Supplemental Materials

Association of an HDL apolipoproteomic score with the presence of coronary atherosclerosis and incident cardiovascular death

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Supplementary Table 1. Baseline characteristics

Characteristic	Value
Age, y	66.6 (11.3)
Female sex	267 (28.3%)
Ethnicity	
Caucasian	884 (93.7%)
African	22 (2.3%)
Asian / Pacific	11 (1.2%)
Hispanic	19 (2.0%)
Native American	2 (0.2%)
Other / Unknown	5 (0.5%)
Current smoker	118 (12.5%)
Hypertension	692 (73.4%)
Coronary artery disease	481 (51.0%)
Prior myocardial infarction	226 (24.0%)
Prior CVA/TIA	95 (10.1%)
Diabetes mellitus	237 (25.1%)
Systolic blood pressure, mmHg	136.8 (22.4)
Diastolic blood pressure, mmHg	72.9 (11.5)
Plasma lipids, mg/dL	
Total cholesterol	152.6 (37.8)
LDL cholesterol	83.9 (31.7)
HDL cholesterol	45.4 (15.6)
Triglycerides	102.0 (75.0-141.5)
Apolipoprotein A1, mg/dL	127.9 (27.4)
Apolipoprotein B, mg/dL	85.4 (24.2)
hsCRP, mg/L	2.5 (1.0-5.4)
Statin prescription	667 (71.1%)

Continuous variables are presented as mean (standard deviation) and categorical variables are presented as count (percentage). Plasma lipids and biomarkers were sampled at the time of angiography. Coronary artery disease was defined by prevalent clinical status prior to diagnostic coronary angiography.
* Triglycerides and hsCRP are represented as median (interquartile range)

Supplementary Table 2. Multivariable association of cardiovascular risk factors, including plasma lipids, with pCAD

Parameter	Parameter estimate	Standard error	*P*
Age	-0.0083	0.027	0.76
Male sex	-0.048	0.057	0.39
Statin prescription	0.15	0.057	0.009
Diabetes mellitus	0.24	0.058	<0.001
Current smoker	-0.10	0.080	0.17
Systolic blood pressure (mmHg)	-0.073	0.025	0.004
History of hypertension	0.083	0.059	0.163
HDL cholesterol	-0.64	0.026	<0.001
Non-HDL cholesterol	0.060	0.027	0.025

Continuous variables are standardized to mean = 0 and standard deviation = 1.

Supplementary Table 3. Multivariable association of cardiovascular risk factors, including plasma apoA-1 and apoB, with pCAD

Parameter	Parameter estimate	Standard error	*P*
Age	-0.026	0.027	0.34
Male sex	-0.051	0.058	0.38
Statin prescription	0.28	0.058	<0.001
Diabetes mellitus	0.23	0.059	<0.001
Current smoker	-0.13	0.077	0.088
Systolic blood pressure (mmHg)	-0.061	0.026	0.019
History of hypertension	0.14	0.061	0.018
Log(apoA-1)	-0.61	0.027	<0.001
Log(apoB)	0.21	0.027	<0.001

Continuous variables are standardized to mean = 0 and standard deviation = 1.

Supplementary Table 4. Association statistics for pCAD with varying degrees of angiographic CAD severity

		Model 1			Model 2		
CAD severity	**N (%)**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
≥30% lesion in ≥1 vessel	736 (78.0%)	1.60	1.36-1.88	<0.001	1.45	1.15-1.82	0.002
≥50% lesion in ≥1 vessel	650 (68.9%)	1.56	1.35-1.81	<0.001	1.34	1.09-1.64	0.006
≥70% lesion in ≥1 vessel	587 (62.2%)	1.64	1.42-1.90	<0.001	1.39	1.14-1.69	0.001
≥70% lesion in ≥2 vessels	340 (36.1%)	1.65	1.42-1.92	<0.001	1.40	1.14-1.73	0.002

Model 1 represents univariate analyses. Model 2 represents multivariable analysis, adjusted for age, sex, statin prescription, diabetes mellitus, smoking status, systolic blood pressure, hypertension, log(apoA-1), and log(apoB).

Supplementary Table 5. Optimal cut-off points for pCAD across varying degrees of angiographic CAD severity

CAD severity	N Correctly Predicted Cases	N Correctly Predicted Non-Cases	N Non-Cases Predicted as Cases	N Cases Predicted as Non-Cases	Sensitivity	Specificity	Optimal cut point	Youden value
≥30% lesion in ≥1 vessel	476	123	79	260	64.7%	60.9%	1.26	0.26
≥50% lesion in ≥1 vessel	434	167	121	216	66.80%	58.80%	1.26	0.25
≥70% lesion in ≥1 vessel	404	200	151	183	68.8%	57.0%	1.26	0.26
≥70% lesion in ≥2 vessels	251	301	297	89	73.8%	50.3%	1.27	0.24

Supplementary Table 6. Multivariable association of HDL apolipoproteins with angiographic CAD.

Parameter	Parameter estimate	Standard error	*P*
HDL apoA-1	-0.17	0.18	0.33
HDL apoC-1	-0.45	0.16	0.004
HDL apoC-2	0.10	0.18	0.58
HDL apoC-3	0.10	0.13	0.47
HDL apoC-4	0.17	0.13	0.18
Age	0.30	0.08	0.0004
Male sex	1.03	0.18	<0.0001
Statin prescription	0.60	0.17	0.0005
Diabetes mellitus	0.56	0.19	0.003
Current smoker	0.36	0.24	0.13
Systolic blood pressure (mmHg)	0.04	0.08	0.60
History of hypertension	0.28	0.18	0.11
Log(apoA-1)	0.004	0.16	1.00
Log(apoB)	-0.01	0.09	0.99

Continuous variables are standardized to mean = 0 and standard deviation = 1.

Supplementary Table 7. C-statistics for the presence of CAD across clinical CAD risk factors, plasma apolipoproteins, and pCAD.

Variable	C-statistic (95% CI)	C-statistic difference versus pCAD (95% CI)	*P* for C-statistic difference
Age	0.57 (0.53-0.61)	-0.063 (-0.12- -0.0065)	0.029
Sex	0.61 (0.58-0.64)	-0.022 (-0.070-0.025)	0.36
Statin	0.59 (0.56-0.62)	-0.039 (-0.086-0.0085)	0.11
Diabetes mellitus	0.57 (0.54-0.60)	-0.060 (-0.10- -0.018)	0.0054
Smoker	0.51 (0.49-0.53)	-0.12 (-0.17- -0.080)	<0.0001
Systolic blood pressure	0.52 (0.48-0.56)	-0.11 (-0.16- -0.052)	0.0002
Hypertension	0.57 (0.54-0.60)	-0.065 (-0.11- -0.020)	0.0051
Log(ApoB)	0.55 (0.51-0.58)	-0.085 (-0.14- -0.029)	0.0030
Log(ApoA1)	0.61 (0.58-0.65)	-0.016 (-0.050-0.018)	0.35
pCAD	0.63 (0.59-0.67)	NA	NA

Supplementary Table 8. Multivariable model fit metrics with and without the presence of pCAD

Criterion	Intercept Only	Intercept and Covariates
Model 1		
AIC	1194.069	1072.531
SC	1198.875	1125.394
-2 Log Likelihood	1192.069	1050.531
Model 2		
AIC	1194.069	1081.268
SC	1198.875	1129.325
-2 Log Likelihood	1192.069	1061.268

Model 1 represents multivariable analysis, adjusted for age, sex, statin prescription, diabetes mellitus, smoking status, systolic blood pressure, hypertension, log(apoA-1), and log(apoB). Model 2 represents multivariable analysis, adjusted for age, sex, statin prescription, diabetes mellitus, smoking status, systolic blood pressure, hypertension, log(apoA-1), log(apoB), and pCAD.
AIC = Akaike Information Criteria; HDL = high-density lipoprotein; SC = Schwarz Criterion

Supplementary Table 9. Multivariable association of pCAD with incident cardiovascular mortality

	All		***Without* CAD**		***With* CAD**	
Parameter	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age	2.55 (1.98-3.28)	<0.0001	2.85 (1.55-5.23)	0.0008	2.51 (1.89-3.33)	<0.0001
Male sex	1.05 (0.66-1.68)	0.84	1.16 (0.41-3.33)	0.78	0.93 (0.55-1.58)	0.80
Statin prescription	0.85 (0.53-1.37)	0.51	0.48 (0.18-1.29)	0.15	1.00 (0.55-1.80)	0.99
Diabetes mellitus	2.33 (1.51-3.60)	0.0001	7.01 (2.43-20.24)	0.0003	1.76 (1.08-2.86)	0.023
Current smoker	1.68 (0.89-3.18)	0.11	0 (0,)	1.00	2.12 (1.09-4.11)	0.027
Systolic blood pressure (mmHg)	0.67 (0.53-0.85)	0.0007	0.66 (0.37-1.17)	0.16	0.68 (0.53-0.88)	0.0029
History of hypertension	1.34 (0.76-2.35)	0.31	1.21 (0.40-3.69)	0.74	1.41 (0.73-2.72)	0.31
Log(apoA-1)	1.03 (0.78-1.34)	0.86	0.86 (0.41-1.76)	0.67	1.14 (0.85-1.54)	0.38
Log(apoB)	0.99 (0.79-1.25)	0.94	1.01 (0.67-1.51)	0.97	0.96 (0.72-1.27)	0.75
Prevalent CAD	1.28 (0.75-2.20)	0.36	NA	NA	NA	NA
HDL pCAD	1.24 (0.93-1.66)	0.15	0.75 (0.38-1.49)	0.42	1.48 (1.07-2.05)	0.019

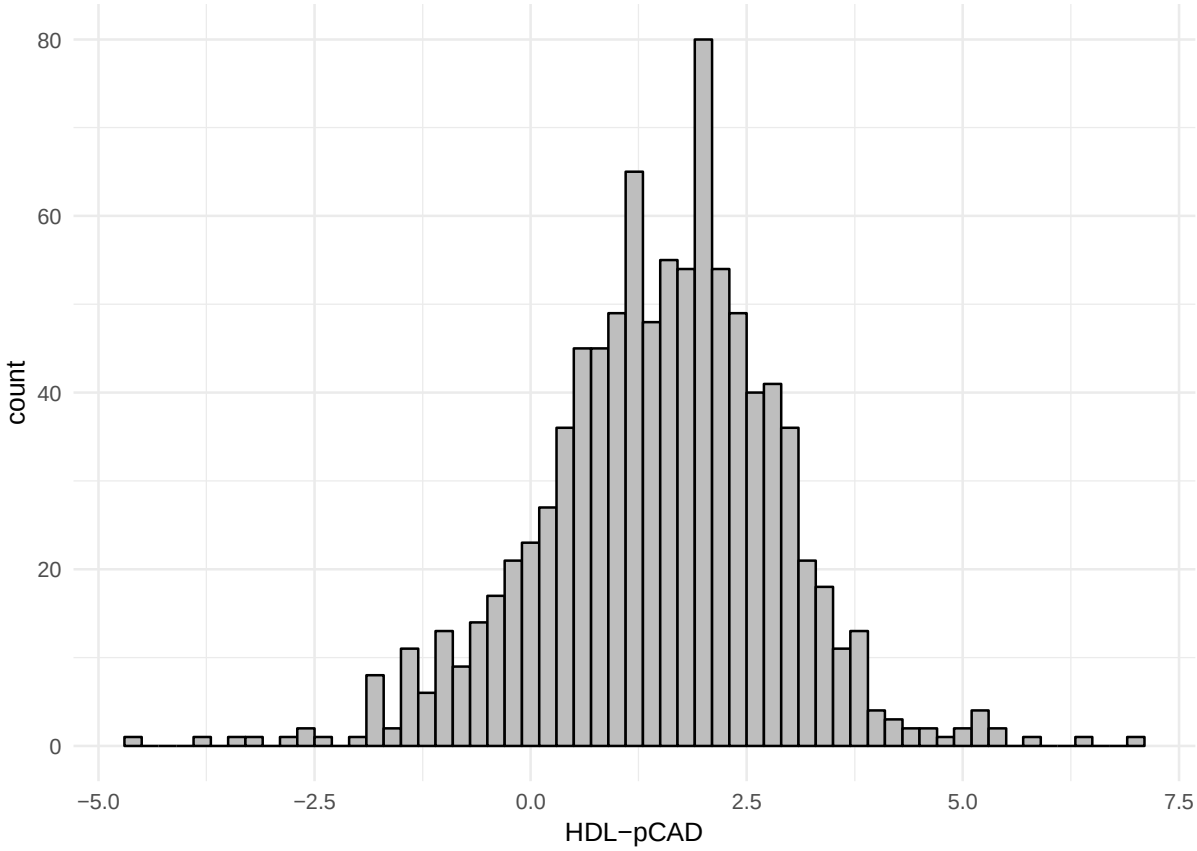
CAD is defined as the presence of coronary artery stenosis (≥70% luminal obstruction in at least one major coronary artery).

Supplementary Table 10. Multivariable association of HDL apolipoproteins with incident cardiovascular mortality

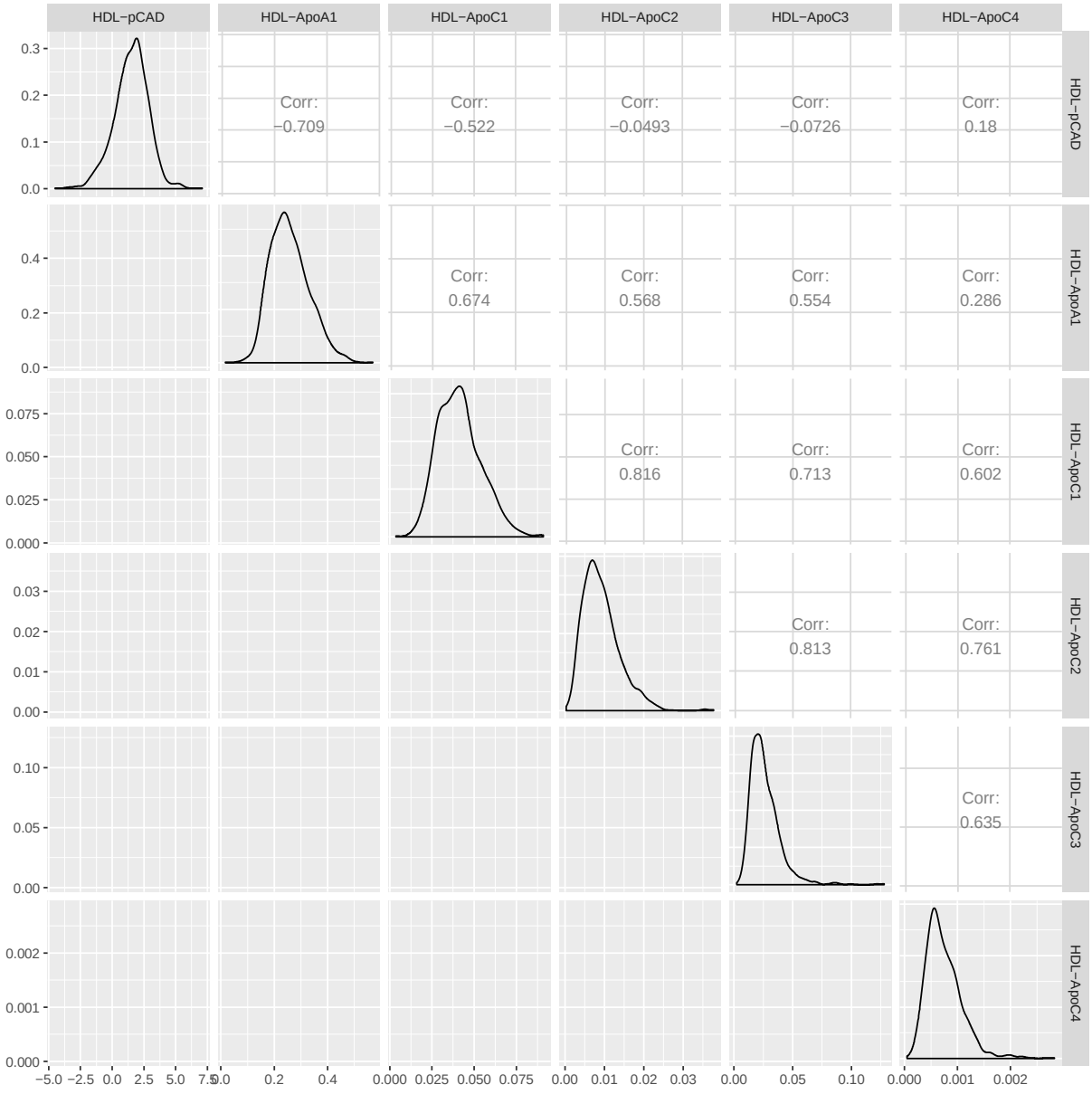
	All		***Without* CAD**		***With* CAD**	
Parameter	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
HDL apoA-1	1.02 (0.65-1.60)	0.93	1.28 (0.35-4.70)	0.71	0.89 (0.53-1.49)	0.66
HDL apoC-1	1.00 (0.68-1.48)	1.00	2.41 (0.80-7.23)	0.12	0.97 (0.64-1.48)	0.89
HDL apoC-2	0.98 (0.62-1.56)	0.95	0.11 (0.03-0.52)	0.005	1.35 (0.79-2.29)	0.27
HDL apoC-3	1.82 (1.44-2.30)	<0.0001	2.38 (1.48-3.82)	0.0003	1.60 (1.16-2.22)	0.004
HDL apoC-4	0.79 (0.56-1.12)	0.19	1.23 (0.50-3.03)	0.65	0.76 (0.51-1.13)	0.18
Age	2.51 (1.95-3.22)	<0.0001	3.36 (1.70-6.63)	0.0005	2.46 (1.86-3.25)	<0.0001
Male sex	1.18 (0.72-1.96)	0.51	1.39 (0.42-4.62)	0.59	1.10 (0.62-1.94)	0.75
Statin prescription	0.93 (0.57-1.53)	0.78	0.44 (0.15-1.29)	0.13	1.19 (0.64-2.18)	0.59
Diabetes mellitus	2.18 (1.40-3.40)	0.0006	5.74 (1.69-19.56)	0.005	1.78 (1.09-2.90)	0.02
Current smoker	1.80 (0.95-3.42)	0.07	0 (0,0)	1.00	2.23 (1.14-4.34)	0.02
Systolic blood pressure (mmHg)	0.68 (0.54-0.86)	0.001	0.72 (0.43-1.19)	0.72	0.71 (0.55-0.91)	0.008
History of hypertension	1.25 (0.71-2.20)	0.44	1.03 (0.31-3.39)	1.03	1.26 (0.65-2.44)	0.50
Log(apoA-1)	0.68 (0.47-0.99)	0.04	0.63 (0.19-2.06)	0.44	0.71 (0.46-1.10)	0.12
Log(apoB)	1.05 (0.82-1.33)	0.71	1.12 (0.70-1.78)	0.64	1.02 (0.76-1.37)	0.91
Prevalent CAD	1.34 (0.79-2.29)	0.28	NA	NA	NA	NA

CAD is defined as the presence of coronary artery stenosis (≥70% luminal obstruction in at least one major coronary artery).

Supplementary Figure 1. Distribution of pCAD in the CASABLANCA study

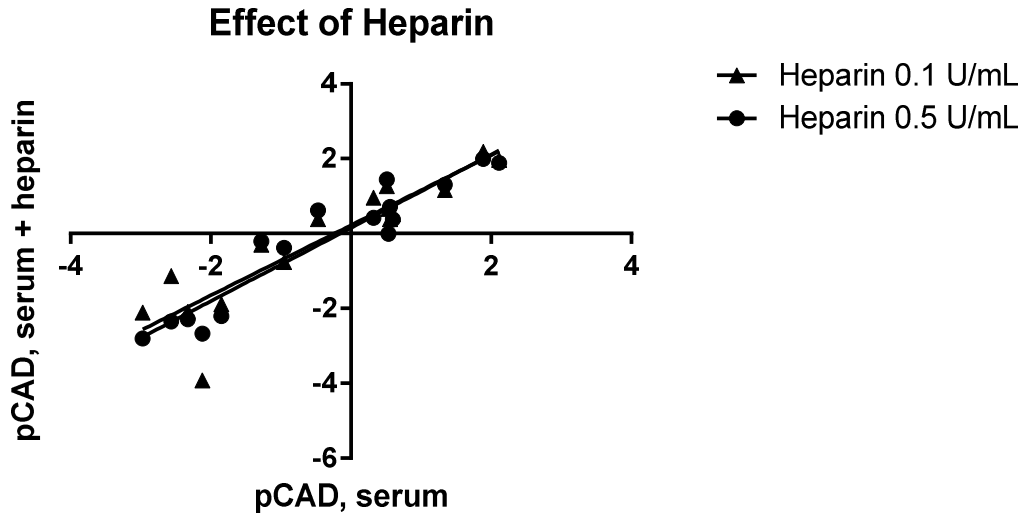


Supplementary Figure 2. Pairwise correlation of HDL proteins, including composite pCAD score



Density plots and pairwise correlations of each of the HDL proteins and composite pCAD score are depicted, including Pearson correlation coefficients.

Supplementary Figure 3. Effect of *in vitro* heparin administration to pCAD scores.



Across 17 serum samples representing a range of pCAD values, the influence of *in vitro* heparin supplementation was assessed. Heparin was administered at two doses – 0.1 U/mL (triangles in plot) and 0.5 U/mL (circles in plot).

Supplementary Figure 3. pCAD distributions among those with obstructive CAD by plasma apoA-1 quantile, diabetes mellitus, and incident cardiovascular death