

# **SUPPLEMENTAL MATERIAL**

**Table S1. Baseline and HIV characteristics for AIDS Clinical Trials Group (ACTG) cohort.**

<b>Demographic and Cardiovascular Characteristics of AIDS Clinical Trials Group (ACTG) cohort</b>				
<b>Characteristic</b>		<b>ACTG (N=4837)</b>	<b>Non-ACTG (N=2932)</b>	<b>Total (N=7769)</b>
<b>Demographics and Behavioral</b>				
Age (years)	Median (Q1,Q3)	49 (45,54)	51 (46,55)	50 (45,55)
	40-49	2,455 (51%)	1,275 (43%)	3,730 (48%)
	50-59	1,992 (41%)	1,369 (47%)	3,361 (43%)
	60+	390 (8%)	288 (10%)	678 (9%)
Natal sex	Male	3,048 (63%)	2,302 (79%)	5,350 (69%)
	Female	1,789 (37%)	630 (21%)	2,419 (31%)
Gender identity	Cisgender	4,665 (96%)	2,702 (92%)	7,367 (95%)
	Transgender Spectrum	78 (2%)	49 (2%)	127 (2%)
	Not reported	94 (2%)	181 (6%)	275 (4%)
Race	Black/African American	2,233 (46%)	975 (33%)	3,208 (41%)
	White	1,143 (24%)	1,561 (53%)	2,704 (35%)
	Asian	1,110 (23%)	28 (1%)	1,138 (15%)
	Other	351 (7%)	368 (13%)	719 (9%)
Ethnicity	N	2,066	1,852	3,918
	Hispanic or Latino	396 (19%)	302 (16%)	698 (18%)
	Not Hispanic or Latino	1,652 (80%)	1,534 (83%)	3,186 (81%)
	Unknown	18 (1%)	16 (1%)	34 (1%)
Smoking status	Current	1,055 (22%)	879 (30%)	1,934 (25%)
	Former	1,051 (22%)	853 (29%)	1,904 (25%)
	Never	2,725 (56%)	1,198 (41%)	3,923 (51%)
Substance use	Current	71 (1%)	81 (3%)	152 (2%)
	Former	1,103 (23%)	1,173 (40%)	2,276 (29%)
	Never	3,656 (76%)	1,677 (57%)	5,333 (69%)
<b>Cardiovascular and Metabolic</b>				
Hypertension		1,636 (34%)	1,138 (39%)	2,774 (36%)
Pre-existing diabetes mellitus		17 (<0.5%)	20 (1%)	37 (<0.5%)
BMI (kg/m <sup>2</sup> )	Median (Q1,Q3)	25.3 (22.2,29.1)	26.3 (23.6,29.9)	25.8 (22.8,29.4)
	<18.5	240 (5%)	47 (2%)	287 (4%)
	18.5-24.9	2,051 (42%)	1,067 (36%)	3,118 (40%)
	25-29.9	1,559 (32%)	1,104 (38%)	2,663 (34%)
	30+	985 (20%)	710 (24%)	1,695 (22%)
Triglycerides (mg/dL)	Median (Q1,Q3)	986 (20%)	124 (87,181)	114 (81,169)
LDL-C (mg/dL)	Median (Q1,Q3)	987 (20%)	111 (90,129)	108 (87,128)
HDL-C (mg/dL)	Median (Q1,Q3)	988 (20%)	46 (38,57)	48 (39,59)
<b>HIV Disease Characteristics and Other Co-morbid Conditions</b>				
<b>Characteristic</b>		<b>ACTG (N=4837)</b>	<b>Non-ACTG (N=2932)</b>	<b>Total (N=7769)</b>
<b>HIV-Related Health Status</b>				
Years since HIV diagnosis	Median (Q1,Q3)	12 (8,18)	14 (7,21)	13 (8,19)
Mode of HIV acquisition	Heterosexual Contact	2,927 (61%)	1,028 (35%)	3,955 (51%)
	Homosexual Contact	1,392 (29%)	1,362 (46%)	2,754 (35%)
	Injection Drug Use	73 (2%)	126 (4%)	199 (3%)
	Multiple Modes	130 (3%)	154 (5%)	284 (4%)
	Other	59 (1%)	40 (1%)	99 (1%)
	Unknown	254 (5%)	220 (8%)	474 (6%)
Nadir CD4 (cells/mm <sup>3</sup> )	<50	871 (18%)	538 (18%)	1,409 (18%)
	50-199	1,595 (33%)	797 (27%)	2,392 (31%)
	200-349	1,295 (27%)	746 (25%)	2,041 (26%)
	350+	952 (20%)	713 (24%)	1,665 (21%)
	Unknown	124 (3%)	138 (5%)	262 (3%)
History of AIDS-defining event		1,259 (26%)	554 (19%)	1,813 (23%)
CD4 count (cells/mm <sup>3</sup> )	Median (Q1,Q3)	616 (445,811)	627 (453,849)	621 (448,827)
HIV-1 RNA (copies/mL)	<LLQ	2,853 (88%)	2,397 (87%)	5,250 (88%)

	LLQ ≤400	310 (10%)	307 (11%)	617 (10%)
	400+	69 (2%)	61 (2%)	130 (2%)
HIV-1 RNA (log <sub>10</sub> copies/mL)	Median (Q1,Q3)	1.8 (1.5,2.4)	1.8 (1.5,2.2)	1.8 (1.5,2.3)
Total ART use (years)	Median (Q1,Q3)	9 (5,14)	10 (6,17)	10 (5,15)
ART regimen class	NRTI + INSTI	1,001 (21%)	990 (34%)	1,991 (26%)
	NRTI + NNRTI	2,708 (56%)	961 (33%)	3,669 (47%)
	NRTI + PI	809 (17%)	627 (21%)	1,436 (18%)
	NRTI-sparing	99 (2%)	104 (4%)	203 (3%)
	Other NRTI-containing	220 (5%)	250 (9%)	470 (6%)
<b>Other Co-morbidities</b>				
History of cancer		133 (3%)	123 (4%)	256 (3%)
History of non-AIDS cancer		65 (1%)	49 (2%)	114 (1%)
History of kidney disease		4 (<0.5%)	1 (<0.5%)	5 (<0.5%)
Chronic active HBV		124 (3%)	84 (3%)	208 (3%)
Chronic active HCV		80 (2%)	74 (3%)	154 (2%)

(Q1,Q3): interquartile range; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; ART: antiretroviral therapy; LLQ: lower limit of quantitation; NRTI: nucleoside reverse transcriptase inhibitor; INSTI: integrase strand transfer inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; HBV: hepatitis B virus; HCV: hepatitis C virus

**Table S2. Baseline characteristics for all participants, stratified by ASCVD tertiles.**

<b>Baseline characteristics for all participants, stratified by ASCVD category</b>					
<b>Variable</b>	<b>All participants (N = 4495)</b>	<b>Mean (SD)</b>			<b>P-value</b>
		<b>ASCVD risk 0% to &lt; 5% (n = 2644)</b>	<b>ASCVD risk 5% to 7.5% (n = 1040)</b>	<b>ASCVD risk &gt; 7.5% (n = 804)</b>	
Age (years)	49.9 (6.4)	47.3 (5.0)	52.1 (5.9)	55.6 (6.1)	<0.0001
Body Mass Index (kg/m <sup>2</sup> )	26.2 (5.9)	26.1 (6.1)	26.4 (5.6)	26.1 (5.5)	0.399
Total years smoked	20.2 (12.3)	17.5 (11.5)	20.7 (11.8)	24.1 (13.1)	<0.0001
CD4 count (cells/mm <sup>3</sup> )	654.1 (291.1)	661.4 (292.1)	650.7 (288.3)	634.5 (291.1)	0.0062
eGFR (mL/min)	99.1 (19.2)	101.5 (18.9)	96.1 (19.1)	95.1 (19.3)	<0.0001
LDL-C concentration (mg/dL)	107.2 (30.8)	106.7 (30.7)	109.6 (31.7)	105.9 (29.8)	0.79
HDL-C concentration (mg/dL)	51.5 (16.9)	52.7 (17.4)	50.1 (16.0)	49.2 (16.1)	<0.0001
Triglyceride concentration (mg/dL)	131.6 (82.0)	123.2 (75.3)	141.6 (84.7)	145.6 (94.9)	<0.0001
Glucose concentration (mg/dL)	89.6 (14.3)	88.8 (12.9)	90.2 (11.9)	91.8 (19.8)	<0.0001
<b>Variable</b>	<b>All participants</b>	<b>Participants, No./total No. (%)</b>			
		<b>ASCVD risk 0% to &lt; 5%</b>	<b>ASCVD risk 5% to 7.5%</b>	<b>ASCVD risk &gt; 7.5%</b>	
Sex					
Female	1652 / 4488 (36.8%)	1345 / 2644 (50.9%)	196 / 1040 (18.8%)	111 / 804 (13.8%)	
Male	2836 / 4488 (63.2%)	1299 / 2644 (49.1%)	844 / 1040 (81.2%)	693 / 804 (86.2%)	
Race					
African	2327 / 4495 (51.8%)	1186 / 2644 (44.9%)	609 / 1040 (58.6%)	528 / 804 (65.7%)	
European	1118 / 4495 (24.9%)	667 / 2644 (25.2%)	271 / 1040 (26.1%)	177 / 804 (22%)	
East Asian	600 / 4495 (13.3%)	471 / 2644 (17.8%)	82 / 1040 (7.9%)	47 / 804 (5.8%)	
South Asian	450 / 4495 (10%)	320 / 2644 (12.1%)	78 / 1040 (7.5%)	52 / 804 (6.5%)	
Hypertension	1485 / 4495 (33%)	588 / 2644 (22.2%)	423 / 1040 (40.7%)	474 / 804 (59%)	
Physical Activity					
Poor	1739 / 4471 (38.9%)	1023 / 2631 (38.9%)	403 / 1038 (38.8%)	313 / 802 (39%)	
Intermediate	2211 / 4471 (49.5%)	1298 / 2631 (49.3%)	512 / 1038 (49.3%)	401 / 802 (50%)	
Ideal	521 / 4471 (11.7%)	310 / 2631 (11.8%)	123 / 1038 (11.8%)	88 / 802 (11%)	
Diet					
Poor	1292 / 4479 (28.8%)	737 / 2636 (28%)	311 / 1040 (29.9%)	244 / 803 (30.4%)	
Intermediate	2388 / 4479 (53.3%)	1381 / 2636 (52.4%)	564 / 1040 (54.2%)	443 / 803 (55.2%)	
Ideal	799 / 4479 (17.8%)	518 / 2636 (19.7%)	165 / 1040 (15.9%)	116 / 803 (14.4%)	

Table of baseline characteristics for all 4495 participants, including stratification into ASCVD tertiles (0% to <5%, 5% to 7.5%, and >7.5%). The top section of baseline characteristics (rows 'Age' to 'Triglyceride concentration') lists the mean (SD) value, in addition to stratification by ASCVD tertiles. P-value corresponds to Students' t-test between <5% and >7.5% ASCVD risk cohorts. The bottom section (rows 'Sex' to 'Diet') counts the number of participants in each variable subcategory among all participants, in addition to stratification by ASCVD tertiles. eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

**Table S3. Relationships between CAD PRS and subclinical CAD phenotypes.**

Variable	Without phenotype		With phenotype		P-value
	Mean	95% CI	Mean	95% CI	
Stenosis Over 50%	48.2	[45.9 - 50.5]	66.1	[55.6 - 76.5]	p = 0.0033
Plaque with Vulnerable Features	47.2	[44.6 - 49.7]	55.2	[50.7 - 59.8]	p = 0.0027
Partially Calcified Plaque	46.1	[43.4 - 48.9]	54.5	[50.7 - 58.2]	p = 0.0005
Noncalcified Plaque	48.1	[45.7 - 50.4]	56.8	[49.8 - 63.7]	p = 0.0166
Visible Noncalcified Plaque Segments	45.5	[42.6 - 48.3]	54.2	[50.8 - 57.7]	p = 0.0001
Visible Noncalcified Plaque or Plaque with Vulnerable Features	45.2	[42.3 - 48.1]	54.2	[50.8 - 57.6]	p = 0.0001
Plaque Present	45.0	[41.9 - 48.0]	53.2	[50.0 - 56.4]	p = 0.0003

Table showing the mean CAD PRS and 95% confidence intervals (CI) for participants with or without each CAD phenotype listed in each row, among the 662 participants with CCTA measurements. P-values were derived from Students' t-test between participants with or without each CAD phenotype. 95% CI: 95% confidence interval

**Table S4. Comparison of logistic regression model using original versus spline representation of  $GPS_{Mult}$ .**

<b>CCTA phenotype</b>	<b>AIC</b>		<b>RMSE</b>	
	<b>Original</b>	<b>Spline</b>	<b>Original</b>	<b>Spline</b>
Stenosis Over 50%	200.97	198.79	0.1823	0.1813
Plaque with Vulnerable Features	695.14	689.52	0.4072	0.4073
Partially Calcified Plaque	805.72	806.86	0.4500	0.4493
Noncalcified Plaque	465.17	457.97	0.3076	0.3106
Visible Noncalcified Plaque Segments	840.95	836.41	0.4628	0.4638
Visible Noncalcified Plaque or with Vulnerable Features	852.40	850.77	0.4669	0.4688
Plaque Present	837.82	834.09	0.4615	0.4617

Table showing two measures of logistic regression model performance (Akaike Information Criterion and Root Mean Square Error) for the ‘Original’ model with outcome of subclinical CCTA measurements and covariates of  $GPS_{Mult}$ , age, sex, and top 10 principal components from genotype, compared to a similar ‘Spline’ model with  $GPS_{Mult}$  and age modeled with natural cubic splines. AIC: Akaike Information Criterion; RMSE: Root Mean Square Error.

**Table S5. Linear Regression coefficients for estimate of subclinical CAD.**

<b>Linear Regression coefficients for polygenic risk score</b>				
<b>Outcome variable</b>	<b>Estimate</b>	<b>Std. Error</b>	<b>t value</b>	<b>Pr(&gt; t )</b>
Leaman score	0.402	0.104	3.877	0.00012
Natural log of Coronary Artery Calcium (CAC) score	0.308	0.074	4.138	0.00004

Table showing Beta coefficients from linear regression (Estimate) to predict each outcome variable (rows) using  $GPS_{Mult}$ . Std. Error: Standard Error of each estimate; Pr(>|t|): P-value associated with the t value in regression.

**Table S6. Linear Regression coefficients for estimate of cardiometabolic traits.**

<b>Linear Regression coefficients for polygenic risk score</b>				
<b>Outcome variable</b>	<b>Estimate</b>	<b>Std. Error</b>	<b>t value</b>	<b>Pr(&gt; t )</b>
LDL cholesterol (mg/dL)	8.857	0.439	20.197	1.04E-86
Oxidized LDL cholesterol (mg/dL)	2.971	0.788	3.772	1.76E-04
Total cholesterol (mg/dL)	9.226	0.517	17.855	7.76E-69
Triglycerides (mg/dL)	14.772	1.166	12.665	4.06E-36
HDL cholesterol (mg/dL)	4.523	0.235	19.246	3.06E-79
Systolic blood pressure (mmHg)	2.057	0.211	9.730	3.70E-22
Diastolic blood pressure (mmHg)	1.257	0.144	8.755	2.84E-18

Beta coefficients from linear regression (Estimate) to predict each outcome variable (rows) using the respective PRS. LDL cholesterol: low-density lipoprotein cholesterol; HDL cholesterol: high-density lipoprotein cholesterol; Std. Error: Standard Error of each estimate; Pr(>|t|): P-value associated with the t value in regression.



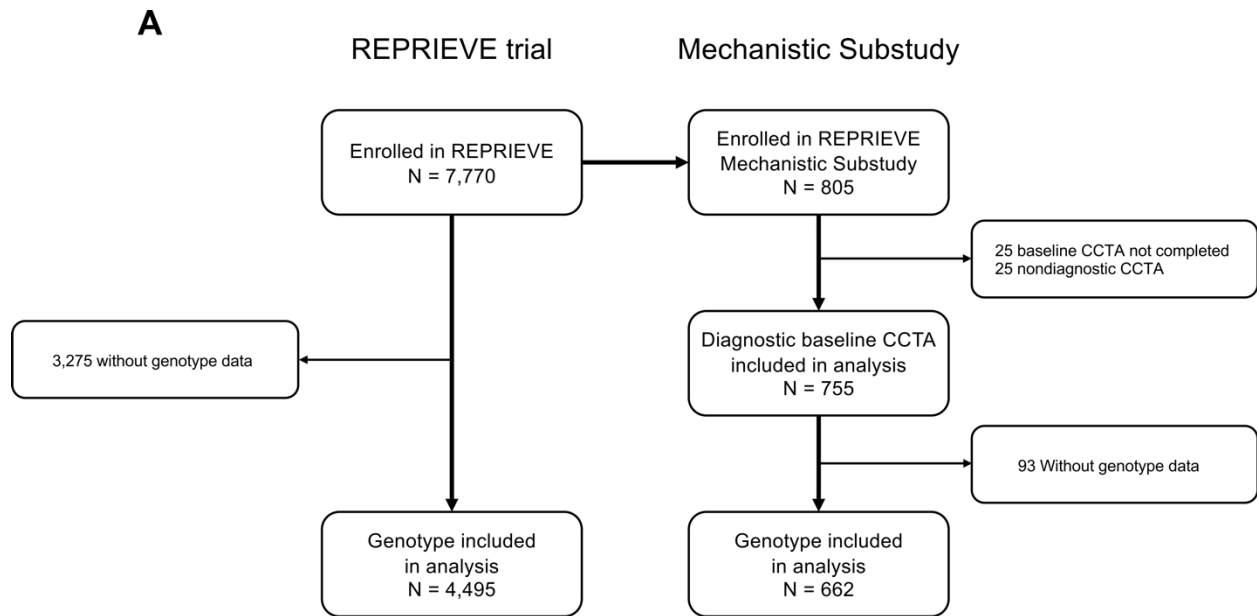
**Table S7. Associations between different cardiometabolic PRS and subclinical CAD.**

**Cardiometabolic PRS association with CAD phenotypes**

CAD Phenotype	Cardiometabolic PRS											
	LDL-C		HDL-C		Total Cholesterol		Triglycerides		Systolic BP		Diastolic BP	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Plaque Present	<b>1.21</b>	<b>0.0393</b>	0.96	0.6245	1.14	0.1448	1.00	0.9500	1.06	0.4903	1.01	0.9410
Stenosis Over 50%	1.31	0.2275	1.28	0.2075	1.35	0.1732	1.04	0.8221	1.20	0.3949	1.01	0.9485
Plaque with Vulnerable Features	1.07	0.5134	1.02	0.8412	1.05	0.6013	1.05	0.5746	1.05	0.5713	0.92	0.3575
Partially Calcified Plaque	<b>1.21</b>	<b>0.0408</b>	1.04	0.6268	1.18	0.0705	0.93	0.3587	1.02	0.8268	1.02	0.7993
Noncalcified Plaque Only	1.04	0.7617	0.86	0.2024	1.00	0.9714	1.20	0.1223	<b>1.33</b>	<b>0.0218</b>	1.10	0.4379
Visible Noncalcified Plaque Segments	1.17	0.0852	0.95	0.4964	1.13	0.1491	1.02	0.8198	1.04	0.6285	0.97	0.6819
Visible Noncalcified Plaque or Plaque with Vulnerable Features	1.17	0.0730	0.96	0.6140	1.13	0.1606	1.02	0.7515	1.06	0.4410	0.98	0.8439

Table of the odds ratios (OR) and associated p-values for the associations between different cardiometabolic PRS (LDL-C, HDL-C, Total Cholesterol, Triglycerides, Systolic and Diastolic blood pressures) and measures of subclinical CAD phenotypes. Statistically significant associations ( $p < 0.05$ ) are highlighted with red text. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BP: blood pressure; OR: odds ratio.

**Figure S1. Consort Diagram and LDL-C/ASCVD inclusion criteria.**



- B** **Inclusion criteria based on LDL-C thresholds and 10-year ASCVD risk score**  
 If ASCVD risk score <7.5%, then LDL-C must be less than 190 mg/dL.  
 If ASCVD risk score ≥7.5% and ≤10%, then LDL-C must be less than 160 mg/dL.  
 If ASCVD risk score >10% and ≤15%, then LDL-C must be less than 130 mg/dL.  
 If LDL-C is less than 70 mg/dL, the participant is eligible regardless of ASCVD risk score.

**A)** Consort diagram that led to the 4495 total genotyped participants in this study, including 662 with CCTA.

**B)** Inclusion criteria for the REPRIEVE trial based on LDL-C thresholds and 10-year ASCVD risk scores.

CCTA: coronary computed tomography angiography; LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

**Figure S2. Relationships between CAD PRS and subclinical CAD phenotypes.**



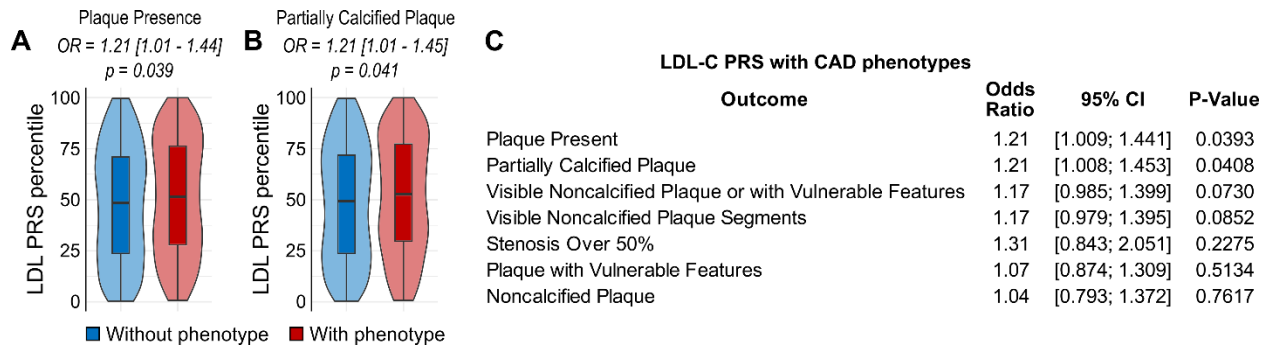
**A)** Plots of Nagelkerke  $R^2$  (y-axis) for each CAD risk factor (x-axis), for predicting three different subclinical CAD. No asterisk is  $p \geq 0.05$ , \* is  $p < 0.05$ , \*\* is  $p < 0.01$ , and \*\*\* is  $p < 0.001$ . Figure S2B-C lists the corresponding plot values and p-values, respectively.

**B-C)** Table showing B) Nagelkerke  $R^2$  and C) associated p-values, for the relative contributions of each CAD risk factor (columns) to predict subclinical CAD (rows). Green and red conditional formatting correlates to  $R^2$  strength and strength of significance ( $p < 0.05$ ), respectively.

**D-E)** Table showing the D) increase in C-statistic from inclusion of each ASCVD risk factor and E) associated p-values. Green and red conditional formatting correlates to strength of C-statistic increase and strength of significance ( $p < 0.05$ ), respectively.

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; HTN med: use of anti-hypertensive medication

**Figure S3. Statistical analyses of cardiometabolic PRS and subclinical CAD phenotypes.**

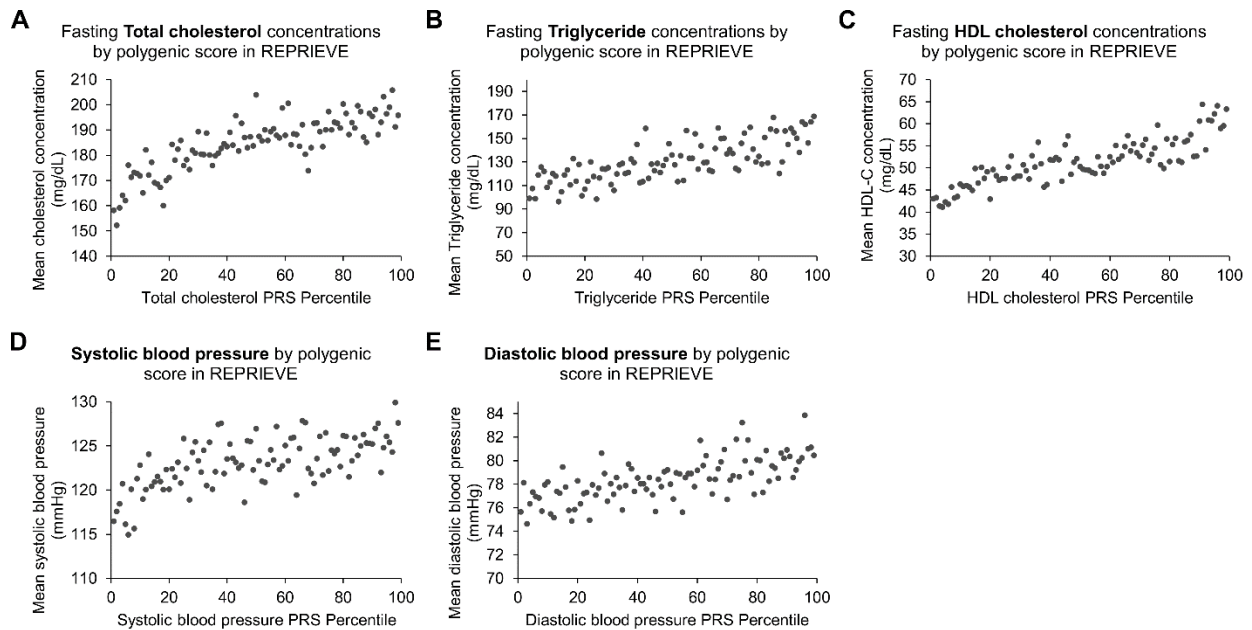


**A-B)** Violin plots with box and whiskers summarizing the LDL-C PRS percentiles (y-axis) for participants with or without evidence of A) any plaque and B) partially calcified plaque. The whiskers represent max and min, box span from first to third quartiles, middle line represents median.

**C)** Table of OR for the association between LDL-C PRS and different measures of subclinical CAD among participants with CCTA measurements. Table includes 95% confidence intervals (CI) and p-value of the OR.

95% CI: 95% confidence interval

**Figure S4. Efficacy of genome-wide PRS for lipid traits and blood pressures.**



**A)** Plot of the mean baseline total cholesterol concentration (mg/dL) (y-axis), among participants in each total cholesterol PRS percentile (x-axis).

**B)** Plot of the mean baseline triglyceride concentration (mg/dL), among participants in each triglyceride PRS percentile (x-axis).

**C)** Plot of the mean baseline high density lipoprotein cholesterol (HDL-C) concentration (mg/dL), among participants in each HDL-C PRS percentile (x-axis).

**D)** Plot of the mean baseline systolic blood pressure (mmHg), among participants in each PRS percentile (x-axis).

**E)** Plot of the mean baseline diastolic blood pressure (mmHg), among participants in each PRS percentile (x-axis).

HDL: high-density lipoprotein