

SUPPLEMENTAL MATERIAL

for

**de Lemos et al. A Multimodality Strategy for Cardiovascular Risk Assessment: Performance in Two
Population-Based Cohorts**

Supplementary Table 1. Spearman correlation coefficients between individual test results in MESA

VARIABLE	ECG Voltage*	CAC	NT-proBNP	hs-cTnT	Hs-CRP
ECG Voltage*		-0.03	0.02	0.03	-0.05
CAC	-0.03		0.20	0.37	-0.01
NT-proBNP	0.02	0.20		0.20	0.08
hs-cTnT	0.03	0.37	0.20		0.02
Hs-CRP	-0.05	-0.01	0.08	0.02	

*ECG voltage by Sokolow-Lyon method. Spearman rho correlation coefficients are reported

Supplementary Table 2. Spearman correlation coefficients between individual test results in DHS

VARIABLE	ECG Voltage*	CAC	NT-proBNP	hs-cTnT	Hs-CRP
ECG Voltage*		-0.03	-0.05	0.04	-0.09
CAC	-0.03		0.01	0.24	0.18
NT-proBNP	-0.05	0.01		0.02	0.12
hs-cTnT	0.04	0.24	0.02		-0.01
Hs-CRP	-0.09	0.18	0.12	-0.01	

*ECG voltage by Sokolow-Lyon method. Spearman rho correlation coefficients are reported

Supplementary Table 3. Association of test results with the composite coronary heart disease (CHD)

endpoint.

Variable	Unadjusted HR (95% CI)		Model 1 HR (95% CI)	Model 2 HR (95% CI)
	MESA	DHS	MESA	MESA
Continuous Test Results				
ECG-LVH *	1.48 (1.06, 2.06)	2.42 (1.26, 4.65)	1.09 (0.77, 1.53)	0.96 (0.68, 1.36)
Ln (CAC+1)	2.26 (2.03, 2.53)	1.33 (1.02, 1.74)	1.73 (1.52, 1.98)	1.63 (1.43, 1.86)
Ln (NT-proBNP)	1.78 (1.59, 2.00)	1.53 (1.18, 1.98)	1.58 (1.39, 1.80)	1.31 (1.17, 1.46)
Ln (hs-cTnT)	1.85 (1.71, 2.00)	1.83 (1.57, 2.13)	1.50 (1.35, 1.66)	1.32 (1.18, 1.47)
Ln (hs-CRP)	1.10 (0.98, 1.22)	1.33 (1.02, 1.74)	1.05 (0.93, 1.18)	1.01 (0.89, 1.14)
Categorical test results				
ECG-LVH *	1.48 (1.06, 2.06)	2.42 (1.26, 4.65)	1.09 (0.77, 1.53)	1.02 (0.72, 1.44)
CAC > 10 U	4.92 (3.80, 6.38)	6.95 (4.16, 11.63)	2.76 (2.07, 3.68)	2.63 (1.97, 3.51)
NT-proBNP ≥100 pg/mL	2.50 (2.00, 3.11)	3.44 (1.97, 6.03)	1.92 (1.49, 2.47)	1.77 (1.37, 2.28)
hs-cTnT ≥ 5 ng/L	3.21 (2.52, 4.08)	4.58 (2.75, 7.62)	1.57 (1.20, 2.06)	1.42 (1.08, 1.86)
hs-CRP ≥ 3 mg/L	1.21 (0.97, 1.52)	1.81 (1.09, 3.02)	1.16 (0.91, 1.47)	1.10 (0.87, 1.39)

Only unadjusted results are presented in DHS, due to small numbers of endpoint events. Model 1 is adjusted for age, sex, race, smoking status, diabetes, total cholesterol, HDL-cholesterol, systolic blood pressure and blood pressure medications, and statin medications. Model 2 includes the components of model 1 and all 5 test results. The Hazard Ratio (HR) for continuous test results reflects a one standard deviation change in Ln value of the test result. Coefficients were determined separately for each model.

* ECG-LVH was treated as a categorical variable in both analyses.

Supplementary Table 4. Association of test results with incident heart failure

Variable	Unadjusted HR (95% CI)		Model 1 HR (95% CI)	Model 2 HR (95% CI)
	MESA	DHS	MESA	MESA
Continuous Test Results				
ECG-LVH*	2.63 (1.93, 3.57)	7.27 (3.40, 15.52)	1.93 (1.40, 2.65)	1.50 (1.08, 2.07)
Ln (CAC+1)	2.06 (1.82, 2.32)	1.49 (1.12, 1.99)	1.42 (1.23, 1.63)	1.26 (1.09, 1.45)
Ln (NT-proBNP)	2.73 (2.42, 3.09)	2.72 (2.11, 3.52)	2.50 (2.16, 2.90)	2.05 (1.76, 2.39)
Ln (hs-cTnT)	2.08 (1.92, 2.25)	1.96 (1.59, 2.42)	1.71 (1.53, 1.92)	1.43 (1.27, 1.61)
Ln (hs-CRP)	1.33 (1.18, 1.50)	1.57 (1.04, 2.36)	1.29 (1.23, 1.42)	1.21 (1.05, 1.39)
Categorical test results				
ECG-LVH*	2.63 (1.93, 3.57)	7.27 (3.40, 15.52)	1.93 (1.40, 2.65)	1.64 (1.19, 2.27)
CAC > 10 U	3.54 (2.70, 4.64)	2.07 (0.93, 4.56)	1.66 (1.23, 2.24)	1.49 (1.10, 2.02)
NT-proBNP ≥100 pg/mL	4.77 (3.70, 6.14)	12.06 (5.71, 25.51)	3.58 (2.69, 4.78)	3.15 (2.35, 4.22)
hs-cTnT ≥ 5 ng/L	5.45 (4.02, 7.40)	7.47 (3.55, 15, 69)	2.47 (1.76, 3.46)	2.19 (1.56, 3.08)
hs-CRP ≥ 3 mg/L	1.80 (1.41, 2.30)	2.64 (1.19, 5.82)	1.61 (1.23, 2.10)	1.51(1.15, 1.97)

Only unadjusted results are presented in DHS, due to small numbers of endpoint events. Model 1 is adjusted for age, sex, race, smoking status, diabetes, total cholesterol, HDL-cholesterol, systolic blood pressure and blood pressure medications, statin medications, BMI and creatinine. Model 2 includes the components of model 1 and all 5 test results. The Hazard Ratio (HR) for continuous test results reflects a one standard deviation change in Ln value of the test result. Coefficients were determined separately for each model.

* ECG-LVH was treated as a categorical variable in both analyses.

Supplementary Table 5. Association of test results with all-cause mortality

Variable	Unadjusted HR (95% CI)		Model 1 HR (95% CI)	Model 2 HR (95% CI)
	MESA	DHS	MESA	MESA
Continuous Test Results				
ECG-LVH*	1.45 (1.18, 1.79)	1.73 (0.96, 3.11)	1.03 (0.84, 1.29)	0.93 (1.07, 1.25)
Ln (CAC+1)	1.83 (1.72, 1.96)	1.74 (1.50, 2.01)	1.23 (1.14, 1.33)	1.16 (1.07, 1.25)
Ln (NT-proBNP)	1.95 (1.81, 2.09)	1.84 (1.51, 2.23)	1.51 (1.39, 1.64)	1.37 (1.26, 1.49)
Ln (hs-cTnT)	1.81 (1.73, 1.90)	1.89 (1.67, 2.13)	1.38 (1.29, 1.47)	1.25 (1.16, 1.35)
Ln (hs-CRP)	1.15 (1.07, 1.23)	1.40 (1.13, 1.75)	1.12 (1.03, 1.20)	1.08 (1.01, 1.17)
Categorical test results				
ECG-LVH*	1.45 (1.18, 1.79)	1.73 (0.96, 3.11)	1.03 (0.84, 1.28)	0.97 (0.79, 1.21)
CAC > 10 U	3.00 (2.60, 3.48)	3.22 (2.14, 4.85)	1.36 (1.16, 1.50)	1.28 (1.09, 1.50)
NT-proBNP ≥100 pg/mL	2.92 (2.54, 3.34)	3.89 (2.51, 6.02)	1.78 (1.53, 2.08)	1.70 (1.45, 1.98)
hs-cTnT ≥ 5 ng/L	3.33 (2.87, 3.88)	4.82 (3.20, 7.25)	1.44 (1.22, 1.71)	1.35 (1.13, 1.60)
hs-CRP ≥ 3 mg/L	1.27 (1.10, 1.46)	1.77 (1.18, 2.67)	1.25 (1.08, 1.45)	0.97 (0.79, 1.21)

Only unadjusted results are presented in DHS, due to small numbers of endpoint events. Model 1 is adjusted for age, sex, race, smoking status, diabetes, total cholesterol, HDL-cholesterol, systolic blood pressure blood pressure medications, and statin medications. Model 2 includes the components of model 1 and all 5 test results. The Hazard Ratio (HR) for continuous test results reflects a one standard deviation change in Ln value of the test result. Coefficients were determined separately for each model.

* ECG-LVH was treated as a categorical variable in both analyses.

Supplementary Table 6. Association of test results with cardiovascular mortality

Variable	Unadjusted HR (95% CI)		Model 1 HR (95% CI)	Model 2 HR (95% CI)
	MESA	DHS	MESA	MESA
Continuous Test Results				
ECG-LVH*	1.53 (1.06, 2.22)	1.92 (0.86, 4.29)	1.55 (1.06, 2.27)	1.30 (0.89, 1.92)
Ln (CAC+1)	1.58 (1.36, 1.84)	1.86 (1.51, 2.29)	1.37 (1.16, 1.61)	1.25 (1.07, 1.48)
Ln (NT-proBNP)	1.66 (1.32, 1.92)	1.70 (1.28, 2.25)	1.87 (1.59, 2.20)	1.60 (1.35, 1.90)
Ln (hs-cTnT)	1.52 (1.35, 1.70)	1.82 (1.52, 2.17)	1.51 (1.32, 1.73)	1.28 (1.11, 1.48)
Ln (hs-CRP)	1.16 (1.00, 1.34)	1.39 (1.02, 1.90)	1.15 (0.98, 1.34)	1.10 (0.94, 1.29)
Categorical test results				
ECG-LVH*	2.35 (1.63, 3.40)	1.92 (0.86, 4.29)	1.55 (1.06, 2.27)	1.42 (0.97, 2.08)
CAC > 10 U	4.11 (2.96, 5.69)	3.33 (1.86, 5.96)	1.62 (1.14, 2.31)	1.49 (1.04, 2.12)
NT-proBNP \geq100 pg/mL	4.10 (3.06, 5.49)	3.03 (1.57, 5.85)	2.43 (1.75, 3.36)	2.21 (1.59, 3.07)
hs-cTnT \geq 5 ng/L	4.21 (3.02, 5.87)	4.11 (2.27, 7.43)	1.54 (1.06, 2.23)	1.36 (0.94, 1.98)
hs-CRP \geq 3 mg/L	1.52 (1.14, 2.03)	1.77 (0.98, 3.18)	1.40 (1.03, 1.90)	1.33 (0.98, 1.80)

Only unadjusted results are presented in DHS, due to small numbers of endpoint events. Model 1 is adjusted for age, sex, race, smoking status, diabetes, total cholesterol, HDL-cholesterol, systolic blood pressure and blood pressure medications, and statin medications. Model 2 includes the components of model 1 and all 5 test results. The Hazard Ratio (HR) for continuous test results reflects a one standard deviation change in Ln value of the test result. Coefficients were determined separately for each model.

* ECG-LVH was treated as a categorical variable in both analyses.

Supplementary Table 7. Change in risk prediction metrics in MESA for ASVD endpoint, with addition of other biomarkers to models including coronary calcium

	C-statistic	Category Free NRI	IDI
Base Model	0.748	NA	NA
Base Model + CAC	0.771 [†]	0.449 (0.344,0.554)	0.021 (0.015, 0.027)
Base Model + CAC + ECG LVH*	0.772	-0.011 (-0.142, 0.120)	0.0005 (-0.002, 0.003)
Base Model + CAC + NT-proBNP*	0.776 [‡]	0.118 (0.024, 0.212)	0.017 (0.009, 0.025)
Base Model + CAC + hs-cTnT*	0.775 [‡]	0.164 (0.07,0.257)	0.019 (0.011, 0.026)
Base Model + CAC + hs-CRP*	0.771	0.051 (-0.014,0.227)	-0.0001 (-0.002, 0.001)
Base Model + all 5 tests*	0.779 [†]	0.228 (0.124,0.333)	0.028 (0.016, 0.039)

* Comparisons vs base model + CAC.

[†]p<0.001; [‡]p<0.05 vs base model

Supplementary Table 8. Change in risk prediction metrics with MESA models directly applied to DHS

	Coefficients Derived in DHS*				Coefficients Derived in MESA and Applied to DHS			
	C-statistic Base Model	C-statistic Base Model + Test Results	Category free NRI	IDI	C-statistic Base Model	C-statistic Base Model + Test Results	Category free NRI	IDI
Global CVD	0.832	0.850 [†]	0.261 (0.052,0.47)	0.024 (0.008, 0.04)	0.810	0.828 [‡]	0.199 (0.083, 0.621)	0.048 (0.027, 0.069)
ASCVD	0.859	0.873 [†]	0.355 (0.129,0.581)	0.021 (0.001, 0.041)	0.823	0.841 [‡]	0.416 (0.123, 0.822)	0.019 (0.002, 0.036)
CHD	0.865	0.889 [†]	0.585 (0.294,0.877)	0.058 (0.023, 0.093)	0.857	0.861	0.522 (-0.571,0.913)	0.021 (-0.004, 0.045)
Heart Failure	0.840	0.871 [‡]	0.719 (0.381,0.989)	0.13 (0.042, 0.218)	0.759	0.790 [§]	0.824 (0.431,1.401)	0.25 (0.142, 0.350)
All-Cause Mortality	0.817	0.829	0.061 (-0.516,0.638)	0.03 (0.005, 0.055)	0.777	0.794 [‡]	0.230 (-0.157,0.704)	0.02 (0.001, 0.038)
Cardiovascular Mortality	0.840	0.858	0.308 (-0.045,0.662)	0.012 (-0.01, 0.034)	0.781	0.796	0.238 (-0.168,0.753)	0.001 (-0.02, 0.025)

* The data for the coefficients derived in DHS is reproduced from Table 4 in the main manuscript and is shown here for comparison vs the models directly applied from MESA to DHS

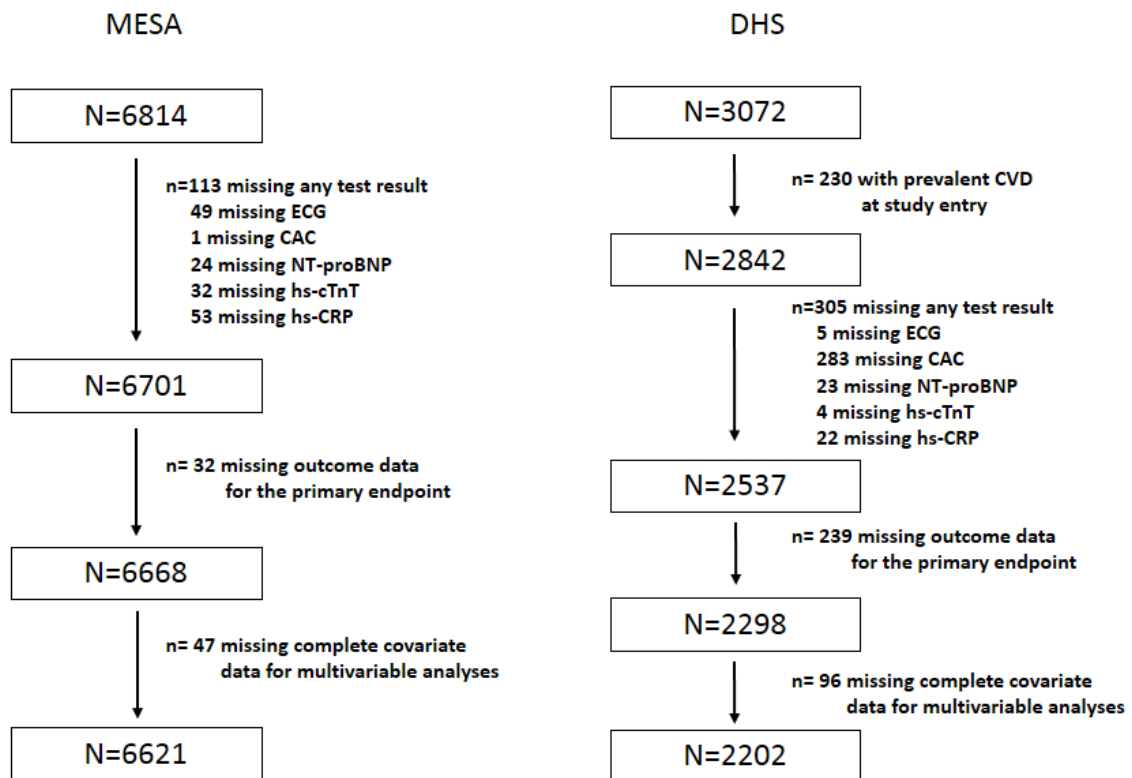
[†]p<0.01; [‡]p<0.05; [§]p<0.0001 vs base model

Supplementary Table 9. Association of Number of Multimodality Risk Score with Demographic Variables and Risk Factors in MESA

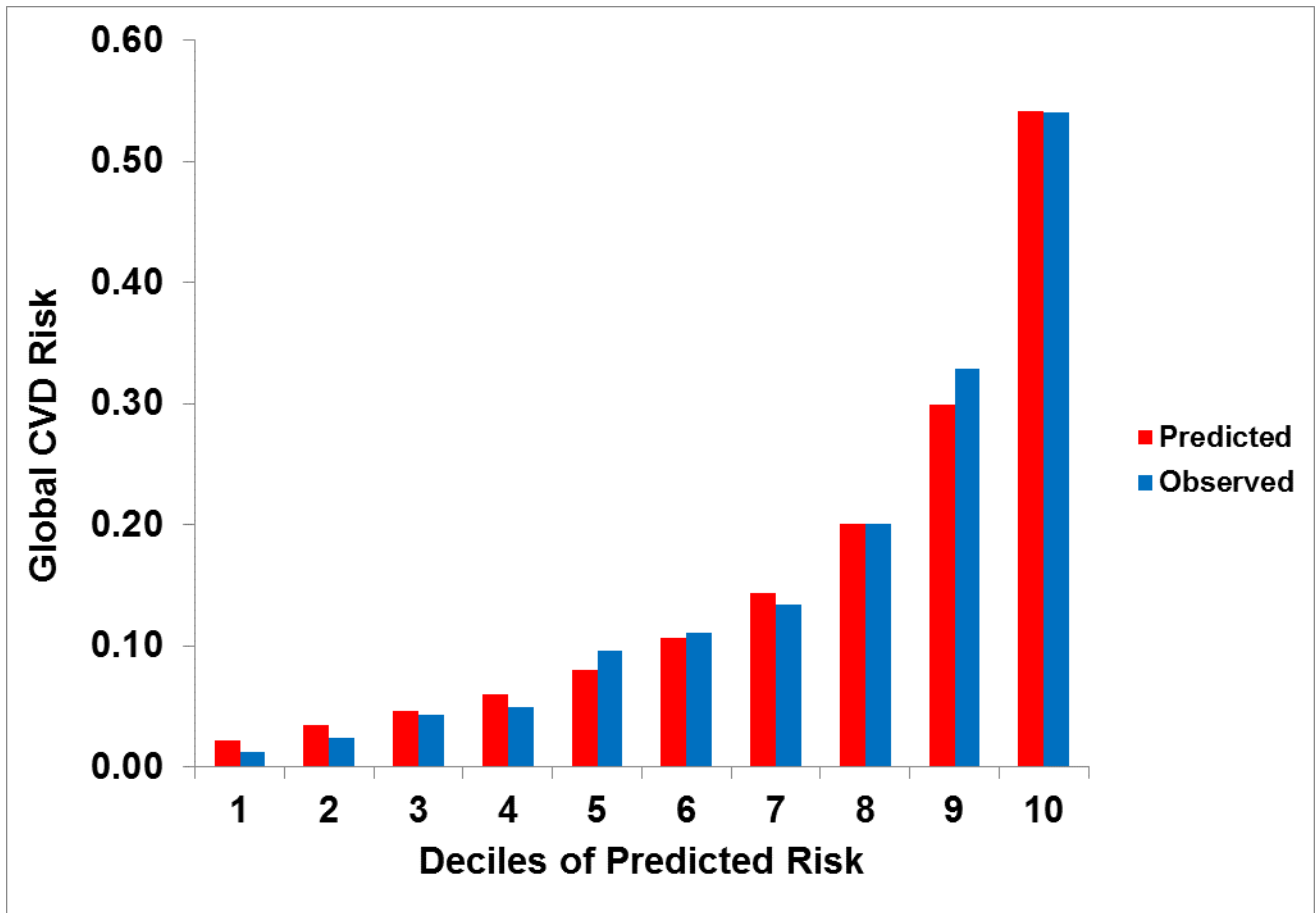
Variable	Multimodality Risk Score/Number of Abnormal Tests					p-trend
	0	1	2	3	≥4	
N	1332	2009	1789	1096	395	
Age	53 [49, 61]	58 [52, 66]	65 [57, 72]	70 [63, 76]	72 [67, 78]	<.0001
Male	539 (40%)	880 (44%)	942 (53%)	568 (52%)	200 (51%)	<.0001
White	447 (34%)	702 (35%)	753 (42%)	462 (42%)	176 (45%)	<.0001
Black	305 (23%)	568 (28%)	499 (28%)	319 (29%)	124 (31%)	0.0003
Hispanic	315 (24%)	468 (23%)	372 (21%)	238 (22%)	78 (20%)	0.03
Asian/Other	265 (20%)	271 (13%)	165 (9%)	77 (7%)	17 (4%)	<.0001
BMI	26.0 [23.2, 28.9]	27.7 [24.6, 31.2]	28.2 [25.1, 31.7]	28.4 [25.1, 32.3]	29.1 [25.5, 33.0]	<.0001
Hypertension	274 (21%)	738 (37%)	928 (52%)	722 (66%)	306 (77%)	<.0001
Medication for hypertension	219 (16%)	607 (30%)	787 (44%)	594 (54%)	256 (65%)	<.0001
SBP	115 [105, 128]	120 [109, 135]	127 [115, 142]	135 [121, 149]	141 [126, 160]	<.0001
DBP	71 [64, 78]	72 [65, 78]	73 [66, 79]	72 [66, 80]	73 [65, 82]	<.0001
Diabetes	66 (5%)	211 (11%)	262 (15%)	217 (20%)	77 (19%)	<.0001
Current smoker	155 (12%)	290 (14%)	234 (13%)	122 (11%)	59 (15%)	<.0001
Hypercholesterolemia	423 (32%)	731 (36%)	715 (40%)	451 (41%)	146 (37%)	<.0001
Statin medication	124 (9%)	277 (14%)	301 (17%)	214 (20%)	69 (17%)	<.0001
Total Cholesterol	192 [172, 214]	193 [170, 215]	193 [172, 217]	189 [168, 215]	190 [167, 215]	0.13
LDL Cholesterol	116 [97, 136]	116 [96, 137]	118 [98, 137]	113 [93, 135]	113 [93, 134]	0.03
HDL Cholesterol	50 [42, 60]	48 [41, 59]	48 [40, 58]	48 [40, 59]	47 [40, 59]	<.0001
Triglycerides	101 [70, 149]	112 [78, 159]	114 [81, 164]	115 [79.5, 169]	112 [82, 165]	<.0001

Supplementary Table 10. Association of Multimodality Risk Score with Demographic Variables and Risk Factors in DHS

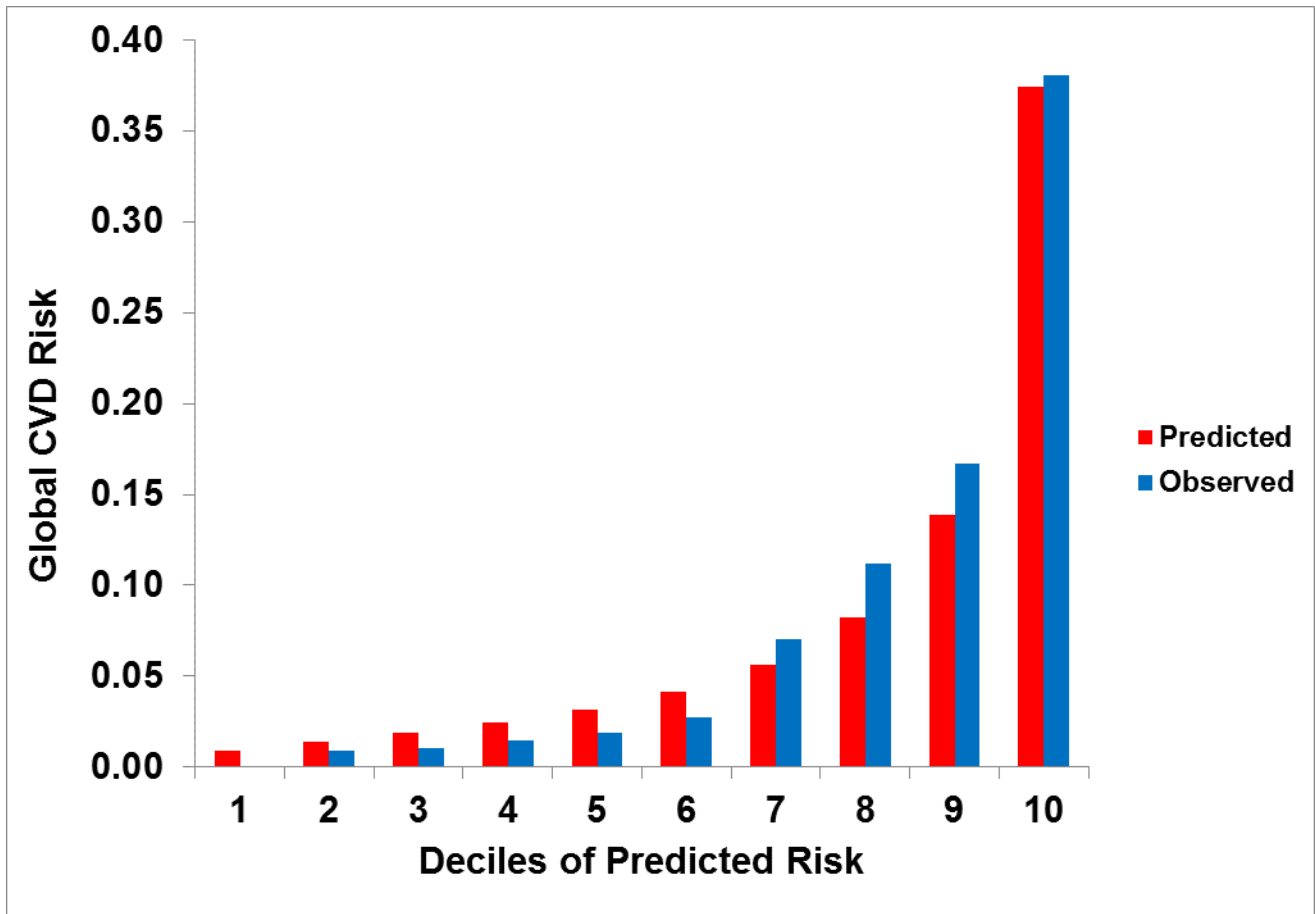
Variable	Multimodality Risk Score/Number of Abnormal Tests				p-trend
	0	1	2	≥3	
N	762	915	381	144	
Age	40 [35, 46]	44 [37, 52]	49 [43, 56]	54 [48, 60]	<.0001
Male	386 (51%)	333 (36%)	181 (48%)	77 (53%)	0.14
White	306 (40%)	293 (32%)	125 (33%)	33 (23%)	<.0001
Black	279 (37%)	447 (49%)	216 (57%)	99 (69%)	<.0001
Hispanic	147 (19%)	162 (18%)	36 (9%)	12 (8%)	<.0001
Asian/Other	30 (4%)	13 (1%)	4 (1%)	0 (0%)	<.0001
BMI	26.4 [23.4, 29.4]	29.4 [25.5, 33.6]	29.2 [25.6, 34.5]	30.0 [24.9, 34.2]	<.0001
Hypertension	115 (15%)	276 (31%)	185 (50%)	102 (72%)	<.0001
Medication for hypertension	73 (10%)	171 (19%)	112 (29%)	59 (41%)	<.0001
SBP	116 [109, 125]	121 [112, 131]	127 [118, 142]	140 [127, 158]	<.0001
DBP	74 [69, 81]	77 [72, 84]	80 [74, 87]	84 [77, 91]	<.0001
Diabetes	22 (3%)	85 (9%)	59 (15%)	38 (26%)	<.0001
Current smoker	195 (26%)	234 (26%)	110 (29%)	57 (40%)	0.02
Hypercholesterolemia (self report)	66 (9%)	122 (13%)	69 (18%)	30 (21%)	<.0001
Statin medication	24 (3%)	50 (5%)	31 (8%)	20 (14%)	<.0001
Total Cholesterol	176 [154, 202]	180 [158, 206]	186 [162, 209]	179 [158, 209]	0.0002
LDL Cholesterol	104 [81, 125]	107 [85, 130]	110 [87, 132]	110 [83, 132]	0.003
HDL Cholesterol	48 [41, 58]	48 [40, 57]	47 [40, 57]	47 [39, 55]	0.24
Triglycerides	89 [64, 138]	100 [70, 147]	108 [73, 152]	101 [74, 154]	<.0001



Supplementary Figure 1. Consort diagram showing the numbers of individuals excluded from the statistical analyses in MESA and DHS

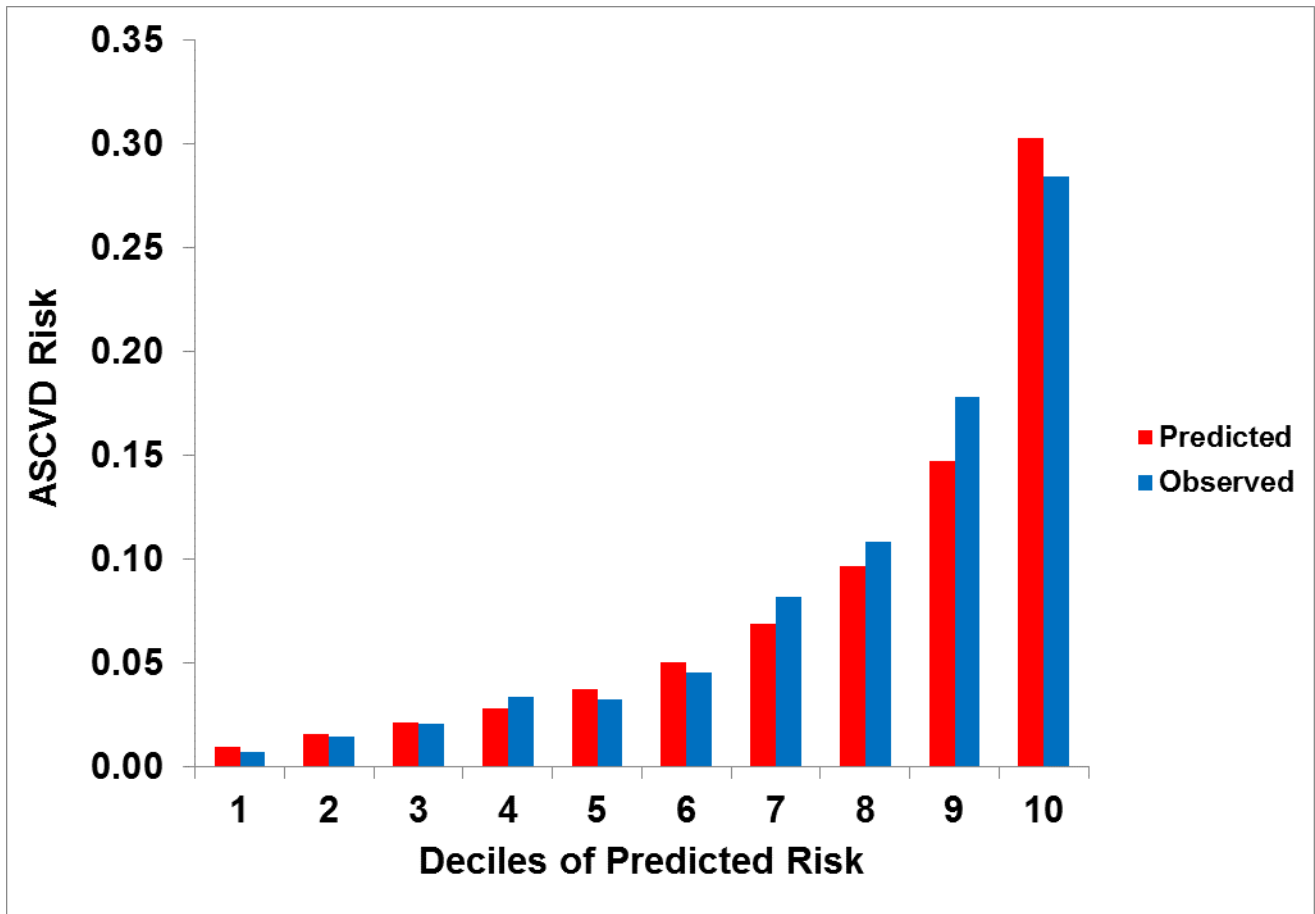


Supplementary Figure 2, Panel A

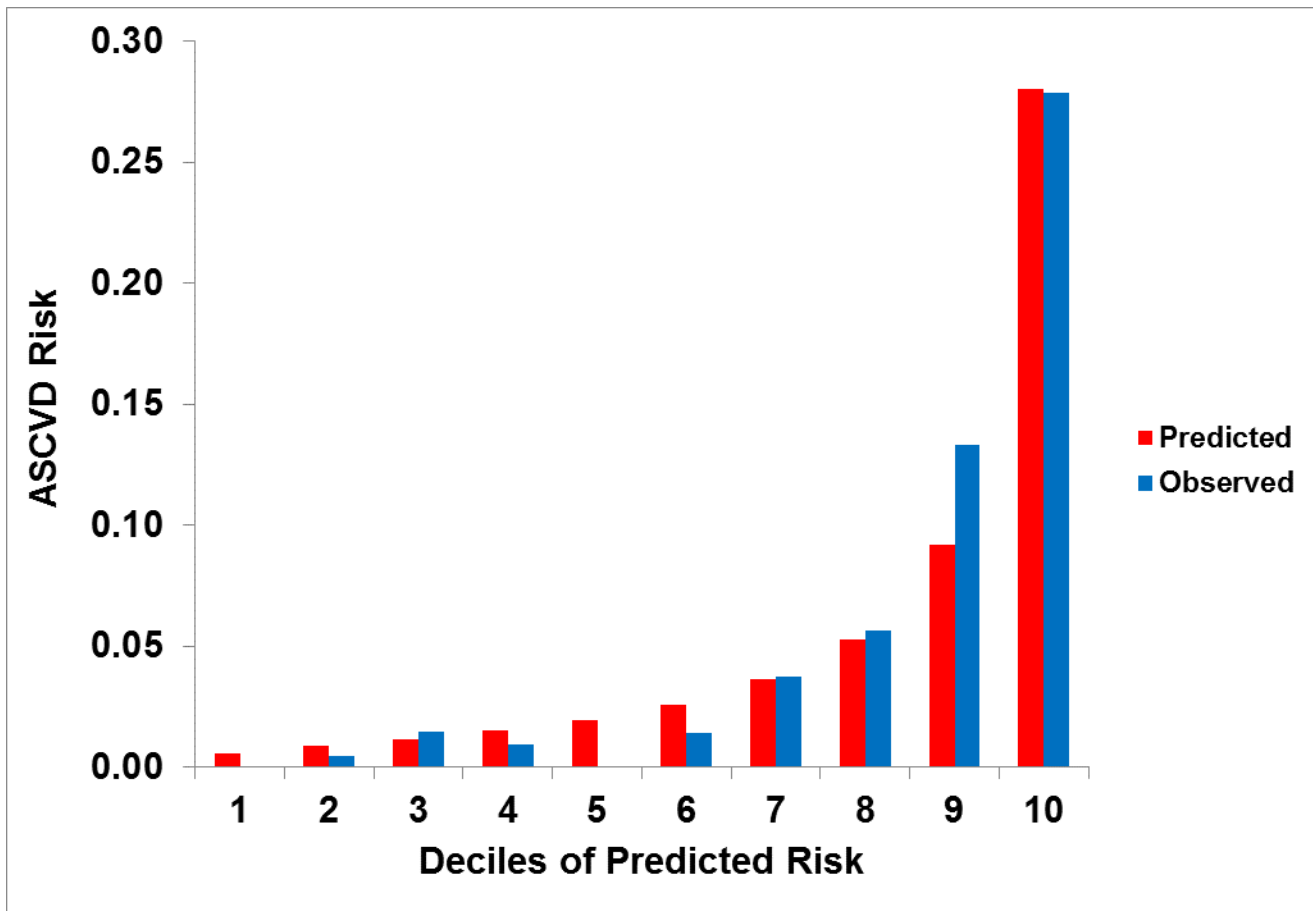


Supplementary Figure 2, Panel B.

Supplementary Figure 2. Calibration for the global cardiovascular disease endpoint for the fully adjusted model including traditional risk factors, creatinine, and the 5 test results. Panel A is from MESA (Nam-D'Agostino $\chi^2=12.2$, $p=0.20$) and Panel B is from DHS (Nam-D'Agostino $\chi^2=11.5$, $p=0.24$)

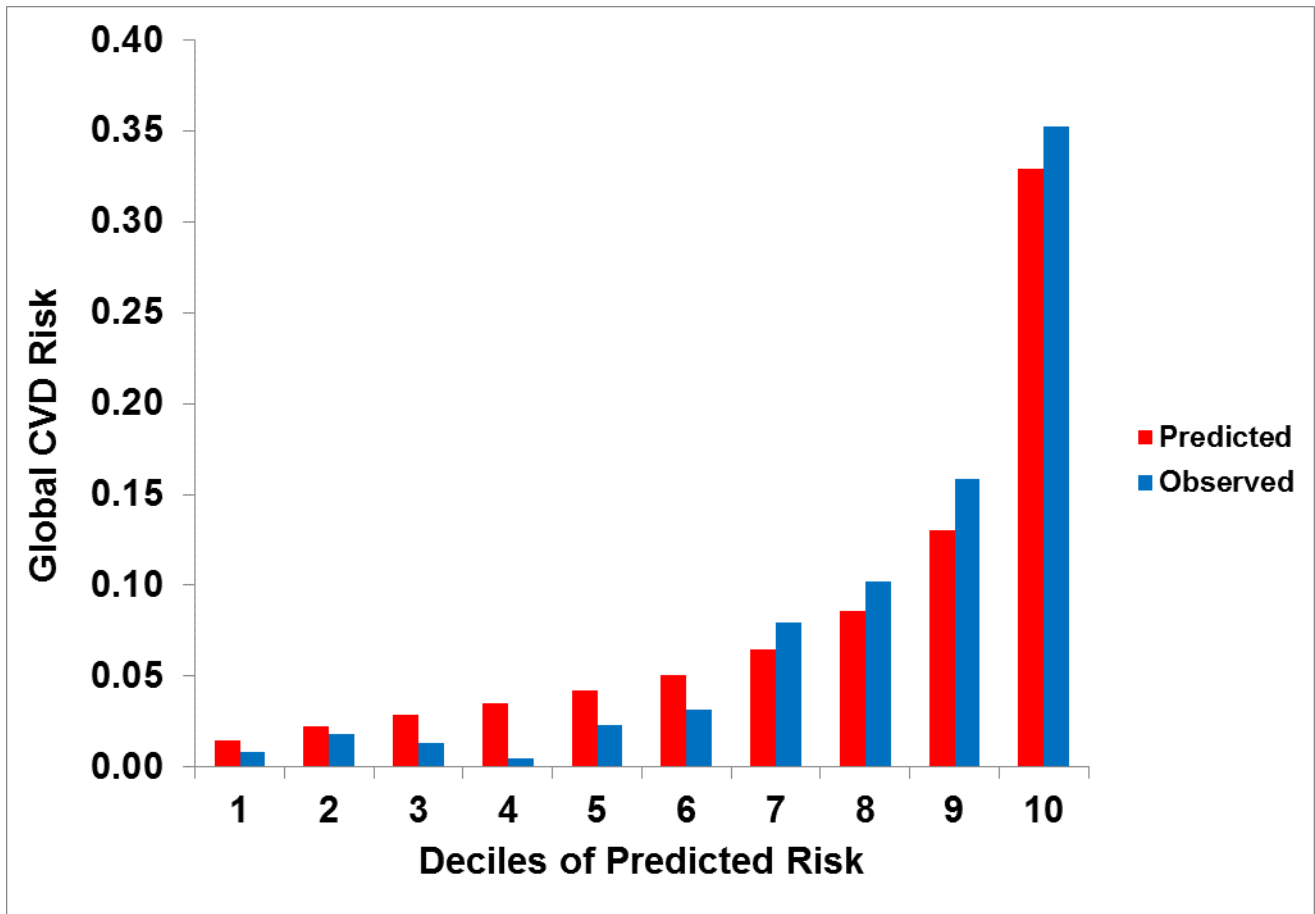


Supplementary Figure 3, Panel A.

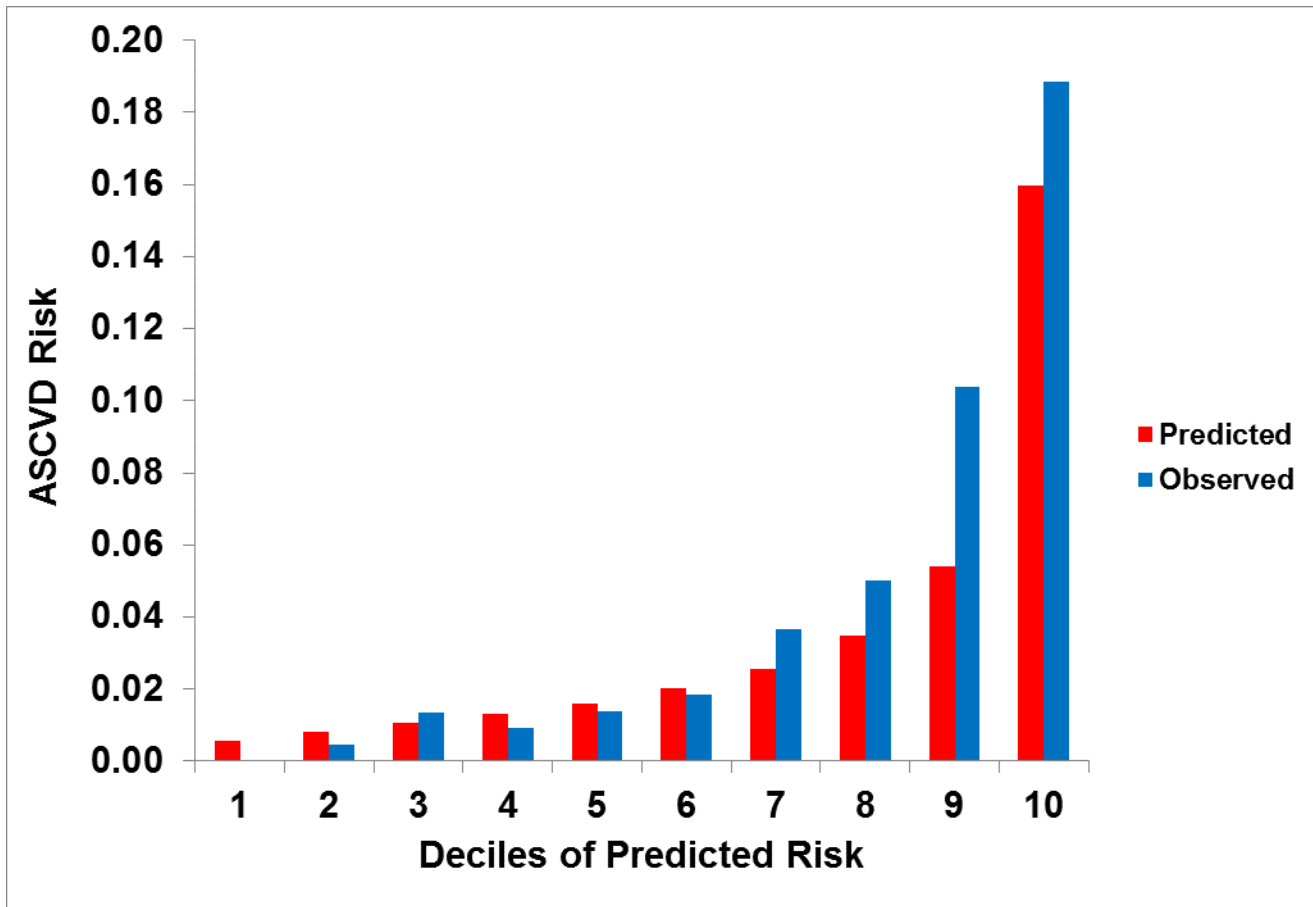


Supplementary Figure 3, Panel B.

Supplementary Figure 3. Calibration for the atherosclerotic cardiovascular disease (ASCVD) endpoint for the fully adjusted model including traditional risk factors and the 5 test results. Panel A is from MESA (Nam-D'Agostino $\chi^2=11.1$, $p=0.27$) and Panel B is from DHS (Nam-D'Agostino $\chi^2=12.5$, $p=0.19$)

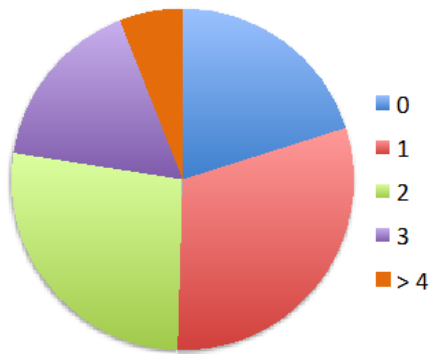


Supplementary Figure 4, Panel A.

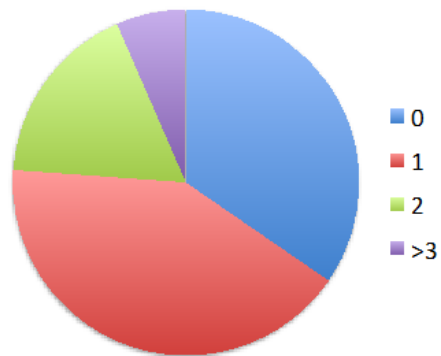


Supplementary Figure 4, Panel B

Supplementary Figure 4. Calibration plots from MESA models directly applied to DHS (using coefficients from MESA). Panel A is for Global CVD: Nam-D'Agostino χ^2 16.05, $p=0.07$; calibration slope=1.028. Panel B is for ASCVD: Nam-D'Agostino $\chi^2=17.1$, $p=0.05$; calibration slope=1.184.

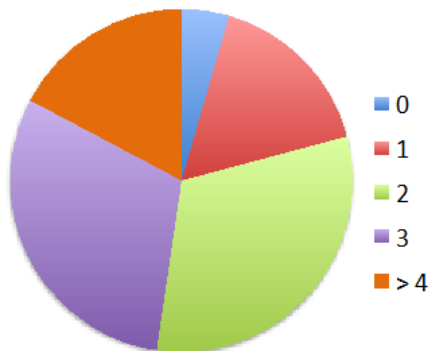


MESA

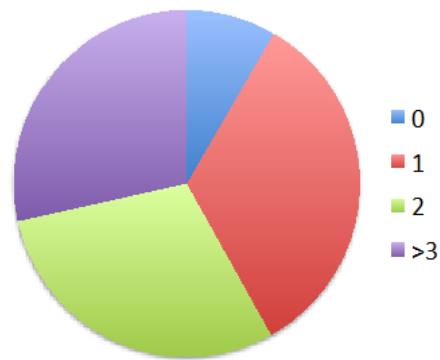


DHS

Supplementary Figure 5, Panel A.



MESA

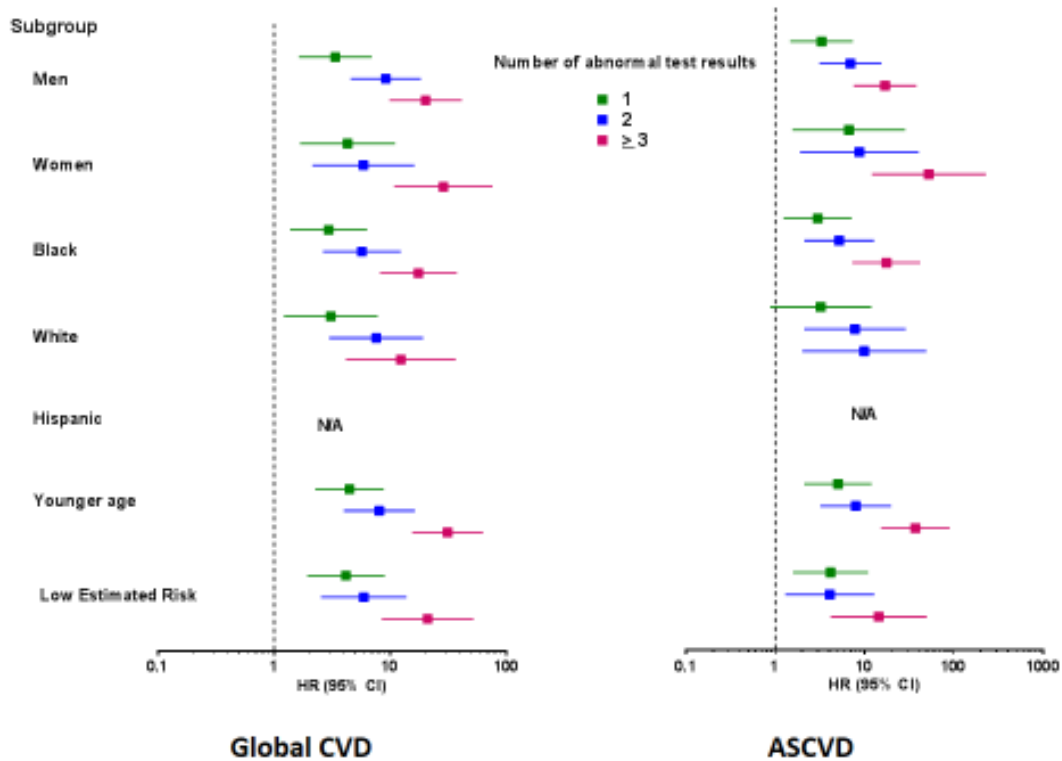


DHS

Supplementary Figure 5, Panel B.

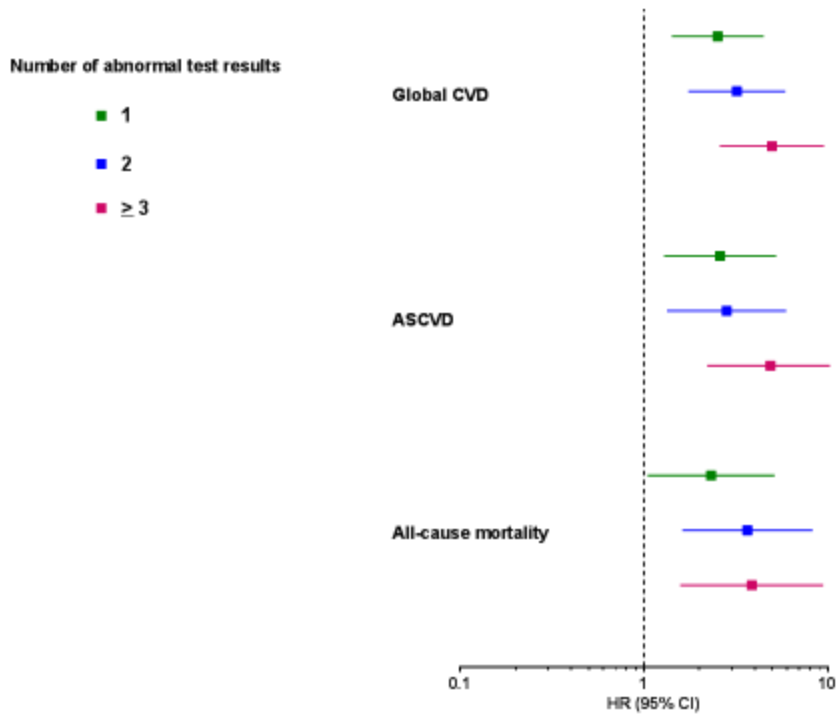
Supplementary Figure 5. Panel A: Distribution of Multimodality Risk Score in the overall MESA and DHS study cohorts. Panel B: Proportion of Global CVD Events Occurring in Different Risk Score Categories.

In MESA, participants with scores ≥ 2 comprised $<50\%$ of the cohort but accounted for 79% of the events. In the younger DHS population, participants with a score ≥ 2 comprised 24% of the cohort but accounted for 58% of events.



Supplementary Figure 6. Unadjusted associations between the number of abnormal test results and the composite global and atherosclerotic cardiovascular disease outcomes in selected subgroups in the DHS.

All comparisons are versus participants with a risk score =0. No significant interactions were seen across subgroups ($p > 0.05$ for each). Younger age is defined as age <55 in men and <65 in women. Low estimated risk is defined as 10-year estimated ASCVD risk < 7.5% using the pooled cohort equations.



Supplementary Figure 7. Multivariable-adjusted association between the number of abnormal test results and cardiovascular endpoints in the DHS.

All comparisons are versus participants with a risk score=0. Models are adjusted for age, sex, race, smoking status, diabetes, total cholesterol, HDL-cholesterol, systolic blood pressure and blood pressure medications, and statin medications. The global CVD model was additionally adjusted for serum creatinine. Other endpoints were not evaluated in DHS due to small endpoint numbers