

## **Supplemental Material**

## 1. Supplementary Tables

**Table S1.** Distribution of continuous risk markers in the Multi-ethnic Study of Atherosclerosis.

	<b>Mean (SD)</b>	<b>Median (IQR)</b>
Coronary Artery Calcium Score, AU	146.07 (417.21)	0 (0, 87.23)
Carotid Intima-Media Thickness, mm	0.87 (0.19)	0.85 (0.74, 0.97)
Flow-Mediated Dilation, % change	4.39 (2.86)	3.8 (2.3, 6)
Ankle-Brachial Index	1.11 (0.12)	1.12 (1.05, 1.18)
HsCRP, mg/L	3.78 (5.89)	1.92 (0.84, 4.26)
Homocysteine, $\mu\text{mol/L}$	9.33 (3.75)	8.6 (7.3, 10.5)
NT-ProBNP, pg/mL	102.53 (250.05)	54.51 (24.02, 112.5)

Variables presented as mean (SD) or median (IQR).

AU indicates Agatston Units; HsCRP, High Sensitivity C-Reactive Protein; and NT-ProBNP, N-terminal pro-brain natriuretic peptide.

**Table S2.** Mean diagnostic likelihood ratios (SD) of CAC=0 for coronary heart disease and cardiovascular disease events by racial/ethnic group, adjusted for traditional risk factors and 10-year atherosclerotic cardiovascular disease predicted risk.

	White	African-American	Hispanic	Chinese-American
<b>All CHD Events</b>				
Risk Factors*	0.40 (0.11)	0.48 (0.12)	0.46 (0.12)	0.44 (0.12)
ASCVD Risk†	0.33 (0.05)	0.39 (0.06)	0.39 (0.07)	0.37 (0.06)
<b>Hard CHD Events</b>				
Risk Factors*	0.50 (0.11)	0.57 (0.12)	0.56 (0.12)	0.54 (0.12)
ASCVD Risk†	0.42 (0.05)	0.49 (0.06)	0.48 (0.07)	0.46 (0.06)
<b>All CVD Events</b>				
Risk Factors*	0.51 (0.11)	0.59 (0.12)	0.57 (0.12)	0.55 (0.12)
ASCVD Risk†	0.43 (0.06)	0.51 (0.07)	0.50 (0.07)	0.48 (0.07)

\* Age, gender, smoking status, diabetes, total and HDL cholesterol, systolic blood pressure, hypertension medication use and race/ethnicity.

† 10-year atherosclerotic cardiovascular disease risk, calculated using the American College of Cardiology / American Heart Association 2013 Pooled Cohort Equations.

CHD indicates coronary heart disease; ASCVD, atherosclerotic cardiovascular disease; and CVD, cardiovascular disease.

**Table S3.** Mean diagnostic likelihood ratios (SD) of hsCRP <1mg/L, hsCRP <3mg/L, CIMT Z score <0, and the combinations CIMT ≤25<sup>th</sup> percentile plus no carotid plaque and CIMT ≤50<sup>th</sup> percentile plus no carotid plaque for coronary heart disease and cardiovascular disease events, adjusted for traditional risk factors and 10-year atherosclerotic cardiovascular disease predicted risk.

	<b>HsCRP &lt; 1mg/L</b>	<b>HsCRP &lt; 3mg/L</b>	<b>CIMT Z score &lt;0</b>	<b>CIMT ≤25th Percentile + No Carotid Plaque</b>	<b>CIMT ≤50th Percentile + No Carotid Plaque</b>
<b>All CHD Events</b>					
Risk Factors*	1.00 (0.01)	0.89 (0.04)	0.81 (0.09)	0.68 (0.04)	0.78 (0.06)
ASCVD Risk <sup>†</sup>	0.99 (0.01)	0.91 (0.02)	0.72 (0.08)	0.49 (0.03)	0.66 (0.05)
<b>Hard CHD Events</b>					
Risk Factors*	1.15 (0.04)	0.95 (0.02)	0.88 (0.07)	0.79 (0.03)	0.82 (0.05)
ASCVD Risk <sup>†</sup>	1.11 (0.02)	0.94 (0.01)	0.80 (0.07)	0.60 (0.03)	0.69 (0.05)
<b>All CVD Events</b>					
Risk Factors*	0.97 (0.01)	0.89 (0.04)	0.89 (0.06)	0.82 (0.03)	0.85 (0.05)
ASCVD Risk <sup>†</sup>	0.93 (0.01)	0.89 (0.03)	0.76 (0.07)	0.62 (0.03)	0.71 (0.05)

\* Age, gender, smoking status, diabetes, total and HDL cholesterol, systolic blood pressure, hypertension medication use and race/ethnicity.

<sup>†</sup> 10-year atherosclerotic cardiovascular disease risk, calculated using the American College of Cardiology / American Heart Association 2013 Pooled Cohort Equations.

HsCRP indicates high sensitivity C-reactive protein; CIMT, carotid intima-media thickness; CHD, coronary heart disease; ASCVD, atherosclerotic cardiovascular disease; and CVD, cardiovascular disease.

**Table S4.** Mean diagnostic likelihood ratios (SD) of continuous risk markers, considering a result of less than the study sample median as the threshold for a negative result, for coronary heart disease and cardiovascular disease events, adjusted for traditional risk factors and 10-year atherosclerotic cardiovascular disease predicted risk.

	All CHD Events		Hard CHD Events		All CVD Events	
	Risk Factors*	ASCVD Risk <sup>†</sup>	Risk Factors*	ASCVD Risk <sup>†</sup>	Risk Factors*	ASCVD Risk <sup>†</sup>
Coronary Artery Calcium Score < 0 AU	0.44 (0.12)	0.36 (0.07)	0.54 (0.12)	0.46 (0.07)	0.55 (0.12)	0.47 (0.07)
Carotid Intima-Media Thickness ≤ 50th Percentile	0.90 (0.04)	0.80 (0.05)	0.99 (0.02)	0.89 (0.03)	0.92 (0.04)	0.82 (0.04)
Flow-Mediated Dilatation ≥ 3.8% Change	0.94 (0.13)	0.94 (0.09)	0.83 (0.18)	0.80 (0.06)	0.94 (0.18)	0.93 (0.11)
Ankle-Brachial Index < 1.12	1.15 (0.07)	1.08 (0.02)	1.16 (0.07)	1.11 (0.02)	1.12 (0.05)	1.09 (0.01)
HsCRP < 1.92 mg/L	0.91 (0.03)	0.91 (0.02)	0.99 (0.01)	0.97 (0.01)	0.91 (0.03)	0.89 (0.02)
Homocysteine < 8.6 μmol/L	0.94 (0.02)	0.84 (0.03)	0.85 (0.05)	0.77 (0.03)	0.94 (0.02)	0.86 (0.03)
NT-ProBNP < 54.5 pg/mL	0.80 (0.10)	0.88 (0.04)	0.72 (0.10)	0.76 (0.04)	0.82 (0.08)	0.86 (0.04)

\* Age, gender, smoking status, diabetes, total and HDL cholesterol, systolic blood pressure, hypertension medication use and race/ethnicity.

<sup>†</sup> 10-year atherosclerotic cardiovascular disease risk, calculated using the American College of Cardiology / American Heart Association 2013 Pooled Cohort Equations.

CHD indicates coronary heart disease; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; AU, Agatston units; HsCRP, high sensitivity C-reactive protein; and NT-ProBNP, N-terminal pro-brain natriuretic peptide.

**Table S5.** Traditional risk factor-adjusted diagnostic likelihood ratios of each negative risk marker for coronary heart disease events (all) in specific clinical scenarios.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
CAC=0 AU	0.60	0.66	0.67	0.51	0.35	0.41	0.33	0.38	0.36
CIMT $\leq$ 25th Percentile	0.73	0.75	0.69	0.69	0.66	0.67	0.64	0.61	0.60
No Carotid Plaque	0.96	1.01	0.92	0.87	0.87	0.79	0.79	0.79	0.79
FMD $\geq$ 5% Change	0.68	0.94	0.83	0.92	0.84	1.14	0.92	0.86	0.92
ABI $>$ 0.9 - $<$ 1.3	1.01	1.01	0.99	0.97	1.01	0.94	0.97	0.98	0.94
HsCRP $<$ 2mg/L	0.89	0.87	0.83	0.84	0.93	0.82	0.84	0.83	0.87
Homocysteine $<$ 10 $\mu$ mol/L	1.00	1.01	1.00	1.00	0.97	0.98	0.96	0.97	0.96
NT-ProBNP $<$ 100pg/mL	0.91	0.85	0.86	0.78	0.83	0.92	0.92	0.75	0.88
No Microalbuminuria	0.95	0.97	0.96	0.98	0.89	0.94	0.87	0.89	0.83
No FH of CHD (any)	0.86	1.05	0.81	0.82	0.99	0.77	0.81	0.75	0.83
No Premature FH of CHD	1.07	1.08	1.02	1.00	1.25	0.93	1.07	1.15	1.23
No Metabolic Syndrome	1.00	0.85	0.85	0.88	0.88	0.78	0.83	0.77	-
Healthy Lifestyle	1.04	0.76	0.87	0.87	0.75	0.77	0.83	0.80	0.81

**Case 1:** 50-year-old Hispanic woman, non-smoker, SBP 120mmHg (no medication), non-diabetic, HDL-C 60mg/dL, total cholesterol 160mg/dL.

**Case 2:** 50-year-old Chinese American man, non-smoker, SBP 130mmHg (no medication), non-diabetic, HDL-C 40mg/dL, total cholesterol 170mg/dL.

**Case 3:** 55-year-old African American man, non-smoker, SBP 125mmHg (no medication), non-diabetic, HDL-C 40mg/dL, total cholesterol 170mg/dL.

**Case 4:** 60-year-old White man, non-smoker, SBP 130mmHg (no medication), non-diabetic, HDL-C 50mg/dL, total cholesterol 170mg/dL.

**Case 5:** 65-year-old Chinese American woman, non-smoker, SBP 145mmHg on medication, non-diabetic, HDL-C 50mg/dL, total cholesterol 230mg/dL.

**Case 6:** 60-year-old White man, smoker, SBP 135mmHg on medication, non-diabetic, HDL-C 40mg/dL, total cholesterol 200mg/dL.

**Case 7:** 65-year-old Hispanic woman, current smoker, SBP 160mmHg on medication, non-diabetic, HDL-C 45mg/dL, total cholesterol 220mg/dL.

**Case 8:** 75-year-old African American man, non-smoker, SBP 145mmHg on medication, non-diabetic, HDL-C 40mg/dL, total cholesterol 230mg/dL.

**Case 9:** 65-year-old African American man, non-smoker, SBP 140mmHg on medication, diabetic, HDL-C 40mg/dL, total cholesterol 210mg/dL. CAC indicates coronary artery calcium; AU, Agatston units; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; ABI, ankle-brachial index; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; FH, family history; CHD, coronary heart disease; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S6.** Traditional risk factor-adjusted diagnostic likelihood ratios of each negative risk marker for cardiovascular disease events in specific clinical scenarios.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
CAC=0 AU	0.74	0.57	0.58	0.46	0.47	0.38	0.45	0.36	0.41
CIMT $\leq$ 25th Percentile	0.82	0.81	0.76	0.76	0.77	0.75	0.75	0.69	0.70
No Carotid Plaque	0.97	0.99	0.91	0.87	0.90	0.82	0.84	0.79	0.82
FMD $\geq$ 5% Change	0.87	0.97	0.74	0.85	1.05	1.02	1.12	0.75	0.68
ABI $>$ 0.9 - $<$ 1.3	0.96	0.97	0.96	0.95	0.96	0.94	0.94	0.95	0.92
HsCRP $<$ 2mg/L	0.90	0.98	0.92	0.95	0.95	0.96	0.90	0.93	0.92
Homocysteine $<$ 10 $\mu$ mol/L	1.00	0.99	0.98	0.98	0.98	0.96	0.97	0.95	0.96
NT-ProBNP $<$ 100pg/mL	0.93	1.05	1.03	0.94	0.88	0.87	0.77	0.91	1.00
No Microalbuminuria	1.00	0.97	0.97	0.98	0.92	0.94	0.95	0.90	0.86
No FH of CHD (any)	0.79	0.91	0.77	0.75	0.80	0.71	0.73	0.68	0.72
No Premature FH of CHD	1.02	1.07	0.93	0.97	1.11	0.94	1.02	0.96	0.97
No Metabolic Syndrome	0.90	0.90	0.89	0.92	0.81	0.83	0.77	0.83	-
Healthy Lifestyle	1.08	0.90	0.99	0.99	0.88	0.92	0.91	0.95	0.99

**Case 1:** 50-year-old Hispanic woman, non-smoker, SBP 120mmHg (no medication), non-diabetic, HDL-C 60mg/dL, total cholesterol 160mg/dL.

**Case 2:** 50-year-old Chinese American man, non-smoker, SBP 130mmHg (no medication), non-diabetic, HDL-C 40mg/dL, total cholesterol 170mg/dL.

**Case 3:** 55-year-old African American man, non-smoker, SBP 125mmHg (no medication), non-diabetic, HDL-C 40mg/dL, total cholesterol 170mg/dL.

**Case 4:** 60-year-old White man, non-smoker, SBP 130mmHg (no medication), non-diabetic, HDL-C 50mg/dL, total cholesterol 170mg/dL.

**Case 5:** 65-year-old Chinese American woman, non-smoker, SBP 145mmHg on medication, non-diabetic, HDL-C 50mg/dL, total cholesterol 230mg/dL.

**Case 6:** 60-year-old White man, smoker, SBP 135mmHg on medication, non-diabetic, HDL-C 40mg/dL, total cholesterol 200mg/dL.

**Case 7:** 65-year-old Hispanic woman, current smoker, SBP 160mmHg on medication, non-diabetic, HDL-C 45mg/dL, total cholesterol 220mg/dL.

**Case 8:** 75-year-old African American man, non-smoker, SBP 145mmHg on medication, non-diabetic, HDL-C 40mg/dL, total cholesterol 230mg/dL.



**Case 9:** 65-year-old African American man, non-smoker, SBP 140mmHg on medication, diabetic, HDL-C 40mg/dL, total cholesterol 210mg/dL. CAC indicates coronary artery calcium; AU, Agatston units; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; ABI, ankle-brachial index; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; FH, family history; CHD, coronary heart disease; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S7.** Beta coefficients used for calculating the diagnostic likelihood ratios of each negative risk marker for coronary heart disease events (all).

	<b>CAC=0 AU</b>	<b>CIMT ≤ 25th Percentile</b>	<b>No Carotid Plaque</b>	<b>FMD ≥ 5% Change</b>	<b>ABI &gt; 0.9 - &lt; 1.3</b>	<b>HsCRP &lt;2mg/L</b>	<b>Homocysteine &lt; 10μmol/L</b>	<b>NT-ProBNP &lt; 100pg/mL</b>
<b>Age</b>	-0.020	-0.005	-0.005	-0.001	-0.0002	0.001	-0.001	-0.009
<b>Male</b>	-0.214	-0.038	-0.022	-0.065	0.008	0.051	-0.018	0.083
<b>Chinese</b>	0.084	0.043	0.105	-0.046	0.039	0.051	0.001	-0.020
<b>Black</b>	0.189	-0.014	0.041	-0.148	0.018	-0.010	-0.004	0.030
<b>Hispanic</b>	0.131	0.027	0.048	-0.160	0.026	-0.005	0.001	-0.007
<b>Smoker</b>	-0.089	0.002	-0.042	0.135	-0.023	-0.024	-0.005	0.117
<b>SBP</b>	-0.001	-0.0004	0.00001	0.002	0.00002	-0.001	-0.00002	-0.002
<b>Hypertension Medication Use</b>	-0.079	-0.017	-0.039	0.023	-0.005	0.009	-0.012	0.017
<b>Diabetes</b>	-0.071	-0.024	-0.024	0.127	-0.054	-0.002	-0.0004	0.001
<b>HDL-C</b>	0.002	0.001	0.001	-0.006	0.0001	0.001	0.0002	-0.002
<b>Total Cholesterol</b>	-0.001	-0.0001	-0.0004	-0.0003	-0.00004	-0.0001	-0.00004	0.001
<b>Constant</b>	2.104	0.441	0.549	0.255	0.176	0.054	0.171	0.896
<b>Risk Marker Coefficient</b>	<b>-1.380</b>	<b>-0.495</b>	<b>-0.367</b>	<b>-0.192</b>	<b>-0.194</b>	<b>-0.188</b>	<b>-0.110</b>	<b>-0.419</b>

CAC indicates coronary artery calcium; AU, Agatston units; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; ABI, ankle-brachial index; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S7, continued.** Beta coefficients used for calculating the diagnostic likelihood ratios of each negative risk marker for coronary heart disease events (all).

	No Microalbuminuria	No FH of CHD	No Premature FH of CHD	No Metabolic Syndrome	Healthy Lifestyle
<b>Age</b>	-0.001	-0.001	0.001	0.0003	-0.005
<b>Male</b>	-0.023	0.024	0.032	0.069	0.02
<b>Chinese</b>	-0.025	0.228	0.090	0.023	-0.115
<b>Black</b>	-0.034	-0.016	0.037	0.010	0.044
<b>Hispanic</b>	-0.026	0.017	0.052	-0.004	0.078
<b>Smoker</b>	-0.011	-0.004	-0.113	0.002	-0.059
<b>SBP</b>	-0.001	0.001	0.001	-0.001	-0.0003
<b>Hypertension Medication Use</b>	-0.020	-0.058	0.016	-0.054	0.007
<b>Diabetes</b>	-0.073	0.064	0.071	-0.090	-0.036
<b>HDL-C</b>	-0.0004	-0.0001	0.001	0.005	0.007
<b>Total Cholesterol</b>	-0.0002	-0.0004	0.001	-0.0004	0.0003
<b>Constant</b>	0.507	0.330	-0.154	0.083	-0.042
<b>Risk Marker Coefficient</b>	<b>-0.282</b>	<b>-0.521</b>	<b>-0.252</b>	<b>-0.284</b>	<b>-0.182</b>

FH indicates family history; CHD, coronary heart disease; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S8.** Beta coefficients used for calculating the diagnostic likelihood ratios of each negative risk marker for hard coronary heart disease events.

	CAC=0 AU	CIMT ≤ 25th Percentile	No Carotid Plaque	FMD ≥ 5% Change	ABI > 0.9 - < 1.3	HsCRP <2mg/L	Homocysteine < 10μmol/L	NT-ProBNP < 100pg/mL
<b>Age</b>	-0.016	-0.002	-0.004	-0.003	-0.001	0.001	-0.003	-0.009
<b>Male</b>	-0.170	-0.035	-0.017	-0.329	-0.006	0.007	-0.035	0.094
<b>Chinese</b>	0.074	0.032	0.088	-0.087	0.060	0.018	0.001	0.065
<b>Black</b>	0.149	-0.018	0.028	-0.117	0.023	0.007	-0.009	0.110
<b>Hispanic</b>	0.108	0.027	0.057	-0.178	0.027	0.002	0.003	0.023
<b>Smoker</b>	-0.070	0.011	-0.033	0.024	-0.020	0.005	-0.011	-0.205
<b>SBP</b>	-0.001	0.0002	0.0004	-0.0003	0.0001	-0.0002	-0.0001	-0.003
<b>Hypertension Medication Use</b>	-0.065	-0.015	-0.025	-0.124	-0.004	0.007	-0.024	0.007
<b>Diabetes</b>	-0.056	-0.020	-0.035	0.080	-0.087	-0.0001	-0.001	0.056
<b>HDL-C</b>	0.002	-0.0003	0.001	-0.013	-0.0003	0.0002	0.0003	-0.002
<b>Total Cholesterol</b>	-0.001	0.0001	-0.0004	0.0002	0.00003	0.0001	-0.0001	0.001
<b>Constant</b>	1.702	0.174	0.391	1.193	0.466	-0.021	0.332	1.283
<b>Risk Marker Coefficient</b>	<b>-1.064</b>	<b>-0.206</b>	<b>-0.272</b>	<b>-0.328</b>	<b>-0.426</b>	<b>-0.053</b>	<b>-0.216</b>	<b>-0.641</b>

CAC indicates coronary artery calcium; AU, Agatston units; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; ABI, ankle-brachial index; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S8, continued.** Beta coefficients used for calculating the diagnostic likelihood ratios of each negative risk marker for hard coronary heart disease events.

	No Microalbuminuria	No FH of CHD	No Premature FH of CHD	No Metabolic Syndrome	Healthy Lifestyle
<b>Age</b>	-0.001	-0.001	0.00003	0.0004	-0.007
<b>Male</b>	-0.016	0.012	0.013	0.078	-0.022
<b>Chinese</b>	-0.021	0.229	0.048	0.025	-0.146
<b>Black</b>	-0.034	-0.027	0.093	0.010	0.018
<b>Hispanic</b>	-0.025	0.010	0.107	-0.005	0.093
<b>Smoker</b>	-0.010	-0.002	-0.169	0.0035	-0.011
<b>SBP</b>	-0.001	0.0004	-0.001	-0.001	-0.001
<b>Hypertension Medication Use</b>	-0.017	-0.076	0.085	-0.058	0.166
<b>Diabetes</b>	-0.085	0.042	-0.022	-0.101	0.043
<b>HDL-C</b>	0.00002	-0.0003	0.001	0.006	0.007
<b>Total Cholesterol</b>	-0.0001	-0.001	0.002	-0.0004	0.001
<b>Constant</b>	0.407	0.316	0.095	0.084	0.022
<b>Risk Marker Coefficient</b>	<b>-0.253</b>	<b>-0.464</b>	<b>-0.206</b>	<b>-0.322</b>	<b>-0.039</b>

FH indicates family history; CHD, coronary heart disease; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S9.** Beta coefficients used for calculating the diagnostic likelihood ratios of each negative risk marker for cardiovascular disease events.

	<b>CAC=0 AU</b>	<b>CIMT ≤ 25th Percentile</b>	<b>No Carotid Plaque<sup>†</sup></b>	<b>FMD ≥ 5% Change</b>	<b>ABI &gt; 0.9 - &lt; 1.3</b>	<b>HsCRP &lt;2mg/L</b>	<b>Homocysteine &lt; 10μmol/L</b>	<b>NT-ProBNP &lt; 100pg/mL</b>
<b>Age</b>	-0.017	-0.004	-0.005	-7.89x10 <sup>-6</sup>	0.0004	0.001	-0.001	-0.008
<b>Male</b>	-0.175	-0.015	-0.015	-0.194	-0.004	0.049	-0.014	0.073
<b>Chinese</b>	0.070	0.038	0.089	0.007	0.025	0.052	0.001	0.006
<b>Black</b>	0.155	-0.010	0.033	-0.256	0.013	-0.010	-0.003	0.022
<b>Hispanic</b>	0.110	0.011	0.033	-0.052	0.005	-0.007	0.002	0.004
<b>Smoker</b>	-0.071	0.012	-0.019	0.071	-0.005	0.021	-0.002	-0.120
<b>SBP</b>	-0.001	-0.0004	0.0001	0.0002	0.0001	-0.0004	-2.7x10 <sup>-6</sup>	-0.001
<b>Hypertension Medication Use</b>	-0.064	-0.008	-0.026	-0.015	0.009	0.004	-0.008	-0.004
<b>Diabetes</b>	-0.055	-0.027	-0.024	-0.083	-0.040	-0.003	-0.0001	0.036
<b>HDL-C</b>	0.001	0.001	0.001	-0.012	0.0002	0.001	0.0002	-0.002
<b>Total Cholesterol</b>	-0.001	-0.0001	-0.0003	0.0003	-0.0004	-0.0001	-0.00004	0.001
<b>Constant</b>	1.714	0.337	0.432	0.792	0.034	0.050	0.133	0.786
<b>Risk Marker Coefficient</b>	-1.054	-0.338	-0.267	-0.236	-0.063	-0.196	-0.086	-0.379

CAC indicates coronary artery calcium; AU, Agatston units; CIMT, carotid intima-media thickness; FMD, flow-mediated dilation; ABI, ankle-brachial index; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S9, continued.** Beta coefficients used for calculating the diagnostic likelihood ratios of each negative risk marker for cardiovascular disease events.

	No Microalbuminuria	No FH of CHD	No Premature FH of CHD	No Metabolic Syndrome	Healthy Lifestyle
<b>Age</b>	-0.001	-0.0004	-0.002	0.0003	-0.002
<b>Male</b>	-0.014	-0.004	-0.005	0.064	0.061
<b>Chinese</b>	-0.023	0.180	0.071	0.022	-0.052
<b>Black</b>	-0.020	0.014	-0.047	0.010	0.045
<b>Hispanic</b>	-0.019	0.053	0.045	-0.004	0.057
<b>Smoker</b>	-0.009	0.016	-0.059	0.003	-0.05
<b>SBP</b>	-0.001	0.0002	0.001	-0.001	-0.0004
<b>Hypertension Medication Use</b>	-0.021	-0.054	-0.009	-0.048	0.067
<b>Diabetes</b>	-0.067	0.034	0.010	-0.084	0.006
<b>HDL-C</b>	$7 \times 10^{-6}$	-0.001	-0.00004	0.004	0.006
<b>Total Cholesterol</b>	-0.0002	-0.001	0.001	-0.0003	-0.001
<b>Constant</b>	0.508	0.363	-0.011	0.077	-0.011
<b>Risk Marker Coefficient</b>	<b>-0.294</b>	<b>-0.430</b>	<b>-0.190</b>	<b>-0.263</b>	<b>-0.0184</b>

FH indicates family history; CHD, coronary heart disease; SBP, systolic blood pressure; and HDL-C, high density lipoprotein cholesterol.

**Table S10.** Net reclassification improvement for CVD events with the 13 negative risk markers in MESA participants with a pre-test 10-year CVD risk  $\geq 5\%$  (N=4,655, including 4,001 participants without events and 654 with events). Reclassification was defined as a post-test risk  $< 5\%$ .

	Prevalence of risk marker		Correct reclassification (non-events)		Incorrect reclassification (events)		NRI
	N	%	N	%	N	%	
CAC Score = 0 AU	1,738	37.3	702	17.5	24	3.7	13.88
HsCRP < 2 mg/dL	2,324	50.3	103	2.6	4	0.6	1.96
Homocysteine < 10 $\mu$ mol/L	2,837	61.1	86	2.1	4	0.6	1.54
NT-ProBNP < 100pg/mL	2,522	65.7	92	2.3	3	0.5	1.84
No Microalbuminuria	4,058	87.6	41	1.0	2	0.3	0.72
Ankle-Brachial Index > 0.9 - < 1.3	3,789	82.5	97	2.4	4	0.6	1.81
CIMT $\leq$ 25th Percentile	680	14.8	197	4.9	11	1.7	3.24
No Carotid Plaque	2,261	49.3	193	4.8	6	0.9	3.91
FMD $\geq$ 5% Change	536	27.3	53	1.3	2	0.3	1.02
No Family History of CHD	2,402	55.5	184	4.6	11	1.7	2.92
No Family History of Premature CHD	2,859	81.3	81	2.0	1	0.2	1.87
No Metabolic Syndrome	2,635	56.8	152	3.8	4	0.6	3.19
Healthy Lifestyle	902	26.9	77	1.9	3	0.5	1.47

CVD indicates cardiovascular disease; N, number; NRI, net reclassification improvement; CAC, coronary artery calcium; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; CIMT, carotid intima-media thickness; FMD, flow mediated dilation; CHD, coronary heart disease.



**Table S11.** Net reclassification improvement for CVD events with the 13 negative risk markers in MESA participants with a pre-test 10-year CVD risk  $\geq 7.5\%$  (N=3,833, including 3,227 participants without events and 606 with events). Reclassification was defined as a post-test 10-year CVD risk  $< 5\%$ .

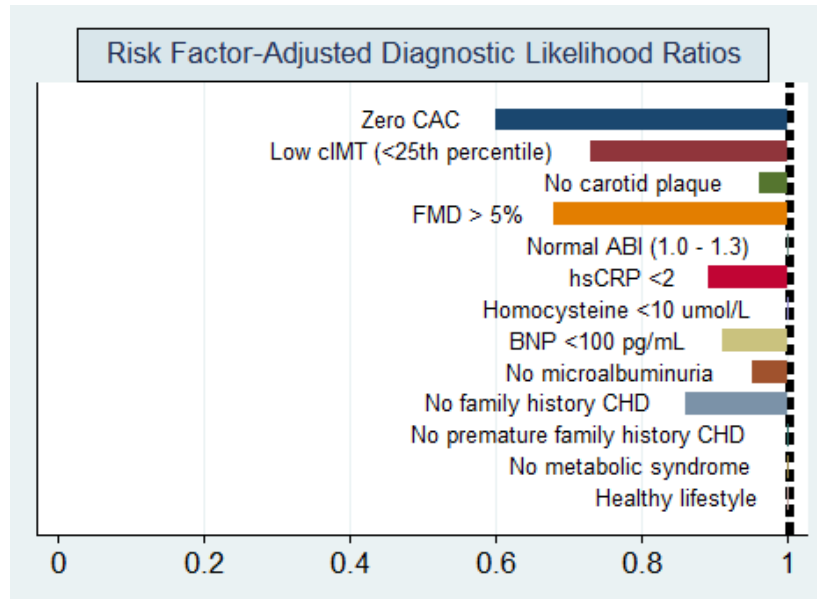
	Prevalence of risk marker		Correct reclassification (non-events)		Incorrect reclassification (events)		NRI
	N	%	N	%	N	%	
CAC Score = 0 AU	1,291	33.6	299	9.3	15	2.5	6.79
HsCRP < 2 mg/dL	1,923	50.4	0	0	0	0	0.00
Homocysteine < 10 $\mu$ mol/L	2,252	58.7	0	0	0	0	0.00
NT-ProBNP < 100pg/mL	1,992	62.5	0	0	0	0	0.00
No Microalbuminuria	3,294	86.1	0	0	0	0	0.00
Ankle-Brachial Index > 0.9 - < 1.3	3,079	81.4	0	0	0	0	0.00
CIMT $\leq$ 25th Percentile	482	12.7	19	0.6	2	0.3	0.26
No Carotid Plaque	1,747	46.2	0	0	0	0	0.00
FMD $\geq$ 5% Change	379	24.0	0	0	0	0	0.00
No Family History of CHD	1,970	55.4	0	0	0	0	0.00
No Family History of Premature CHD	2,341	82.0	0	0	0	0	0.00
No Metabolic Syndrome	2,094	54.6	0	0	0	0	0.00
Healthy Lifestyle	738	26.6	0	0	0	0	0.00

CVD indicates cardiovascular disease; N, number; NRI, net reclassification improvement; CAC, coronary artery calcium; HsCRP, high sensitivity C-reactive protein; NT-ProBNP, N-terminal pro-brain natriuretic peptide; CIMT, carotid intima-media thickness; FMD, flow mediated dilation; CHD, coronary heart disease.

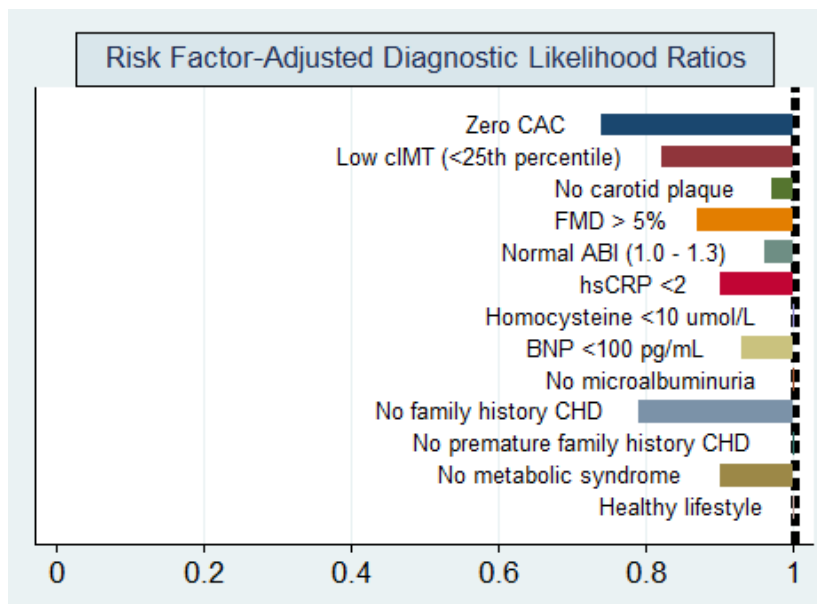
## **2. Supplementary Figures**

**Figure S1.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 50-year-old Hispanic woman, non-smoker, SBP 120mmHg (no medication), non-diabetic, HDL-cholesterol 60mg/dL, total cholesterol 160mg/dL.

**S1.A)** Coronary heart disease events (all)

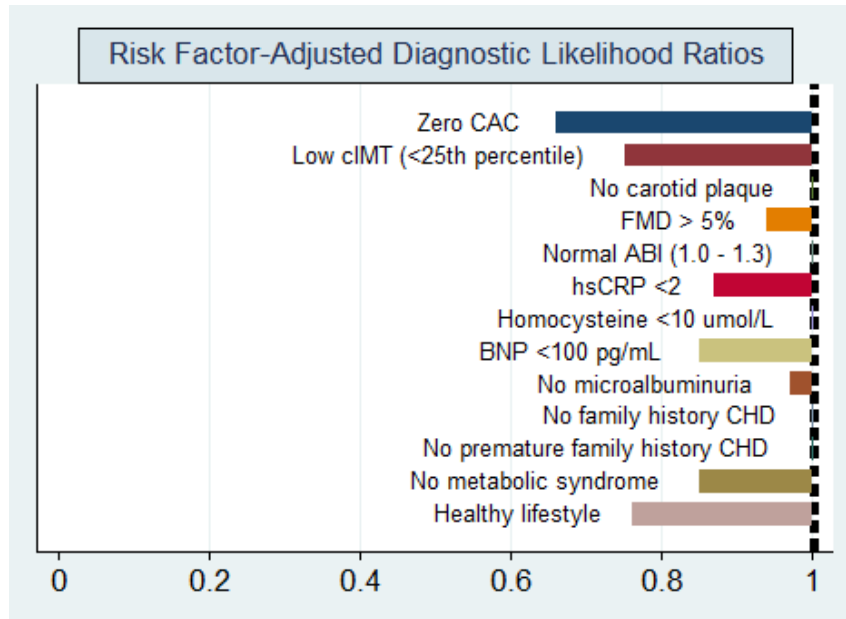


**S1.B)** Cardiovascular disease events

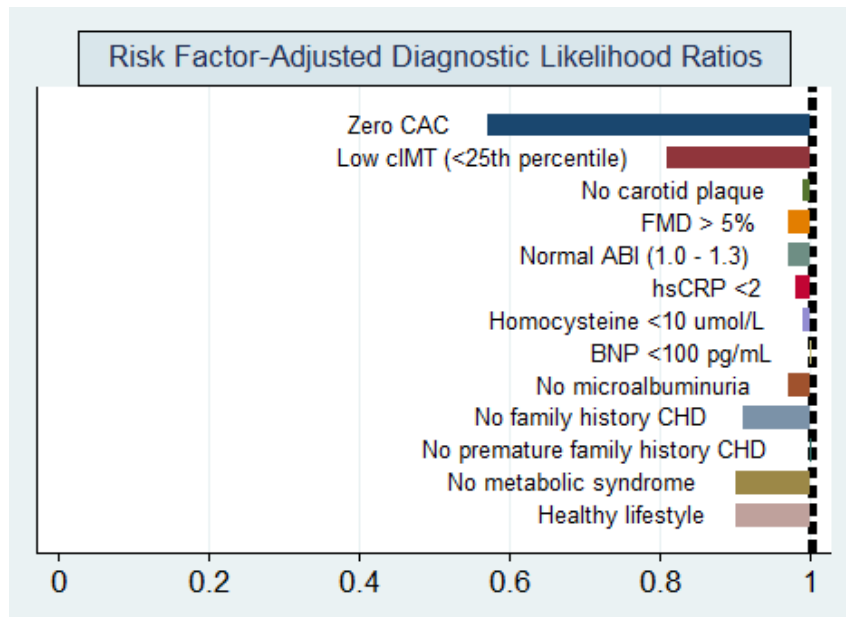


**Figure S2.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 50-year-old Chinese American man, non-smoker, SBP 130mmHg (no medication), non-diabetic, HDL-cholesterol 40mg/dL, total cholesterol 170mg/dL.

**S2.A)** Coronary heart disease events (all)

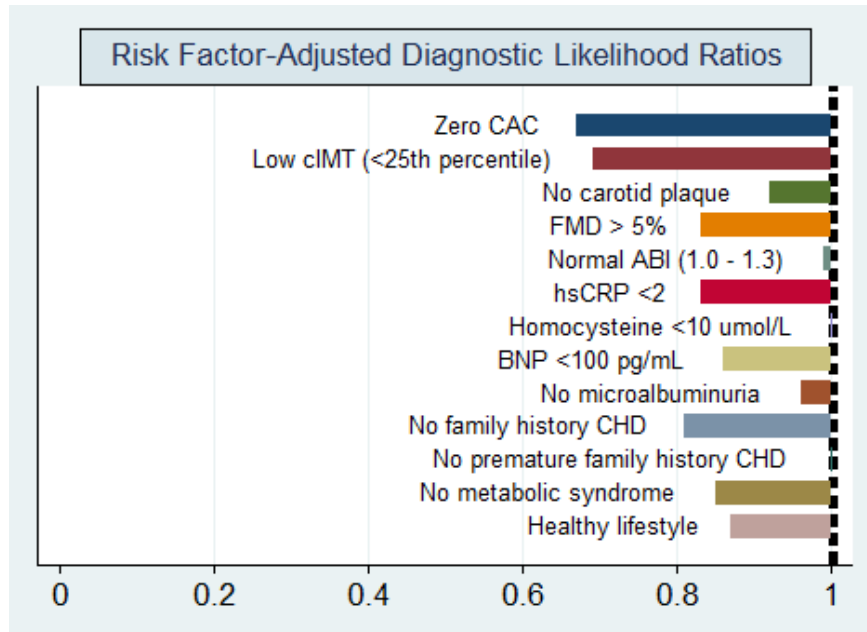


**S2.B)** Cardiovascular disease events

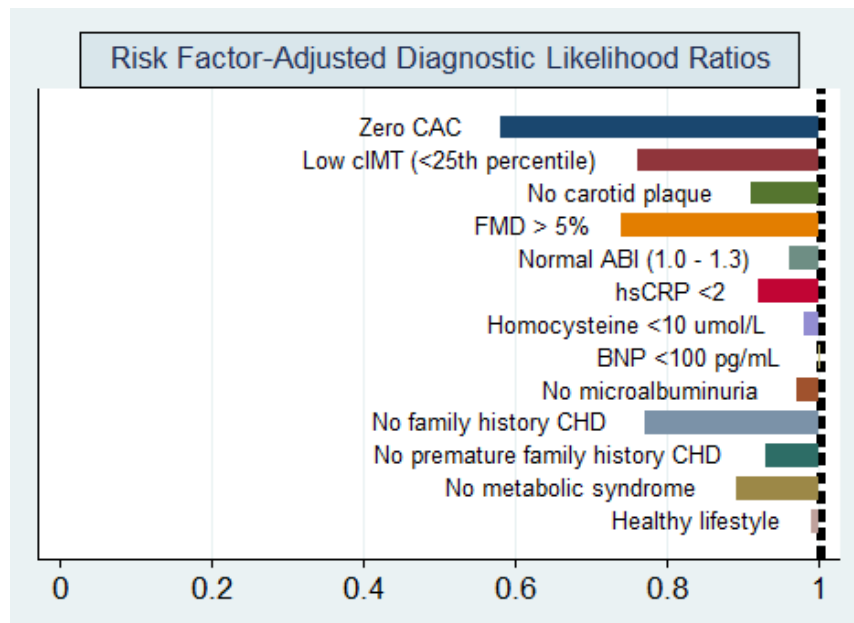


**Figure S3.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 55-year-old African American man, non-smoker, SBP 125mmHg (no medication), non-diabetic, HDL-cholesterol 40mg/dL, total cholesterol 170mg/dL.

**S3.A)** Coronary heart disease events (all)

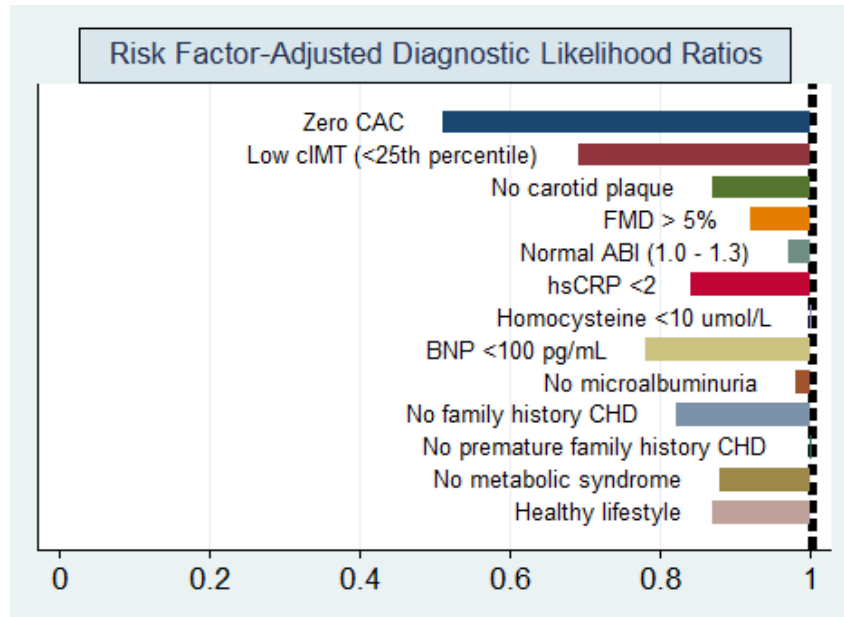


**S3.B)** Cardiovascular disease events

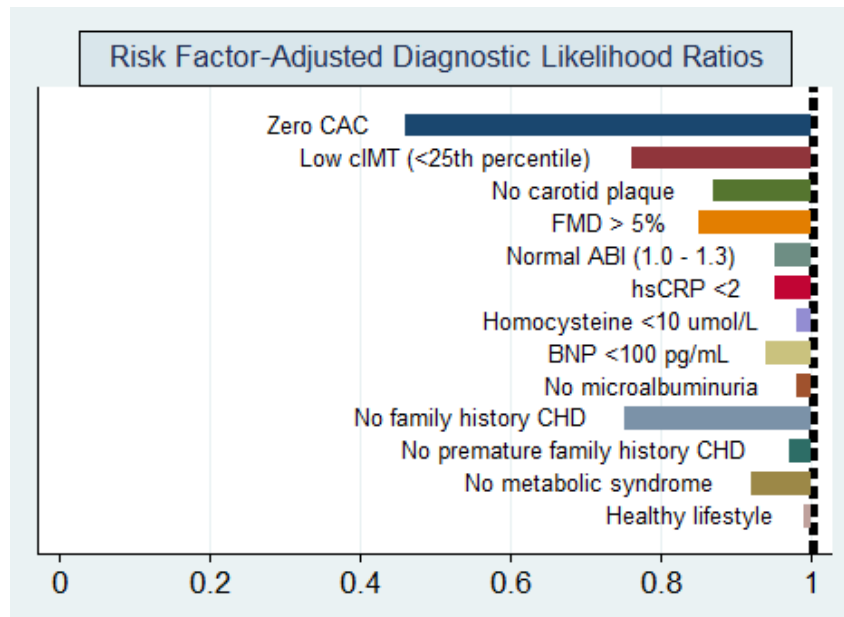


**Figure S4.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 60-year-old White man, non-smoker, SBP 130mmHg (no medication), non-diabetic, HDL-cholesterol 50mg/dL, total cholesterol 170mg/dL.

**S4.A)** Coronary heart disease events (all)

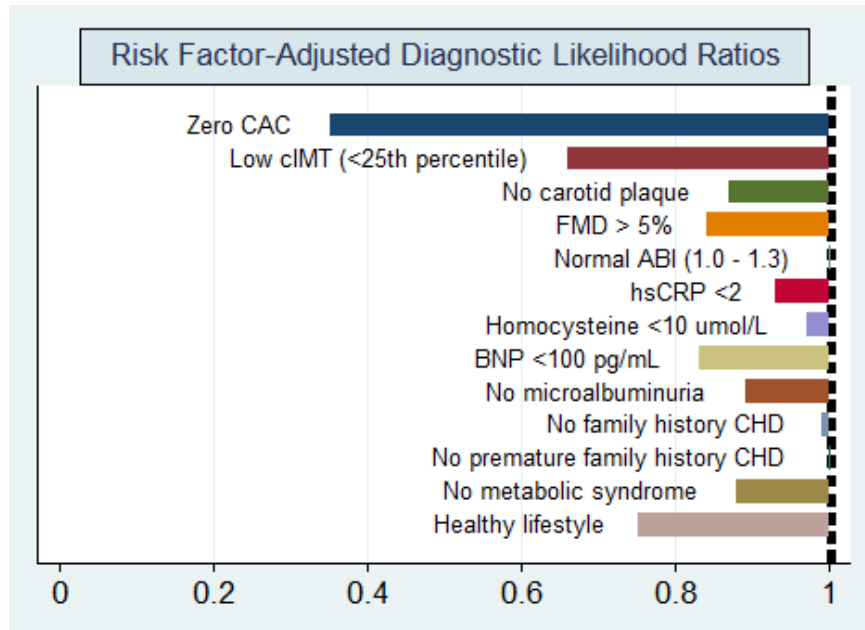


**S4.B)** Cardiovascular disease events

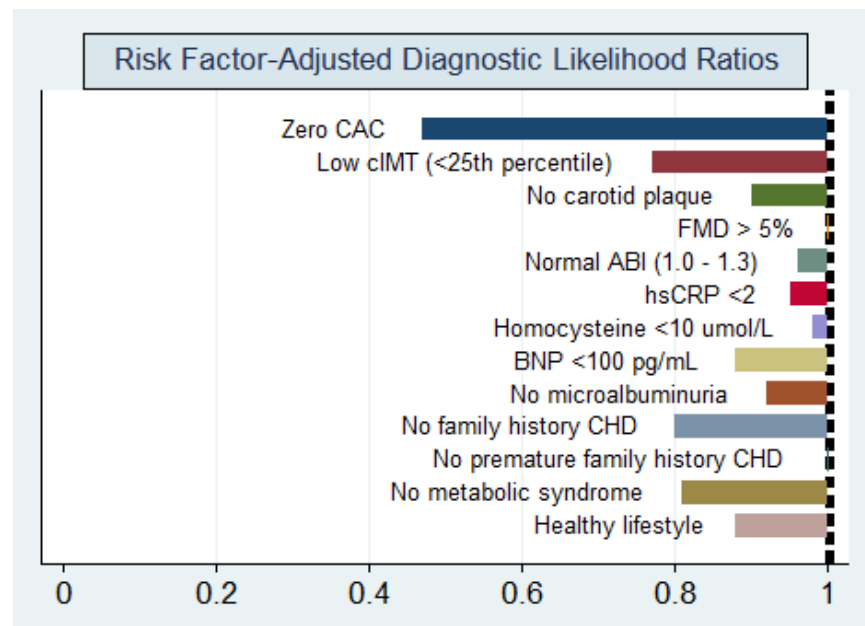


**Figure S5.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 65-year-old Chinese American woman, non-smoker, SBP 145mmHg on medication, non-diabetic, HDL-cholesterol 50mg/dL, total cholesterol 230mg/dL.

**S5.A)** Coronary heart disease events (all)

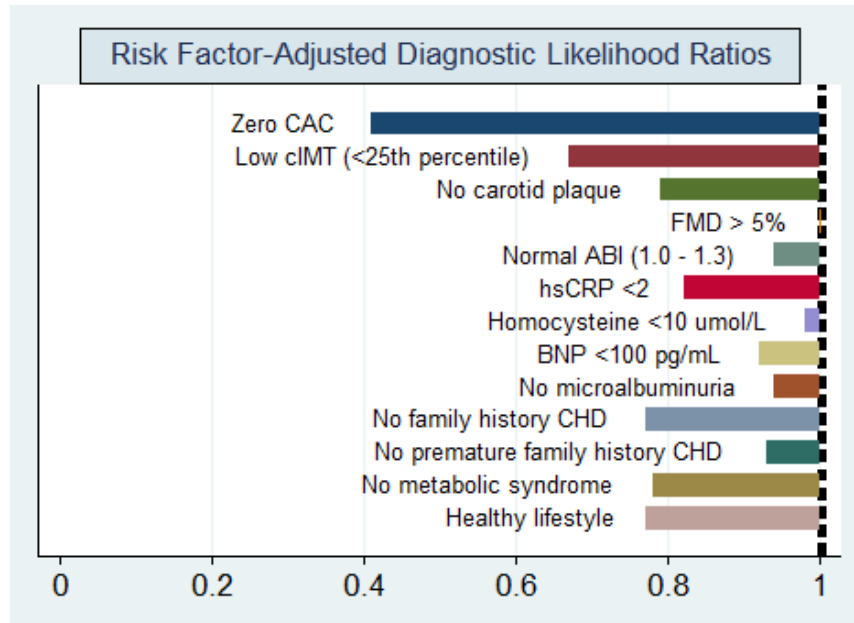


**S5.B)** Cardiovascular disease events

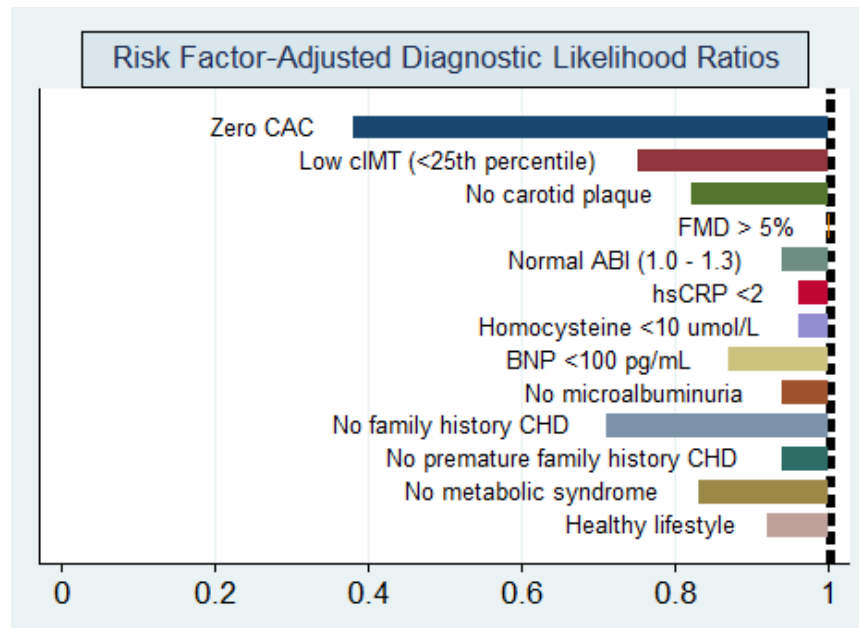


**Figure S6.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 60-year-old White man, smoker, SBP 135mmHg on medication, non-diabetic, HDL-cholesterol 40mg/dL, total cholesterol 200mg/dL.

**S6.A)** Coronary heart disease events (all)



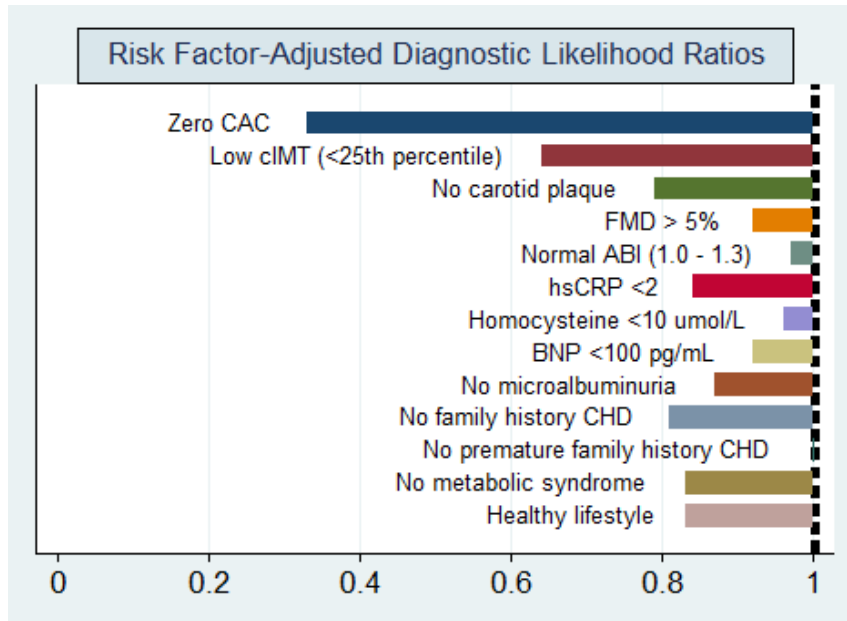
**S6.B)** Cardiovascular disease events



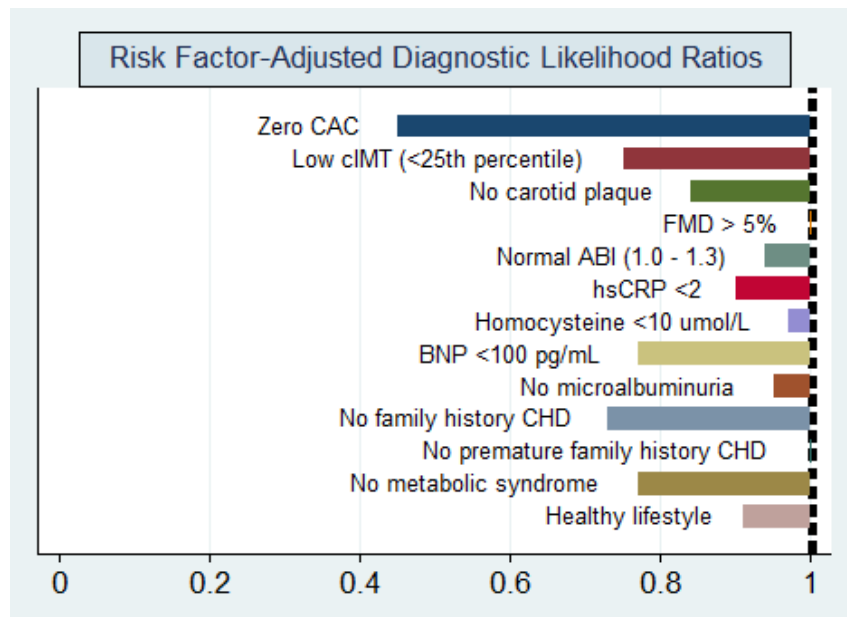


**Figure S7.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 65-year-old Hispanic woman, current smoker, SBP 160mmHg on medication, non-diabetic, HDL-cholesterol 45mg/dL, total cholesterol 220mg/dL.

**S7.A)** Coronary heart disease events (all)

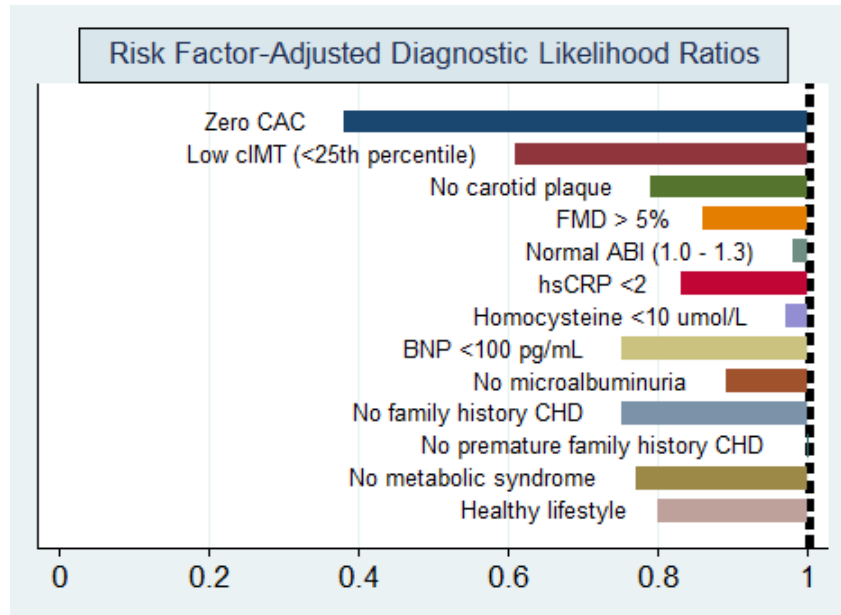


**S7.B)** Cardiovascular disease events

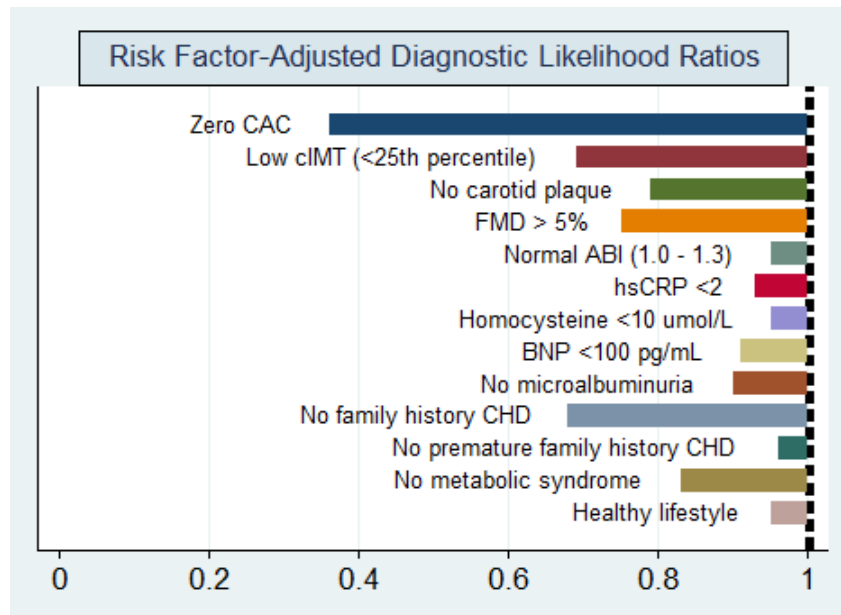


**Figure S8.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 75-year-old African American man, non-smoker, SBP 145mmHg on medication, non-diabetic, HDL-cholesterol 40mg/dL, total cholesterol 230 mg/dL.

**S8.A)** Coronary heart disease events (all)

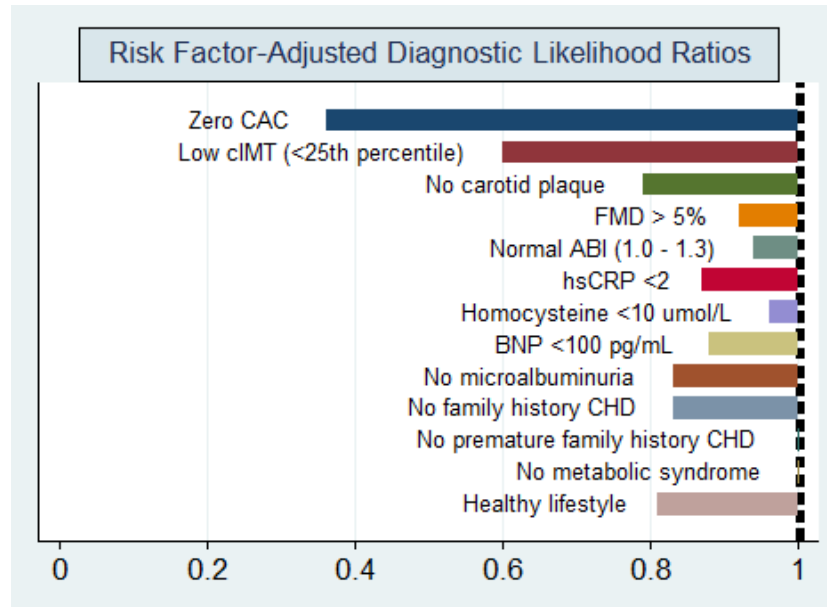


**S8.B)** Cardiovascular disease events

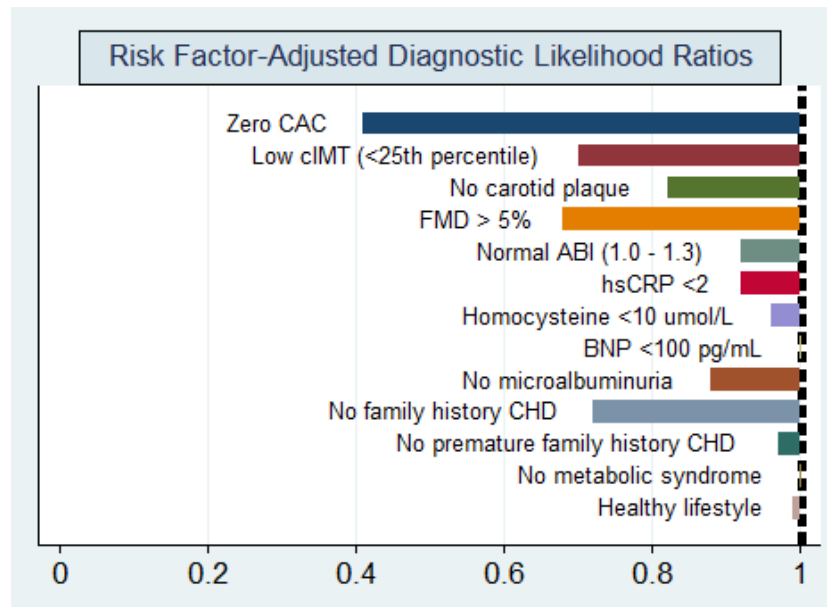


**Figure S9.** Risk factor-adjusted diagnostic likelihood ratios of different negative risk markers for coronary heart disease events (all) (A) and cardiovascular disease events (B) in a 65-year-old African American man, non-smoker, SBP 140mmHg on medication, diabetic, HDL-cholesterol 40mg/dL, total cholesterol 210 mg/dL.

**S9.A)** Coronary heart disease events (all)



**S9.B)** Cardiovascular disease events



## **Supplementary Methods**

## **Measurement Reliability in MESA**

### **Coronary Artery Calcium Scores**

Kappa statistic for inter-observer agreement for the presence of CAC was 0.92.

### **Carotid Intima-Media Thickness**

Blinded repeated readings completed by two readers yielded between-reader correlation coefficients (CC) of 0.84 and 0.86, respectively.

### **Carotid Plaque**

Intra-reader and inter-reader Kappa statistics were 0.83 [95% CI 0.70–0.96] and 0.89 [0.72–1.00], respectively).

### **Flow Mediated Dilation**

Intra-reader intra-class CC were 0.99 for baseline and maximum diameters, and 0.93 for percent FMD. Intra-participant intra-class CC were 0.90, 0.90, and 0.54, respectively.

### **Ankle-Brachial Index**

The inter-reader and intra-reader CC were 0.845 and 0.937, respectively, and the intra-reader and inter-reader coefficients of variation (CV) were 5.14% and 3.27%, respectively.

### **High Sensitivity C-Reactive Protein**

The analytical intra-assay CVs ranged from 2.3 to 4.4%, and the inter-assay CVs from 2.1 to 5.7%.

**Homocysteine**

The CVs ranged 3.8–5.1%.

**NT-ProBNP**

The intra-assay and inter-assay CVs were 1.3% and 4.8%, respectively.

**Urine albumin**

The minimum detectable level of albumin is 0.2 mg/dL, and the normal reference range is <1.9 mg/dL.