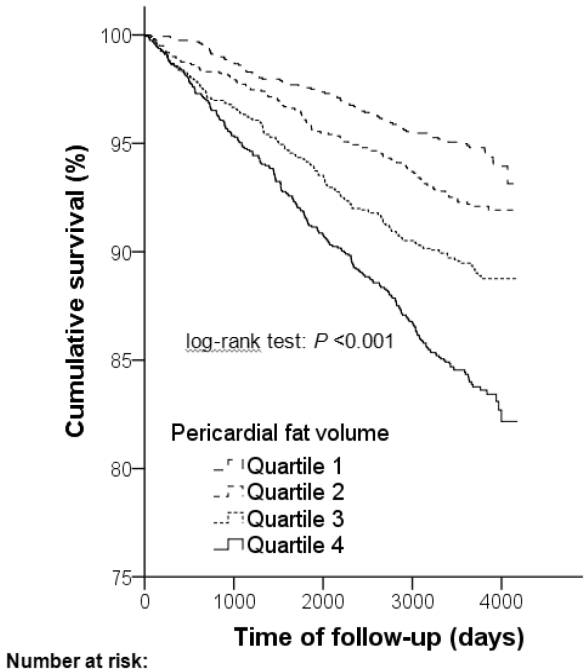
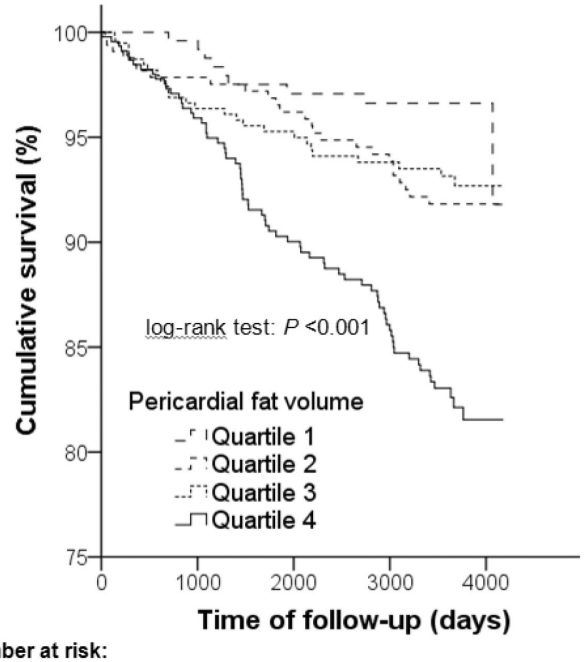
Highlights

- Pericardial fat may be related to systemic inflammation and hemostasis.
- We analysed data from the Multi-Ethnic Study of Atherosclerosis.
- Pericardial fat was associated with several inflammation and hemostasis biomarkers.
- Association of pericardial fat with CVD was independent of biomarkers in Hispanics.



Number at risk:

Quartile 1	1603	1549	1454	1400	223
Quartile 2	1605	1527	1417	1354	193
Quartile 3	1604	1496	1357	1261	179
Quartile 4	1603	1464	1320	1209	155



Number at risk:

Quartile 1	247	244	220	215	38
Quartile 2	327	305	290	278	44
Quartile 3	392	364	329	312	46
Quartile 4	454	406	355	317	42

Figure 1.

Kaplan–Meier cumulative survival curves for incident CVD events across quartiles of pericardial fat volume among (**A**) all participants, and (**B**) Hispanic Americans.

Table 1

Clinical characteristics of participants according to the quartile of pericardial fat volume

Characteristics	All	Quartile 1 (≤49.5 cm^3)	Quartile 2 (49.6-70.7 cm^3)	Quartile 3 (70.8-99.1 cm^3)	Quartile 4 (≥99.2 cm^3)	*P* [a]
n	6415	1603	1605	1604	1603	-
Age (year)	62.1±10.2	58.6±10.0	61.6±10.2	63.6±9.9	64.7±9.8	<0.001
Women (%)	52.8 (3384)	67.3 (1079)	59.7 (958)	51.1 (820)	32.9 (527)	<0.001
Ethnicity (%)						
Caucasian	38.4 (2464)	36.6 (587)	33.1 (531)	37.2 (596)	46.8 (750)	<0.001
African American	12.0 (767)	37.9 (607)	30.5 (490)	25.6 (410)	16.0 (257)	
Hispanic American	27.5 (1764)	15.4 (247)	20.4 (327)	24.4 (392)	28.3 (454)	
Chinese American	22.1 (1420)	10.1 (162)	16.0 (257)	12.8 (206)	8.9 (142)	
Education (%)						
<High school	18.1 (1159)	12.4 (198)	17.1 (274)	20.9 (334)	22.1 (353)	<0.001
High school	41.4 (2655)	37.8 (604)	41.7 (667)	42.9 (686)	43.7 (698)	
>High school	40.2 (2581)	49.8 (795)	41.2 (659)	36.2 (579)	34.3 (548)	
Smoking (%)						
Never	50.3 (3228)	56.1 (896)	53.1 (850)	50.2 (803)	42.5 (679)	<0.001
Former	36.5 (2343)	30.5 (487)	33.4 (535)	37.0 (591)	45.7 (730)	
Current	12.9 (825)	13.5 (215)	13.4 (215)	12.8 (205)	11.9 (190)	
Pack-years of smoking	11.3±20.0	7.2±13.6	9.7±19.6	12.2±21.8	16.2±26.0	<0.001
Current alcohol use (%)	55.3 (3549)	58.5 (930)	55.0 (878)	51.3 (816)	58.0 (925)	0.002
Total gross family income						
<$30 000	36.0 (2312)	31.2 (479)	37.6 (579)	41.0 (632)	40.2 (622)	<0.001
$30 000- $74 999	38.3 (2460)	40.3 (620)	40.1 (617)	40.3 (622)	38.8 (601)	
≥$75 000	21.7 (1395)	28.5 (438)	22.2 (342)	18.7 (289)	21.0 (326)	
BMI (kg/m^2)	28.3±5.5	25.3±4.5	27.1±4.8	29.3±5.2	31.6±5.3	<0.001
Waist-to-hip ratio	0.93±0.08	0.87±0.07	0.92±0.08	0.95±0.06	0.98±0.06	<0.001
Heart rate (beat per minute)	63.1±9.6	62.0±9.0	62.5±9.5	63.2±9.8	64.8±10.0	<0.001
Physical activity (MET-hour/week)	96.5±98.9	104±96	101±107	93±95	88±96	<0.001

Characteristics	All	Quartile 1 (≤49.5 cm^3)	Quartile 2 (49.6-70.7 cm^3)	Quartile 3 (70.8-99.1 cm^3)	Quartile 4 (≥99.2 cm^3)	*P* [a]
Diabetes (%)	12.6 (811)	6.3 (101)	10.1 (162)	14.9 (239)	19.3 (309)	<0.001
Hypertension (%)	44.6 (2864)	32.4 (520)	42.1 (675)	48.0 (770)	56.1 (899)	<0.001
Dyslipidemia (%)	33.6 (2153)	19.0 (304)	30.4 (488)	37.0 (593)	48.0 (768)	<0.001
CRP (mg/l)[b]	1.90 (0.83-4.20)	1.27 (0.56-2.96)	1.67 (0.77-3.96)	2.22 (1.02-4.65)	2.53 (1.20-4.83)	<0.001
Fibrinogen (mg/dl)	346±72.9	332±71	342±70	351±74	358±74	<0.001
IL-6 (pg/ml)[b]	1.21 (0.78-1.90)	0.94 (0.61-1.53)	1.09 (0.73-1.68)	1.30 (0.87-1.98)	1.55 (1.01-2.43)	<0.001
Factor VIII (%)	98.7±37.0	97.0±36.9	96.3±35.6	100.1±37.1	101.5±38.3	<0.001
D-dimer (μg/ml)[b]	0.20 (0.13-0.37)	0.20 (0.10-0.32)	0.20 (0.13-0.35)	0.23 (0.13-0.42)	0.23 (0.13-0.39)	<0.001
PAP (nM)[b]	4.39 (3.43-5.62)	4.70 (3.77-6.02)	4.44 (3.46-5.71)	4.27 (3.37-5.48)	4.11 (3.18-5.23)	<0.001
Incident CVD events (%)	9.5 (607)	5.2 (84)	7.4 (119)	10.2 (163)	15.0 (241)	<0.001

MET, metabolic equivalent.

Data are expressed as mean±SD, percentage (n), or median (interquartile range).

[a] Adjusted for age, sex, and ethnicity.

[b] *P* values were estimated using ln-transformed data.

Table 2

Association of pericardial fat volume with biomarkers

Biomarkers	β				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
ln CRP (mg/l)	0.275‡	0.259‡	0.054‡	0.023	0.083‡
Fibrinogen (mg/dl)	0.184‡	0.179‡	0.019	0.024	0.054‡
ln IL-6 (pg/ml)	0.287‡	0.274‡	0.083‡	0.067‡	0.117‡
Factor VIII (%)	0.070‡	0.060‡	0.016	0.021	0.007
ln D-dimer (μg/ml)	0.057‡	0.049‡	−0.039*	−0.032*	−0.003
ln PAP (nM)	−0.152‡	−0.156‡	−0.105‡	−0.105‡	−0.152‡

Model 1: adjusted for age, sex, and ethnicity.

Model 2: further adjusted for education, smoking, pack-years of smoking, current alcohol use, total gross family income, and physical activity.

Model 3: further adjusted for BMI, heart rate, diabetes, hypertension, and dyslipidemia.

Model 4: further adjusted for all the six biomarkers of interest, where appropriate.

Model 5: same as model 4, except that BMI was replaced by waist-to-hip ratio and height.

*$P<0.05$,

†$P<0.01$ and

‡$P<0.001$.

Table 3

Association of pericardial fat volume with CVD events

Model	HR (95% CI)	*P*	*P* for interaction with ethnicity
Model 1	1.24 (1.16-1.33)	<0.001	0.26
Model 2	1.23 (1.14-1.32)	<0.001	0.16
Model 3	1.10 (1.00-1.20)	0.050	0.087
Model 4	1.09 (0.99-1.19)	0.080	0.080
Model 5	1.07 (0.98-1.16)	0.13	0.081

HR was expressed in terms of per SD 41.6 cm^3 increase in pericardial fat volume. The covariates in different adjustment models were described in Table 2 legend.

Table 4

Association of pericardial fat volume with CVD events by ethnicity

Ethnicity	CVD events, %	Continuous model		Binary categorical model	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Caucasian	10.7	0.97 (0.84-1.12)	0.71	0.90 (0.66-1.24)	0.53
African American	9.5	1.18 (0.96-1.44)	0.11	1.47 (0.97-2.22)	0.070
Hispanic American	9.2	1.31 (1.09-1.57)	0.004	1.66 (1.11-2.50)	0.014
Chinese American	5.9	1.05 (0.63-1.75)	0.85	0.65 (0.28-1.54)	0.33

HR was expressed in terms of per SD 41.6 cm^3 increase in pericardial fat volume in the continuous model, and was expressed in term of the presence of elevated pericardial fat volume in the binary categorical model.

Data were adjusted for all the covariates in the model 4 of Table 2.