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Differential Effect of soluble Intercellular Adhesion Molecule-1 on the Progression of Atherosclerosis as Compared to Arterial Thrombosis: A Prospective Analysis of the Women's Health Study

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Abstract

Background—Soluble intercellular adhesion molecule-1 (sICAM-1) is a transmembrane protein involved in the migration and adhesion of leukocytes to the vascular endothelium. While some studies indicate that elevated baseline sICAM-1 levels predict cardiovascular events, most of these studies were done in men; moreover, uncertainty exists regarding whether sICAM-1 levels predict vascular events consistent with acute thrombosis versus atherosclerotic disease progression.

Methods and Results—In this prospective evaluation of 23,984 apparently healthy women, we measured sICAM-1 levels and followed participants for the development of cardiovascular (CVD) endpoints typically associated with atherosclerotic disease progression with resultant vessel narrowing (percutaneous transluminal angioplasty and coronary artery bypass grafting) and endpoints typically associated with vascular thrombosis and vessel occlusion (myocardial infarction, ischemic stroke and death from a coronary cause). During a mean follow-up of 10 years, there were 741 events. For vascular events indicative of coronary atherosclerotic disease progression with luminal narrowing, Cox-proportional hazards models revealed an increase in vascular event rates from the lowest to highest quintile of baseline sICAM-1 after adjustment for CVD risk factors [Hazard Ratios (HR) 1.0, 1.4, 1.1, 1.6, 1.6, p trend=0.008]. By contrast, for endpoints reflective of acute vessel thrombosis, we found no association with sICAM-1 levels [HR for myocardial infarction (MI): 1.0, 1.2, 0.9, 1.2, 1.0, p trend=0.7; HR for stroke (CVA): 1.0, 0.9, 1.0, 1.0, 1.1, p trend = 0.6; HR for cardiovascular death: 1.0, 0.9, 0.7, 0.7, 0.8, p trend =0.7] except among smokers (RR= 1.0, 1.4, 2.8, 3.8, 3.7, p =0.007).

Conclusions—Among women without a history of cardiovascular disease, sICAM-1 levels are predictive of CVD events that reflect coronary atherosclerotic disease progression and vessel narrowing, but not those events associated with acute thrombosis/vessel occlusion.

Keywords

Cellular adhesion molecule; Cardiovascular disease; Women

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Cellular adhesion molecules are markers of inflammation that are hypothesized to play a major role in the initiation of atherosclerotic lesions (1). Soluble intercellular adhesion molecule-1 belongs to a glycoprotein receptor super-family that includes vascular cell adhesion molecule (VCAM-1) and platelet endothelial cellular adhesion molecule; these molecules mediate the adhesion and migration of leukocytes to vascular endothelium (2). Soluble intercellular adhesion molecule-1 concentrations are elaborated by cytokine stimulation. While sICAM-1 is found in atherosclerotic lesions (3–5), it is unclear whether plasma concentrations are predictive of CVD events associated with plaque thinning and rupture resulting in myocardial infarction (MI) or coronary death, as opposed to events associated with densely encapsulated advanced atherosclerotic lesions that cause angina or claudication.

Research from the Atherosclerosis Risk in Communities Study (ARIC) and Physicians' Health Study (PHS) related to sICAM-1 as a predictor of coronary heart disease risk support the predictive capacity of sICAM-1 for vascular events associated with plaque instability/rupture and thrombosis (6–8). However, other studies show no or a weak association between sICAM-1 levels and events associated with plaque rupture/thrombosis (9–11). By contrast, data regarding sICAM-1 levels and established CHD or peripheral arterial disease have been more consistently positive suggesting that sICAM-1 might be a better indicator of advanced atherosclerotic lesions that symptomatically result in performing coronary revascularization procedures (12–15).

Another area of uncertainty relates to whether the aforementioned data are similar in women since a majority of studies have been limited to men. The latter is of potential importance because some data indicate that short-term oral hormone replacement therapy (HRT) intake decreases sICAM-1 levels, a finding that could affect any relationship of sICAM-1 with CVD events (16–17). Due to these pathophysiologic issues, we sought to examine whether baseline sICAM-1 levels are predictive of CVD events related to plaque thinning and rupture/thrombosis or atherosclerotic disease progression in a large cohort of apparently healthy women.

METHODS

Study Population

Participant data came from the Women's Health Study (WHS), a randomized, placebo controlled trial of vitamin E and aspirin for the primary prevention of cardiovascular events and cancer among apparently healthy post-menopausal women (18). EDTA plasma specimens were collected from 28,345 women and stored in liquid nitrogen until the time of analysis. Of these women, complete baseline data on age, smoking status, weight, height, diabetic status, hormone replacement therapy status, hypertension, family history of myocardial infarction (MI), alcohol use, physical activity and lipoprotein and C-reactive protein levels were available for 23,984 participants who form the basis of this analysis. Participants were followed for 10 years for incident CVD events associated with plaque instability such as ischemic stroke, non-fatal myocardial infarction and cardiovascular death, as well as events indicative of coronary vessel narrowing (percutaneous coronary angioplasty/stenting, coronary artery bypass grafting).

We considered only events confirmed upon review by the trial's endpoint committee. Myocardial infarction was confirmed if symptoms met the criteria of the World Health Organization and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiographic criteria. Stroke was considered confirmed if participant symptoms were consistent with a new neurologic deficit lasting greater than 24 hours. Computed tomographic scans and magnetic resonance images were used to differentiate hemorrhagic and ischemic stroke. Revascularization procedures were confirmed by a review

of hospital records. Coronary heart disease death was confirmed by review of autopsy reports, death certificates, medical records and family member reports regarding the circumstances of death.

Biochemical Measurements

Baseline blood samples were assayed utilizing a standard commercially available assay for sICAM-1 by ELISA (R & D Systems, Minneapolis, MN) that utilized a quantitative sandwich enzyme immunoassay technique. This assay is similar to that used in previously published studies (7–9,12,14). The assay has a sensitivity of 0.35ng/ml and day to day variabilities at concentrations of 64.2, 117, 290 and 453 ng/ml are 10.1, 7.4, 6.0 and 6.1% respectively. C-reactive protein (CRP) levels were obtained by use of a validated, high sensitivity assay (Denka Seiken). Lipid concentrations were determined in a certified Centers for Disease Control and Prevention laboratory on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis).

Statistical Analyses

Baseline demographic and clinical characteristics were reported as means or proportions, and the significance of any differences were assessed by analysis of variance for continuous variables or the chi-square statistic for categorical variables. Since the distribution of sICAM-1 levels are skewed, medians are reported and sICAM-1 concentrations were log-transformed for analyses. Spearman correlation coefficients evaluated the relationship between baseline sICAM-1 levels and individual CVD risk factors.

The relative risk of cardiovascular events in quintiles 2 through 5 of sICAM-1 was calculated for all participants (HRT users and non-users) using Cox-proportional hazards models (referent: quintile 1). Quintiles were based on distributions of sICAM-1 among the 13, 501 women who were not taking hormone replacement therapy (HRT) at study entry. Multivariable adjusted models controlled for age, smoking status, diabetic status, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), body mass index (BMI), history of hypertension, family history of myocardial infarction < 60 years old, alcohol use, physical activity and baseline CRP levels. Stratified analyses were also performed to assess the risk of cardiovascular events among: 1) those women taking and not taking HRT and 2) never smokers, past smokers and smokers. Any difference in the distribution of baseline sICAM-1 levels between women who were taking and not taking HRT was evaluated by the Wilcoxon rank sum test.

We tested for trend across increasing quintiles of sICAM-1 by using a single ordinal term for the quintile in a Cox-proportional hazards model. Testing for deviation from linearity was performed by comparing models containing quintile indicators with those containing a linear term by means of the likelihood ratio test with 3 degrees of freedom. All p values were 2-tailed and are reported at the $\alpha = 0.05$ level.

RESULTS

The mean age and body mass index (BMI) of the 23,984 women at baseline were 54.2 ± 7.1 years and 25.9 ± 5.0 kg/m² respectively; 24.7% of the cohort had a history of hypertension, 2.7% had diabetes, 11.4 % were current smokers and 12.8 % had a family history of MI. The overall distribution of sICAM-1 levels among the women who were not taking HRT is shown in Table 1. In contrast to prior reports, we found no significant differences between baseline sICAM-1 levels among women not taking [343.5 ng/ml, interquartile range (IQR): 300.9, 396.6] and those women who were taking HRT [341.4 ng/ml, IQR: 300.8, 391.3] ($p=0.08$). As shown in Table 2, women who belonged to the highest quintile of sICAM-1 had a higher prevalence of traditional CVD risk factors compared to women in quintiles 1–4 of sICAM-1.

Spearman correlation coefficients regarding the association between baseline levels of sICAM-1 and traditional CVD risk factors demonstrated modest correlations between **log normalized sICAM-1 levels and log normalized CRP ($r=0.29$), BMI ($r=0.22$), HDL ($r=-0.22$), and current smoking ($r=0.29$) [each $p<0.001$].**

Next, in order to examine the issue related to plaque rupture/thrombosis as compared to vessel narrowing due to progressive atherosclerotic disease, we evaluated the individual relationship between myocardial infarction, stroke, coronary revascularization and cardiovascular death and baseline sICAM-1 levels. There were a total of 741 cardiovascular events over a median of 10.2 years (inter-quartile range 9.7, 10.6) of follow-up. As shown in Table 3, after adjustment for age, smoking status, diabetic status, LDL, HDL, BMI, history of hypertension, history of diabetes, family history of myocardial infarction < 60 years old, alcohol, physical activity and CRP, the relative risks of incident CVD events associated with plaque rupture with thrombosis among all participants (i.e users and non-users of HRT) according to quintile of sICAM-1 were for MI (HR: 1.0, 1.2, 0.9, 1.2, 1.0; $p_{\text{trend}}=0.7$), stroke (HR: 1.0, 0.9, 1.0, 1.0, 1.1; $p_{\text{trend}}=0.6$) and cardiovascular death (HR: 1.0, 0.9, 0.7, 0.7, 0.8; $p_{\text{trend}}=0.7$). Of note, trends across quintiles of sICAM-1 were also not significant for MI ($p_{\text{trend}}=0.9$), stroke ($p_{\text{trend}}=0.5$) and CVD death ($p_{\text{trend}}=0.8$) when analyses were repeated without control for CRP. By contrast, for CVD events related to atherosclerotic disease progression and vessel narrowing, there was a statistically significant relationship observed between increasing baseline sICAM-1 concentrations (HR for coronary revascularization: 1.0, 1.4, 1.1, 1.6, 1.6, $p_{\text{trend}}=0.008$). Table 4 shows the relative risks of total cardiovascular events according to baseline sICAM-1 concentration (Fully adjusted model HR: 1.0, 1.1, 1.0, 1.2, 1.2; $p_{\text{trend}}=0.06$). As also shown in Table 4, stratification by HRT use did not alter the relationship between sICAM-1 levels and total cardiovascular events.

Since smoking is known to influence sICAM-1 concentrations, we also evaluated whether smoking modified the relationship between sICAM-1 levels and **total** CVD events. Median sICAM-1 levels were 422.3 (IQR: 358.4, 496.1), 337.5 (298.2, 385.0) and 335.7 (296.6, 379.8) among current smokers, past smokers and never smokers. After determining increasing quintile cut-points for baseline distribution of sICAM-1 levels among never smokers, we observed a significant relationship between increasing sICAM-1 levels and **total** CVD events among smokers (**Fully adjusted** RR= 1.0, 1.4, 2.8, 3.8, 3.7, $p=0.007$), but not among past-smokers (1.0, 1.1, 0.8, 1.0, 1.0, $p=0.95$) or never smokers (1.0, 1.3, 1.1, 1.2, 1.3, $p=0.3$).

DISCUSSION

In this prospective cohort of 23,984 initially healthy women, we observed a statistically significant association between baseline sICAM-1 concentrations and coronary revascularization, an endpoint typically indicative of advanced atherosclerotic disease and vessel narrowing. There was no relationship between baseline sICAM-1 levels and events usually associated with plaque rupture/thrombosis. These findings suggest that baseline sICAM-1 levels do not independently predict incident “vascular thrombotic” CVD events, but elevated sICAM-1 levels may be more indicative of vascular atherosclerotic burden. These data additionally extend prior research by utilizing a large prospective cohort of women and overcome issues related to sample size and the case control nature of previous reports.

From a pathophysiologic standpoint, since adhesion molecules influence atherosclerotic disease progression by playing a role in the recruitment and adhesion of leukocytes to the endothelium (1–2), our data are intriguing because they suggest that while sICAM-1 might serve to propagate lesion activation resulting in anginal episodes or a positive exercise stress test, sICAM-1 does not promote thrombotic lesion formation that might directly lead to acute vessel occlusion. Additionally, since sICAM-1 levels are in part a result of shedding, it is

possible that measurement of this component in plasma does not reflect the actual inflammatory state of the vessel wall that involves bound sICAM-1 but instead reflects a generalized inflammatory state.

With regards to the predictive ability of sICAM-1 and its association with plaque instability/vessel thrombosis or advanced atherosclerotic disease with luminal narrowing, prior studies remain divided. While some studies have found a positive association between sICAM-1 and incident thrombotic vascular events, other studies have found no relationship. Data in support of vascular plaque instability/thrombosis include the ARIC study that demonstrated baseline sICAM-1 levels were higher among patients with incident CHD compared to controls after adjusting for traditional CVD risk factors, white blood cell count, von Willebrand factor and fibrinogen (CHD odds ratio = 5.5, 95% CI 2.5–12.2 for the highest quartile compared to the lowest quartile) (7). Similar findings were also reported in the PHS among initially healthy male physicians where sICAM-1 was associated with risk of MI, particularly among those physicians with sICAM-1 concentrations in the highest quartile (Relative Risk = 1.8, 95% CI 1.1–2.4) (8). Additional data from the PRIME Study support the findings in ARIC and PHS, suggesting a relationship between baseline sICAM-1 levels and thrombotic CVD events among persons without known CAD (21). By contrast, other data demonstrate no association between sICAM-1 and incident vascular thrombotic events. For example, data from the British Regional Heart Study that also included a meta-analysis of several studies indicated no statistically significant relationship between sICAM-1 and incident CHD events (odds ratio = 1.1, 95% CI 0.8–1.6) (9). Similar results were reported by Blankenberg and colleagues where among patients with known CAD, sICAM-1 was not independently associated with future CVD events (10).

Data related to the predictive capacity of baseline sICAM-1 levels in the context of known CAD and peripheral arterial disease have been more consistent. For example, Rhode et al. showed that sICAM-1 levels increased progressively across tertiles of carotid intimal thickness suggesting that levels predict carotid artery disease progression (15). Further research from Kondo et al. on middle aged outpatients showed that baseline sICAM-1 levels are associated with carotid atherosclerosis progression (22). Data from the Edinburgh Artery Study also revealed that sICAM-1 is associated with lower extremity atherosclerotic disease progression (13). Likewise, in the PHS, sICAM-1 levels were significantly related to symptomatic peripheral arterial disease (12), while in the Bezafibrate Infarction Prevention Study of patients with *chronic* CHD, sICAM-1 predicted risk of future coronary events and ischemic stroke (11,23). Thus, our finding of a relationship between sICAM-1 and coronary revascularization is consistent with these results that demonstrate a relationship between baseline sICAM-1 levels with advanced extensive atherosclerotic disease.

The current data also examine the effect of HRT on sICAM-1 levels. This is an important issue since previous studies were mostly comprised of male subjects. Furthermore, studies of HRT use among women participants utilized short-term oral HRT preparations and report that oral HRT decreases sICAM-1 levels (16–17). This reported decrease in sICAM-1 levels was observed for both estrogen only and estrogen-progestin combination therapy preparations. However, in this large cohort of 23,984 women without known CVD, our results indicate no significant differences between baseline sICAM-1 levels among those women not taking HRT compared to those taking HRT. Of note, women taking HRT were older than those women not taking HRT (mean age 55.0 ± 6.2 years versus 53.5 ± 7.7 years).

In this study, smoking was associated with increased levels of sICAM-1. Median sICAM-1 levels were approximately 20% lower among non-smokers (past and never smokers) compared to smokers, and there was no significant difference in the median sICAM-1 levels of past smokers and never smokers. Among smokers, baseline sICAM-1 levels were significantly

associated with incident CVD events, a finding consistent with the “generalized” pro-inflammatory state of smoking and tendency to promote plaque instability. Our findings of higher sICAM-1 levels among smokers also concur with previous data that demonstrate a positive correlation between smoking and elevated sICAM-1 concentrations (19–20), as well as with other data indicating that smoking cessation results in decreased sICAM-1 serum concentrations among quitters compared to continuing smokers (20,24).

In this prospective cohort of apparently healthy women participating in the Women’s Health Study, baseline sICAM-1 levels are associated with subsequent risk of coronary revascularization, suggesting that baseline sICAM-1 concentrations might be more reflective of advanced atherosclerotic disease and angina as a related clinical correlate rather than with vascular atherosclerotic plaque instability/thrombosis. Notwithstanding this, it is important to note that even for the endpoint of revascularization, effect sizes are generally moderate and imply that sICAM-1 might not be a powerful predictor of CVD risk. To the best of our knowledge, these data represent the largest examination of sICAM-1 as a potential predictor of CVD events among women.

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Table 1

Distribution of sICAM-1 levels among 13, 501 Nonusers of HRT at baseline

Age Range	N	5 th	10 th	25 th	50 th	75 th	90 th	95 th
sICAM-1					ng/ml			
45–54 years	8890	239.8	259.1	291.3	332.0	382.7	444.6	494.2
55–64 years	2977	261.8	284.9	319.2	363.0	417.5	486.6	529.7
65–74 years	1484	273.5	292.1	328.6	370.3	421.0	472.1	514.0
≥ 75 years	150	276.1	288.1	329.5	369.4	414.8	453.1	493.3

Table 2

Baseline Characteristics of Participants, All Participants (N=23, 984)

Variable	Quintile 1 sICAM-1 < = 290.5 ng/ml (N=4714)	Quintile 2 sICAM-1 (>290.5–326.4 ng/ml (N= 4957)	Quintile 3 sICAM-1 (>326.4–361.6 ng/ml) (N= 4898)	Quintile 4 sICAM-1 (>361.6–411.2 ng/ml) (N= 4778)	Quintile 5 sICAM-1 >411.2 ng/ml (N=4637)	P trend
Age (yrs)	52.5 ± 6.3	53.5 ± 6.7	54.4 ± 7.2	55.0 ± 7.3	55.4 ± 7.5	<0.001
Smoking						
Never	57.0	56.6	56.0	51.1	38.3	
Past	39.0	38.8	38.0	37.9	29.7	
Current	4.1	4.6	5.9	11.0	32.0	<0.001
BMI (kg/m ²)	24.4 ± 4.0	25.1 ± 4.2	25.9 ± 4.8	26.6 ± 5.1	27.5 ± 5.8	<0.001
Hypertension, %	16.8	20.1	23.8	29.0	34.2	<0.001
Diabetes, %	0.9	1.4	2.1	3.0	6.5	<0.001
Family History of MI, %	12.7	11.7	12.9	13.6	13.2	0.06
Cholesterol (mg/dL)						
Total	203.9 ± 40.3	208.2 ± 41.1	212.1 ± 40.6	215.9 ± 42.3	216.5 ± 42.4	<0.001
LDL	117.0 ± 32.7	121.0 ± 33.1	124.5 ± 33.6	127.5 ± 34.7	128.9 ± 35.0	<0.001
HDL	57.8 ± 15.2	55.8 ± 14.7	54.4 ± 14.5	52.8 ± 14.8	48.4 ± 14.3	<0.001
Triglycerides, IQR	97.5 (71.0, 141.0)	110.0 (78.0, 158.0)	118.0 (84.0, 173.0)	131.0 (90.0, 188.0)	145.0 (100.0, 210.0)	<0.001
Alcohol use, %						
Rare/never	37.1	40.7	44.1	47.2	50.8	
1–3/month	12.5	13.6	13.7	13.8	13.0	
1–6/week	37.4	34.2	32.1	30.4	26.9	
1+/day	12.9	11.6	10.1	8.6	9.4	<0.001
Exercise, %						
Rare/never	31.1	33.1	36.1	39.0	46.8	
<1 X/week	18.9	19.1	19.1	20.1	20.5	
1–3 X/week	36.1	34.6	32.9	30.9	25.5	

Variable	Quintile 1 sICAM-1 < = 290.5 ng/ml (N=4714)	Quintile 2 sICAM-1 >290.5–326.4 ng/ml (N= 4957)	Quintile 3 sICAM-1 >326.4–361.6 ng/ml (N= 4898)	Quintile 4 sICAM-1 (>361.6 –411.2 ng/ml) (N= 4778)	Quintile 5 sICAM-1>411.2 ng/ml (N=4637)	P trend
4 X/week	14.0	13.3	11.9	10.1	7.3	<0.001

Values are represented as means $\pm$ SD; the IQR represents the 25th and 75th percentiles
HDL= High density lipoprotein; LDL = Low density lipoprotein

Fully Adjusted Relative Risk of Cardiovascular Events According to Baseline Plasma Levels of sICAM-1 Among 23, 984 Participants (HRT and non-HRT users)

Table 3

Event	Quintile of sICAM-1					p trend
	1	2	3	4	5	
Myocardial Infarction (N= 187)	1.0	1.2 (0.7–2.2)	0.9 (0.5–1.6)	1.2 (0.7–2.1)	1.0 (0.5–1.7)	0.7
Stroke (N= 256)	1.0	0.9 (0.5–1.4)	1.0 (0.7–1.6)	1.0 (0.6–1.5)	1.1 (0.7–1.6)	0.6
Cardiovascular Death (N= 115)	1.0	0.9 (0.4–1.8)	0.7 (0.4–1.4)	0.7 (0.4–1.4)	0.8 (0.4–1.6)	0.7
Coronary Re-vascularization (N= 415)	1.0	1.4 (0.9–2.0)	1.1 (0.7–1.6)	1.6(1.1–2.4)	1.6(1.1–2.4)	0.008

* fully adjusted model: age, past smoking, current smoking, LDL, HDL, history of hypertension, history of diabetes, family history of MI < 60 years old, alcohol, physical activity, baseline CRP

+ Please note that the total number of events in this table exceeds 741 because some women experienced more than one event

Table 4
Relative Risk of Cardiovascular Events* According to Baseline Plasma Levels of sICAM-1

Model	1	2	3	4	5	p trend
All Participants (N= 23, 984)						
1	1.0	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.8 (1.4–2.4)	2.7 (2.1–3.5)	<0.001
2	1.0	1.1 (0.8–1.5)	1.0 (0.7–1.3)	1.3 (1.0–1.7)	1.3 (1.0–1.7)	0.02
3	1.0	1.1 (0.8–1.5)	1.0 (0.7–1.3)	1.2 (1.0–1.6)	1.2 (1.0–1.6)	0.06
Nonusers of HRT (N=13, 501)						
1	1.0	1.4 (0.9–2.1)	1.4 (0.9–2.1)	2.0 (1.4–3.0)	3.2 (2.2–4.6)	<0.001
2	1.0	1.2 (0.8–1.8)	1.0 (0.7–1.6)	1.3 (0.9–1.9)	1.4 (0.9–2.0)	0.07
3	1.0	1.2 (0.8–1.8)	1.0 (0.7–1.6)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	0.1
Users of HRT (N= 10, 483)						
1	1.0	1.1 (0.7–1.6)	1.0 (0.7–1.6)	1.6 (1.1–2.4)	2.3 (1.6–3.3)	<0.001
2	1.0	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.3 (0.9–1.9)	1.2 (0.8–1.8)	0.1
3	1.0	1.0 (0.7–1.5)	0.9 (0.6–1.4)	1.3 (0.9–1.8)	1.1 (0.8–1.7)	0.3

Model 1 – adjusted for age; Model 2 – adjusted for age, past smoking, current smoking, LDL, HDL, BMI, history of hypertension, history of diabetes, family history of MI < 60 years old, alcohol, physical activity; Model 3 – adjusted for age, past smoking, current smoking, LDL, HDL, BMI, history of hypertension, history of diabetes, family history of MI < 60 years old, alcohol, physical activity, baseline CRP

* Cardiovascular events = MI, ischemic stroke, CVD death, coronary revascularization