

**Supplementary Table 1:** Baseline characteristics of the population stratified by familial risk assessment status <sup>a,b</sup>

	<b>Total population (N= 6192)</b>	<b>Weak FH (N= 1240)</b>	<b>Moderate FH (N= 979)</b>	<b>Strong FH (N= 1240)</b>	<b>p-value <sup>c</sup></b>
Age, years	62 (10)	62 (10)	62 (10)	62 (10)	.87
Males (%)	2950 (48)	1979 (50)	457 (47)	514 (41)	<.001 <sup>d</sup>
Race/Ethnicity (%)					<.001 <sup>d</sup>
White	2499 (40)	1370 (35)	521 (53)	558 (45)	
Chinese-American	727 (12)	629 (16)	55 (6)	43 (4)	
African American	1669 (27)	1087 (27)	219 (22)	363 (29)	
Hispanic	1347 (22)	887 (22)	184 (19)	276 (22)	
BMI, kg/m <sup>2</sup>	28.3 (5.4)	28.0 (5.3)	28.4 (5.4)	29.3 (5.7)	<.001 <sup>d</sup>
LDL, mg/dL	117 (31)	116 (31)	120 (31)	118 (31)	.004 <sup>d</sup>
HDL, mg/dL	51 (15)	51 (15)	51 (15)	51 (15)	.29
Lipid-lowering medication use (%)	1006 (16)	583 (15)	178 (18)	245 (20)	<.001 <sup>d</sup>
SBP, mmHg	126 (21)	126 (21)	126 (21)	127 (20)	.34
Antihypertensive medication use (%)	2275 (37)	1391 (35)	377 (39)	507 (41)	<.001 <sup>d</sup>
Diabetes mellitus (%)	740 (12)	476 (12)	91 (9)	173 (14)	.003 <sup>d</sup>
Cigarette smoking (%)					.001 <sup>d</sup>
Never	3121 (51)	2072 (52)	474 (49)	575 (46)	
Former	2280 (37)	1409 (36)	388 (40)	483 (39)	
Current	774 (13)	479 (12)	115 (12)	180 (15)	

<sup>a</sup> BMI = body mass index, FH = family history, HDL = high density lipoprotein cholesterol, LDL= low density lipoprotein cholesterol, SBP = systolic blood pressure.

<sup>b</sup> Baseline characteristics expressed as means (standard deviation) for continuous variables and numbers, percentages for categorical variables. P-value for difference calculated using ANOVA test for continuous variables and chi-square test for categorical variables.

<sup>c</sup> P-value comparing presence of moderate and strong FRA to weak (i.e. no FH).

<sup>d</sup> Indicated statistically significant results.

**Supplementary Table 2:** Incidence rates (95% confidence interval) of cardiovascular events for each family history definition <sup>a,b</sup>

	N (%)	CHD		Angina		Stroke		PAD		CHF		Composite ASCVD <sup>b</sup>	
		N	IR	N	IR	N	IR	N	IR	N	IR	N	IR
<b>Total Population</b>		250	4.17 (3.69-4.72)	258	4.36 (3.86-4.92)	150	2.50 (2.13-2.93)	75	1.24 (0.99-1.56)	206	3.44 (3.00-3.94)	741	12.92 (12.03-13.89)
<b>Family History Status</b>													
<i>Any Family History</i>													
<b>Any</b>	2211 (36)	108	5.06 (4.19-6.10)	125	5.95 (5.00-7.09)	62	2.89 (2.25-3.71)	27	1.25 (0.86-1.82)	80	3.75 (3.01-4.66)	317	15.69 (12.03-13.89)
<b>Sibling</b>	840 (14)	47	5.88 (4.42-7.83)	48	6.09 (4.59-8.08)	29	3.61 (2.51-5.19)	13	1.60 (0.93-2.76)	33	4.11 (2.92-5.78)	134	17.81 (15.04-21.10)
<b>Child</b>	62 (1)	6	11.17 (5.02-24.86)	7	13.52 (6.45-28.36)	2	3.61 (0.90-14.45)	2	3.59 (0.90-14.37)	4	7.45 (2.80-19.84)	15	30.77 (18.55-51.05)
<b>Parent</b>	1686 (27)	77	4.69 (3.75-5.87)	100	6.20 (5.10-7.54)	42	2.55 (1.88-3.45)	21	1.27 (0.83-1.94)	59	3.60 (2.79-4.64)	235	15.12 (13.30-17.18)
<b>Spouse</b>	338 (5)	19	6.01 (3.84-9.42)	15	4.77 (2.87-7.90)	14	4.40 (2.60-7.42)	6	1.87 (0.84-4.17)	13	4.07 (2.37-7.01)	50	16.54 (12.54-21.82)
<i>Premature Family History</i>													
<b>Premature</b>	983 (16)	48	5.06 (3.81-6.71)	57	6.13 (4.72-7.94)	25	2.62 (1.77-3.88)	17	1.78 (1.11-2.86)	37	3.91 (2.83-5.40)	142	15.83 (13.43-18.66)
<b>Sibling</b>	463 (7)	24	5.44 (3.65-8.12)	27	6.22 (4.26-9.06)	9	2.02 (1.05-3.89)	8	1.80 (0.90-3.59)	21	4.78 (3.12-7.34)	69	16.57 (13.08-20.98)
<b>Child</b>	57 (1)	6	12.29 (5.52-27.36)	7	14.94 (7.12-31.34)	2	3.97 (0.99-15.86)	2	3.94 (0.99-15.77)	4	8.20 (3.08-21.84)	15	34.22 (20.63-56.77)
<b>Parent</b>	554 (9)	25	4.59 (3.10-6.79)	32	5.99 (4.24-8.47)	15	2.75 (1.66-4.56)	10	1.83 (0.98-3.39)	19	3.49 (2.23-5.47)	79	15.36 (12.32-19.15)
<b>Spouse</b>	226 (4)	11	5.11 (3.69-4.72)	10	4.67 (2.51-8.67)	9	4.15 (2.16-7.97)	2	0.91 (0.23-3.65)	7	3.22 (1.54-6.76)	30	14.48 (10.13-20.71)

Familial Risk													
<b>FH Strong</b>	1240 (20)	61	5.10 (3.97- 6.56)	77	6.57 (5.26- 8.22)	37	3.08 (2.23- 4.26)	19	1.57 (1.00- 2.47)	47	3.94 (2.96- 5.24)	187	16.59 (14.38- 19.15)
<b>FH Moderate</b>	1435 (23)	67	5.07 (3.82- 6.73)	75	5.13 (3.87- 6.81)	40	2.63 (1.78- 3.89)	17	0.83 (0.42- 1.67)	49	3.48 (2.47- 4.90)	197	14.55 (12.26- 17.27)
<b>FH Weak</b>	3981 (64)	142	3.67 (3.11- 4.33)	133	3.50 (2.95- 4.14)	88	2.29 (1.86- 2.82)	48	1.25 (0.94- 1.65)	126	3.28 (2.76- 3.91)	424	11.44 (10.40- 12.58)

<sup>a</sup> ASCVD – atherosclerotic cardiovascular disease, CHD = coronary heart disease, CHF = congestive heart failure, FH = family history, IR = Incidence rates (expressed per 1000 per years), N = number.

<sup>b</sup> Composite ASCVD includes CHD, angina, stroke, PAD, and CHF.

**Supplementary Table 3: Hazard ratios (95% confidence interval) for the association of each FH definition and non-coronary cardiovascular events<sup>a</sup>**

	Stroke			PAD			CHF		
	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>
<b>Family History Status</b>									
<b>No FH (ref)</b>	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<i>Any Family History</i>									
<b>Any</b>	1.27 (0.92-1.76)	1.22 (0.87-1.70)	1.19 (0.85-1.67)	1.01 (0.63-1.62)	0.93 (0.58-1.50)	0.90 (0.55-1.46)	1.15 (0.87-1.52)	1.14 (0.85-1.52)	1.11 (0.83-1.48)
<b>Sibling</b>	1.55 (1.03-2.32) <sup>d</sup>	1.17 (0.78-1.77)	1.20 (0.79-1.81)	1.34 (0.74-2.44)	1.01 (0.55-1.85)	0.92 (0.49-1.73)	1.23 (0.85-1.79)	0.95 (0.65-1.39)	0.95 (0.65-1.39)
<b>Parent</b>	1.03 (0.72-1.47)	1.10 (0.77-1.59)	1.06 (0.73-1.53)	1.03 (0.62-1.71)	1.09 (0.65-1.83)	1.02 (0.60-1.73)	1.06 (0.78-1.44)	1.21 (0.88-1.65)	1.16 (0.85-1.59)
<b>Child</b>	1.46 (0.36-5.87)	0.78 (0.19-3.20)	0.77 (0.19-3.17)	2.87(0.70-11.70)	1.57 (0.38-6.55)	1.59 (0.37-6.78)	2.20 (0.82-5.92)	1.21 (0.44-3.28)	1.57 (0.58-4.30)
<b>Spouse</b>	1.84 (1.06-3.19) <sup>d</sup>	1.36 (0.77-2.40)	1.39 (0.79-2.46)	1.54 (0.67-3.55)	1.34 (0.57-3.17)	1.45 (0.61-3.43)	1.20 (0.68-2.10)	0.91 (0.51-1.61)	0.99 (0.55-1.76)
<i>Premature Family History</i>									
<b>Premature</b>	1.06 (0.69-1.63)	1.05 (0.68-1.62)	1.03 (0.67-1.60)	1.56 (0.91-2.67)	1.54 (0.89-2.67)	1.47 (0.84-2.59)	1.17 (0.82-1.67)	1.24 (0.87-1.78)	1.19 (0.83-1.72)
<b>Sibling</b>	0.80 (0.41-1.56)	0.74 (0.37-1.45)	0.76 (0.38-1.49)	1.49 (0.72-3.10)	1.39 (0.67-2.91)	1.24 (0.56-2.72)	1.44 (0.91-2.25)	1.41 (0.89-2.22)	1.46 (0.92-2.30)
<b>Parent</b>	1.11 (0.65-1.89)	1.28 (0.74-2.19)	1.19 (0.69-2.04)	1.55 (0.80-3.01)	1.79 (0.92-3.52)	1.79 (0.91-3.53)	1.02 (0.63-1.63)	1.28 (0.79-2.06)	1.12 (0.69-1.83)
<b>Child</b>	1.60 (0.40-6.45)	0.88 (0.22-3.61)	0.87 (0.21-3.58)	3.15(0.77,12.83)	1.72 (0.41-7.20)	1.77 (0.41-7.58)	2.42 (0.90-6.52)	1.37 (0.50-3.73)	1.87 (0.68-5.14)
<b>Spouse</b>	1.71 (0.87-3.35)	1.45 (0.73-2.88)	1.42 (0.71-2.81)	0.73 (0.18-2.96)	0.71 (0.17-2.94)	0.76 (0.18-3.16)	0.94 (0.44-1.99)	0.86 (0.40-1.84)	0.99 (0.55-1.76)
<b>Familial Risk</b>									
<b>Weak</b>	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
<b>Moderate</b>	1.15 (0.74-1.80)	1.14 (0.73-1.79)	1.09 (0.69-1.73)	0.67 (0.32-1.42)	0.62 (0.29-1.32)	0.64 (0.30-1.37)	1.07 (0.72-1.56)	1.06 (0.71-1.57)	1.06 (0.71-1.58)
<b>Strong</b>	1.35 (0.92-1.98)	1.26 (0.86-1.87)	1.25 (0.85-1.87)	1.27 (0.74-2.15)	1.16 (0.68-1.99)	1.08 (0.62-1.88)	1.20 (0.86-1.68)	1.19 (0.85-1.68)	1.13 (0.80-1.59)

<sup>a</sup> ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, CHF = Congestive Heart Failure, FH = family history, PAD = peripheral artery disease.

<sup>b</sup> Model 1: Adjusted for age, sex, race/ethnicity, education, and MESA site.

<sup>c</sup> Model 2: Adjusted for Model 1 covariates + body mass index, diabetes mellitus, cigarette smoking status, systolic blood pressure, LDL-C, HDL-C, lipid-lowering therapy, and anti-hypertensive medication use.

<sup>d</sup> Indicates statistically significant results.

**Supplementary Table 4:** Hazard ratios (95% confidence interval) for the association of the number of relatives with any-FH or premature-FH and composite ASCVD events <sup>a</sup>

Relatives (n)	Relatives in each category (n)	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>
<b>Any FH</b>				
0	3981	1 (ref)	1 (ref)	1 (ref)
1	1626	1.30 (1.11,1.53) <sup>d</sup>	1.32 (1.12,1.56) <sup>d</sup>	1.25 (1.06,1.48) <sup>d</sup>
2-8	593	1.54 (1.24,1.93) <sup>d</sup>	1.37 (1.09,1.72) <sup>d</sup>	1.34 (1.07,1.68) <sup>d</sup>
<i>P for trend</i>	–	<.001	<.001	.002
<b>Premature FH</b>				
0	5209	1 (ref)	1 (ref)	1 (ref)
1	836	1.20 (0.98,1.47)	1.25 (1.02,1.53) <sup>d</sup>	1.20 (0.98,1.48)
2-6	155	1.63 (1.11,2.37) <sup>d</sup>	1.77 (1.21,2.60) <sup>d</sup>	1.65 (1.13,2.43) <sup>d</sup>
<i>P for trend</i>	–	.004	.001	.003

<sup>a</sup> ASCVD = atherosclerotic cardiovascular disease, FH = family history.

<sup>b</sup> Model 1: Adjusted for age, sex, ethnicity, education, and MESA site.

<sup>c</sup> Model 2: Adjusted for Model 1 covariates + body mass index, diabetes mellitus, cigarette smoking status, systolic blood pressure, LDL-C, HDL-C, lipid-lowering therapy, and anti-hypertensive medication use.

<sup>d</sup> Indicates statistically significant results.

**Supplementary Table 5:** Hazard ratios (95% confidence interval) for the association of parental, sibling, and spousal FH definitions and cardiovascular events <sup>a</sup>

	CHD			Angina			Composite ASCVD		
	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>	Unadjusted	Model 1 <sup>b</sup>	Model 2 <sup>c</sup>
<b>Family History Status</b>									
<b>No FH (ref)</b>	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
<b>Any Family History Status</b>									
<b>Sibling</b>	1.51 (1.10,2.07) <sup>d</sup>	1.18 (0.86,1.63)	1.16 (0.84,1.61)	1.48 (1.08,2.02) <sup>d</sup>	1.31 (0.95,1.81)	1.25 (0.90,1.72)	1.46 (1.21,1.76) <sup>d</sup>	1.16 (0.96,1.40)	1.12 (0.93,1.36)
<b>Parent</b>	1.18 (0.90,1.54)	1.35 (1.02,1.78) <sup>d</sup>	1.35 (1.02,1.78) <sup>d</sup>	1.69 (1.32,2.18) <sup>d</sup>	1.88 (1.45,2.43) <sup>d</sup>	1.70 (1.31,2.22) <sup>d</sup>	1.25 (1.07,1.46) <sup>d</sup>	1.36 (1.16,1.60) <sup>d</sup>	1.30 (1.10,1.52) <sup>d</sup>
<b>Child</b>	2.75 (1.22,6.19) <sup>d</sup>	1.74 (0.77,3.96)	1.96 (0.86,4.47)	3.05 (1.44,6.47) <sup>d</sup>	2.64 (1.23,5.67) <sup>d</sup>	3.31 (1.53,7.15) <sup>d</sup>	2.38 (1.43,3.98) <sup>d</sup>	1.57 (0.93,2.63)	1.82 (1.08,3.06) <sup>d</sup>
<b>Spouse</b>	1.48 (0.93,2.37)	1.30 (0.80,2.10)	1.25 (0.76,2.04)	1.09 (0.65,1.84)	1.11 (0.65,1.89)	1.14 (0.66,1.94)	1.30 (0.97,1.73)	1.12 (0.83,1.50)	1.13 (0.84,1.52)
<b>Premature Family History Status</b>									
<b>Sibling</b>	1.34 (0.88,2.04)	1.30 (0.85,1.98)	1.31 (0.86,2.01)	1.47 (0.98,2.18)	1.51 (1.01,2.26) <sup>d</sup>	1.50 (1.00,2.24) <sup>d</sup>	1.31 (1.02,1.68)	1.27 (0.98,1.63)	1.24 (0.96,1.59)
<b>Parent</b>	1.11 (0.73,1.68)	1.37 (0.90,2.08)	1.32 (0.87,2.00)	1.43 (0.99,2.08)	1.70 (1.17,2.47) <sup>d</sup>	1.53 (1.04,2.24) <sup>d</sup>	1.21 (0.96,1.53) <sup>d</sup>	1.44 (1.14,1.83) <sup>d</sup>	1.34 (1.06,1.71) <sup>d</sup>
<b>Child</b>	3.04 (1.35,6.83) <sup>d</sup>	1.95 (0.86,4.44)	2.25 (0.98,5.15)	3.36 (1.59,7.13) <sup>d</sup>	2.91 (1.35,6.26) <sup>d</sup>	3.70 (1.71,8.01) <sup>d</sup>	2.65 (1.59,4.42) <sup>d</sup>	1.79 (1.06,2.99) <sup>d</sup>	2.10 (1.25,3.53) <sup>d</sup>
<b>Spouse</b>	1.24 (0.68,2.26)	1.29 (0.70,2.37)	1.16 (0.61,2.21)	1.07 (0.57,2.02)	1.23 (0.65,2.33)	1.27 (0.67,2.41)	1.13 (0.78,1.62)	1.12 (0.78,1.63)	1.10 (0.76,1.61)

<sup>a</sup> ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, FH = family history.

<sup>b</sup> Model 1: Adjusted for age, sex, ethnicity, education, and MESA site.

<sup>c</sup> Model 2: Adjusted for Model 1 covariates + body mass index, diabetes mellitus, cigarette smoking status, systolic blood pressure, LDL-C, HDL-C, lipid-lowering therapy, and anti-hypertensive medication use.

<sup>d</sup> Indicates statistically significant results.

**Supplementary Table 6:** Net reclassification improvement (95% confidence interval) analysis for incident cardiovascular events with addition of FRS to model adjusted for FH status in the entire study population and those at intermediate risk by the FRS <sup>a</sup>

FH Variable	CHD			Composite ASCVD		
	Total Population					
	NRI	Reclassified as higher risk	Reclassified as lower risk	NRI (95% CI)	Reclassified as higher risk	Reclassified as lower risk
<b>FH Any + FRS</b>	0.656 (0.541,0.757) <sup>b</sup>			0.614 (0.529,0.692) <sup>b</sup>		
No. of events		11/250	6/250		63/738	63/738
No. with no events		72/5914	56/5914		447/5431	341/5431
<b>FH Premature + FRS</b>	0.652 (0.539,0.763) <sup>b</sup>			0.607 (0.539,0.689) <sup>b</sup>		
No. of events		8/250	5/250		42/738	37/738
No. with no events		37/5914	26/5914		253/5431	226/5431
<b>FH Risk Strata + FRS</b>	0.660 (0.529,0.763) <sup>b</sup>			0.615 (0.540,0.685) <sup>b</sup>		
No. of events		10/250	5/250		67/738	59/738
No. with no events		55/5906	55/5906		430/5423	318/5423
Population at Intermediate Risk by FRS						
	NRI (95% CI)	Reclassified as higher risk	Reclassified as lower risk	NRI (95% CI)	Reclassified as higher risk	Reclassified as lower risk
<b>FH Any + FRS</b>	0.437 (0.285,0.649) <sup>b</sup>			0.361 (0.250,0.462) <sup>b</sup>		
No. of events		15/134	12/134		30/396	28/396
No. with no events		179/3062	125/3062		246/2804	375/2804
<b>FH Premature + FRS</b>	0.468 (0.267,0.639) <sup>b</sup>			0.339 (0.255,0.466) <sup>b</sup>		
No. of events		6/134	4/134		10/396	7/396
No. with no events		75/3062	54/3062		78/2804	92/2804
<b>FH Risk Strata + FRS</b>	0.435 (0.273,0.643) <sup>b</sup>			0.359 (0.259,0.462) <sup>b</sup>		
No. of events		7/134	7/134		27/396	23/396
No. with no events		132/3059	88/3059		199/2804	321/2804

<sup>a</sup> ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, CI = confidence interval, FH = family history, FRS = Framingham risk score, NRI = net reclassification index.

<sup>b</sup> Indicates statistically significant results.