

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med* 2016;375:2349-58. DOI: [10.1056/NEJMoa1605086](https://doi.org/10.1056/NEJMoa1605086)

## Supplementary Appendix

### Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

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## Table of Contents:

<b>Page 3</b>	Acknowledgement of Sources of Funding for Study Cohorts
<b>Page 4</b>	<b>Table S1.</b> Components of the Genetic Risk Score by Study
<b>Page 6</b>	<b>Table S2.</b> Example of Genetic Risk Score Calculation
<b>Page 7</b>	<b>Table S3.</b> Healthy Lifestyle Factor Criteria by Study Population
<b>Page 8</b>	<b>Table S4.</b> Number of Each Component of the Composite Coronary Endpoint within the Prospective Cohorts.
<b>Page 9</b>	<b>Table S5.</b> Risk of Coronary Events According to Genetic Risk Score Quintiles
<b>Page 10</b>	<b>Table S6.</b> Baseline Characteristics by Genetic Risk Category, ARIC
<b>Page 11</b>	<b>Table S7.</b> Baseline Characteristics by Genetic Risk Category, WGHS
<b>Page 12</b>	<b>Table S8.</b> Baseline Characteristics by Genetic Risk Category, MDCS
<b>Page 13</b>	<b>Table S9.</b> ACC/AHA 2013 Atherosclerotic Cardiovascular Disease Risk Score According to Genetic Risk Categories.
<b>Page 14</b>	<b>Table S10.</b> Association of Healthy Lifestyle Factors with Incident Coronary Events
<b>Page 15</b>	<b>Table S11.</b> Risk of Coronary Events According to Number of Healthy Lifestyle Factors
<b>Page 16</b>	<b>Table S12.</b> Baseline Characteristics by Lifestyle Risk Category, ARIC
<b>Page 17</b>	<b>Table S13.</b> Baseline Characteristics by Lifestyle Risk Category, WGHS
<b>Page 18</b>	<b>Table S14.</b> Baseline Characteristics by Lifestyle Risk Category, MDCS
<b>Page 19</b>	<b>Table S15.</b> Risk of Coronary Events According to Genetic and Lifestyle Categories Adjusted for Traditional Risk Factors
<b>Page 20</b>	<b>Table S16.</b> Baseline Characteristics by Genetic Risk Category, BioImage
<b>Page 21</b>	<b>Table S17.</b> Baseline Characteristics by Lifestyle Risk Category, BioImage
<b>Page 22</b>	<b>Figure S1.</b> Distribution of Lifestyle and Genetic Risk by Cohort
<b>Page 23</b>	<b>Figure S2:</b> Distribution of Genetic Risk Score by Cohort
<b>Page 24</b>	<b>Figure S3:</b> Unadjusted Cumulative Hazard Plots by Genetic and Lifestyle Risk Category
<b>Page 25</b>	<b>Figure S4.</b> Sensitivity Analysis: Risk of Myocardial Infarction or Death from Coronary Causes According to Genetic and Lifestyle Category in Prospective Cohorts
<b>Page 26</b>	<b>Figure S5.</b> Sensitivity Analysis: Risk of Coronary Events According to Genetic and Lifestyle Category Adjusted for Traditional Risk Factors.
<b>Page 27</b>	<b>Figure S6:</b> Risk of Coronary Events According to Genetic and Lifestyle Category Among Black Participants

## **Acknowledgement of Sources of Funding for Study Cohorts**

The **Atherosclerosis Risk in Communities** study is carried out as a collaborative study supported by the National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions. Funding support for “Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium” was provided by the NIH through the American Recovery and Reinvestment Act of 2009 (ARRA) (5RC2HL102419).

The **Women’s Genome Health Study** is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467) and the National Cancer Institute (CA047988 and UM1CA182913) with funding for genotyping and collaborative scientific inquiry provided by Amgen.

The **Malmö Diet and Cancer Study** was made possible by grants from the Swedish Cancer Society, the Swedish Medical Research Council, the Swedish Dairy Association, and the Albert Påhlsson and Gunnar Nilsson Foundations and the Malmö city council.

The **BioImage Study** received funding as part of the High-Risk Plaque Initiative, a pre-competitive industry collaboration funded by BG Medicine, Abbott Vascular, AstraZeneca, Merck & Co., Philips, and Takeda with funding for genotyping provided by an investigator-initiated grant from Merck & Co. (to Drs. Kathiresan and Rader).

**Table S1.** Components of the Genetic Risk Score by Study

For single nucleotide polymorphisms (SNPs) not available by direct genotyping, a proxy ( $r^2$ ) is displayed. If no adequate ( $r^2 > 0.8$ ) proxy was available, N/A is displayed. The risk allele refers to the positive strand genotype for the Women's Genome Health Study (WGHS)/BioImage studies and Malmö Diet and Cancer Study (MDCS) for SNPs unavailable in these cohorts. Participants missing more than two SNPs were excluded from analysis; for the remainder, missing values were imputed to the population mean. Genotyping was performed using the Affymetrix 6.0 array (Affymetrix, Santa Clara, California) for the Atherosclerosis Risk in Communities (ARIC) study, the Illumina HumanExome BeadChip v1.0 (Illumina, San Diego, California) in WGHS, a previously reported multiplex method in MDCS,<sup>1</sup> and the Illumina HumanExome Bead-Chip Array v1.1

Locus	Gene	Lead SNP (Literature)	ARIC Proxy ( $r^2$ )	WGHS Proxy ( $r^2$ )	MDCS Proxy ( $r^2$ )	BioImage Proxy ( $r^2$ )	Risk Allele	Risk Estimate (published)	Reference
1p13.3	SORT1	rs599839	rs629301 (0.90)		rs646776 (0.91)		A	1.11	Cardiogram Consortium (2011)
1p32.2	PPAP2B	rs17114036	rs6588635 (0.83)				T	1.11	CARDIoGRAMplusC4D Consortium (2013)
1p32.3	PCSK9	rs11206510					A	1.08	Cardiogram Consortium (2011)
1q21.3	IL6R	rs4845625	rs6694817 (0.81)				A	1.04	CARDIoGRAMplusC4D Consortium (2013)
1q41	MIA3	rs17465637					G	1.14	Cardiogram Consortium (2011)
2p11.2	GGCX/VAMP8	rs1561198	rs2028900 (0.93)		rs2028900 (0.95)		T	1.05	CARDIoGRAMplusC4D Consortium (2013)
2p21	ABCG8	rs6544713	N/A		rs4299376 (1.0)		T	1.06	CARDIoGRAMplusC4D Consortium (2013)
2p24.1	APOB	rs515135	rs12714264 (0.80)				C	1.08	CARDIoGRAMplusC4D Consortium (2013)
2q22.3	ZEB2-AC074093.1	rs2252641					G	1.04	CARDIoGRAMplusC4D Consortium (2013)
2q33.1	WDR12	rs6725887		rs2351524 (0.95)		rs2351524 (0.95)	T	1.12	CARDIoGRAMplusC4D Consortium (2013)
3q22.3	MRAS	rs9818870					T	1.07	CARDIoGRAMplusC4D Consortium (2013)
4q31.22	EDNRA	rs1878406	rs6841581 (0.94)	N/A		N/A	T	1.06	CARDIoGRAMplusC4D Consortium (2013)
4q32.1	GUCY1A3	rs7692387	rs3796587 (1.00)				G	1.06	CARDIoGRAMplusC4D Consortium (2013)
5q31.1	SLC22A4/SLC22A5	rs273909	N/A				C	1.09	CARDIoGRAMplusC4D Consortium (2013)
6p21.2	KCNK5	rs10947789	rs6918122 (0.90)				T	1.06	CARDIoGRAMplusC4D Consortium (2013)
6p21.31	ANKS1A	rs17609940		rs12205331 (0.85)		rs12205331 (0.85)	G	1.07	Cardiogram Consortium (2011)
6p24.1	PHACTR1	rs12526453	N/A	rs9369640 (0.90)		rs9369640 (0.90)	A	1.1	Cardiogram Consortium (2011)
6q23.2	TCF21	rs12190287		N/A		N/A	C	1.07	CARDIoGRAMplusC4D Consortium (2013)
6q25.3	SLC22A3/LPAL2/LPA	rs2048327					C	1.06	CARDIoGRAMplusC4D Consortium (2013)
6q25.3	LPA	rs3798220	N/A				C	1.51	Cardiogram Consortium (2011)
6q25.3	LPA	rs10455872	N/A	N/A		N/A	C	1.45	IBC 50K CAD Consortium (2011)
6q26	PLG	rs4252120					T	1.06	CARDIoGRAMplusC4D Consortium (2013)
7p21.1	HDAC9	rs2023938	rs10245779 (0.85)		rs11984041 (0.86)		C	1.07	CARDIoGRAMplusC4D Consortium (2013)

7q22.3	BCAP29	rs10953541	rs7785962 (1.00)				C	1.08	Coronary Artery Disease (C4D) Genetics Consortium (2011)
7q32.2	ZC3HC1	rs11556924					C	1.09	CARDIoGRAMplusC4D Consortium (2013)
8q24.13	TRIB1	rs2954029	rs2980875 (1.00)				A	1.04	CARDIoGRAMplusC4D Consortium (2013)
9p21.3	CDKN2BAS	rs3217992					T	1.16	CARDIoGRAMplusC4D Consortium (2013)
9p21.3	CDKN2A	rs4977574					G	1.29	Cardiogram Consortium (2011)
9q34.2	ABO	rs579459	rs651007 (1.00)				G	1.07	CARDIoGRAMplusC4D Consortium (2013)
10p11.23	KIAA1462	rs2505083			rs2487928 (0.88)		C	1.06	CARDIoGRAMplusC4D Consortium (2013)
10q11.21	CXCL12	rs2047009		N/A		N/A	G	1.05	CARDIoGRAMplusC4D Consortium (2013)
10q11.21	CXCL12	rs501120			rs1746048 (1.0)		A	1.07	CARDIoGRAMplusC4D Consortium (2013)
10q23.31	LIPA	rs2246833		rs2246942 (1.0)	rs1412444 (0.98)	rs2246942 (1.0)	C	1.06	CARDIoGRAMplusC4D Consortium (2013)
10q24.32	CYP17A1	rs12413409					C	1.12	Cardiogram Consortium (2011)
11q22.3	PDGFD	rs974819	rs2128739 (0.89)		rs11226029 (1.0)		T	1.07	CARDIoGRAMplusC4D Consortium (2013)
11q23.3	APOA5	rs964184					G	1.13	Cardiogram Consortium (2011)
12q24.1	HNF1A	rs2259816					T	1.08	Erdmann et al. (2009)
12q24.12	SH2B3	rs3184504	N/A				T	1.07	CARDIoGRAMplusC4D Consortium (2013)
13q12.3	FLT1	rs9319428	N/A				A	1.05	CARDIoGRAMplusC4D Consortium (2013)
13q34	COL4A1	rs4773144					C	1.07	CARDIoGRAMplusC4D Consortium (2013)
13q34	COL4A1/COL4A2	rs9515203		N/A		N/A	T	1.08	CARDIoGRAMplusC4D Consortium (2013)
14q32.2	HHIPL1	rs2895811	N/A				C	1.06	CARDIoGRAMplusC4D Consortium (2013)
15q25.1	ADAMTS7	rs3825807	rs1994016 (0.87)	N/A			T	1.08	Cardiogram Consortium (2011)
15q25.1	ADAMTS7	rs7173743	rs7168915 (0.93)				T	1.07	CARDIoGRAMplusC4D Consortium (2013)
15q26.1	FURIN/FES	rs17514846	rs1894401 (0.90)				T	1.05	CARDIoGRAMplusC4D Consortium (2013)
17p11.2	RASD1	rs12936587	rs12449964 (0.94)				G	1.06	CARDIoGRAMplusC4D Consortium (2013)
17p13.3	SMG6	rs216172	rs7217226 (1.00)				C	1.07	Cardiogram Consortium (2011)
17q21.32	UBE2Z	rs46522	rs15563 (0.94)		rs318090 (1.0)		T	1.06	Cardiogram Consortium (2011)
19p13.2	LDLR	rs1122608					C	1.1	CARDIoGRAMplusC4D Consortium (2013)
21q22.11	KCNE2	rs9982601	rs9305545 (0.87)				A	1.13	CARDIoGRAMplusC4D Consortium (2013)

## Reference

1. Tada H, Melander O, Louie JZ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. Eur Heart J. 2016;37(6):561-7.

**Table S2.** Example of Genetic Risk Score Calculation

The number of coronary artery disease risk alleles was multiplied by a weighted risk estimate (natural logarithm of the published odds ratio) for each genetic variant. For example, the 2011 CARDIoGRAM Consortium analysis noted that the 'A' allele of rs599839 at the *SORT1* locus was associated with an odds ratio of 1.11 for coronary artery disease. The weight of this variant is expressed as the natural logarithm of 1.11 (0.104) in calculated the genetic risk score. The WGHS participant represented here harbored the risk allele on one of her two chromosomes. The contribution of this variant to her risk score is thus  $1 * 0.104 = 0.104$ . These values were summed across all variants. This WGHS study participant harbored 48 of a possible 88 risk alleles, corresponding to a genetic risk score of 4.187 (90<sup>th</sup> percentile of the cohort).

Locus	Gene Locus	Lead SNP (Literature)	WGHS Proxy	Ln(Published Odds Ratio)	# of Risk Alleles	# of Risk Alleles * Ln(OR)
1p13.3	SORT1	rs599839		0.104	1	0.104
1p32.2	PPAP2B	rs17114036		0.104	2	0.209
1p32.3	PCSK9	rs11206510		0.077	2	0.154
1q21.3	IL6R	rs4845625		0.039	2	0.078
1q41	MIA3	rs17465637		0.131	2	0.262
2p11.2	GGCX/VAMP8	rs1561198		0.049	0	0
2p21	ABCG8	rs6544713		0.058	0	0
2p24.1	APOB	rs515135		0.077	1	0.077
2q22.3	ZEB2-AC074093.1	rs2252641		0.039	2	0.078
2q33.1	WDR12	rs6725887	rs2351524 (0.95)	0.113	2	0.227
3q22.3	MRAS	rs9818870		0.068	1	0.068
4q32.1	GUCY1A3	rs7692387		0.058	2	0.117
5q31.1	SLC22A4/SLC22A5	rs273909		0.086	0	0
6p21.2	KCNK5	rs10947789		0.058	2	0.117
6p21.31	ANKS1A	rs17609940	rs12205331 (0.85)	0.068	1	0.068
6p24.1	PHACTR1	rs12526453	rs9369640 (0.90)	0.095	0	0
6q25.3	SLC22A3/LPAL2/LPA	rs2048327		0.058	1	0.058
6q25.3	LPA	rs3798220		0.412	0	0
6q26	PLG	rs4252120		0.058	2	0.117
7p21.1	HDAC9	rs2023938		0.068	0	0
7q22.3	BCAP29	rs10953541		0.077	1	0.077
7q32.2	ZC3HC1	rs11556924		0.086	1	0.086
8q24.13	TRIB1	rs2954029		0.039	1	0.039
9p21.3	CDKN2BAS	rs3217992		0.148	2	0.297
9p21.3	CDKN2A	rs4977574		0.255	2	0.509
9q34.2	ABO	rs579459		0.068	0	0
10p11.23	KIAA1462	rs2505083		0.058	0	0
10q11.21	CXCL12	rs501120		0.068	1	0.068
10q23.31	LIPA	rs2246833	rs2246942 (1.0)	0.058	0	0
10q24.32	CYP17A1	rs12413409		0.113	2	0.227
11q22.3	PDGFD	rs974819		0.068	2	0.135
11q23.3	APOA5	rs964184		0.122	2	0.244
12q24.1	HNF1A	rs2259816		0.077	1	0.077
12q24.12	SH2B3	rs3184504		0.068	1	0.068
13q12.3	FLT1	rs9319428		0.049	0	0
13q34	COL4A1	rs4773144		0.068	0	0
14q32.2	HHIPL1	rs2895811		0.058	0	0
15q25.1	ADAMTS7	rs7173743		0.068	2	0.135
15q26.1	FURIN/FES	rs17514846		0.049	1	0.049
17p11.2	RASD1	rs12936587		0.058	1	0.058
17p13.3	SMG6	rs216172		0.068	2	0.135
17q21.32	UBE2Z	rs46522		0.058	1	0.058
19p13.2	LDLR	rs1122608		0.095	2	0.191
21q22.11	KCNE2	rs9982601		0.122	0	0
				<b>Total:</b>	<b>48</b>	<b>4.187</b>

**Table S3.** Healthy Lifestyle Factor Criteria by Study Population

	<b>Atherosclerosis Risk in Communities</b>	<b>Women’s Genome Health Study</b>	<b>Malmö Diet and Cancer Study</b>	<b>Biolmage Study</b>
<b>Absence of Current Smoking</b>	Baseline survey self-report	Baseline survey self-report	Baseline survey self-report	Baseline survey self-report
<b>Absence of Obesity</b>	BMI < 30 kg/m <sup>2</sup> at baseline examination	BMI < 30 kg/m <sup>2</sup> via self-reported height and weight	BMI < 30 kg/m <sup>2</sup> at baseline examination	BMI < 30 kg/m <sup>2</sup> via self-reported height and weight
<b>Regular Physical Activity</b>	Self-reported physical activity ≥ once/week	Self-reported strenuous physical activity ≥ once/week	Self-reported strenuous physical activity ≥ once/week	Self-reported moderate physical activity ≥ 5 times/week or vigorous activity ≥ once/week
<b>Healthy Diet</b>	At least 5 of the following 10 characteristics, as assessed by food frequency questionnaire: 1. Fruits: ≥ 3 servings/day 2. Nuts: ≥ 1 serving/week 3. Vegetables: ≥ 3 servings/day 4. Whole grains: ≥ 3 servings/day 5. Fish: ≥ 2 servings/week; 6. Dairy: ≥ 2.5 servings/day 7. Refined grains: ≤ 1.5 servings/day 8. Processed meats: ≤ 1 serving/week 9. Unprocessed red meats ≤ 1.5 servings/week 10. Sugar-sweetened beverages: ≤ 1 serving/week	At least 6 of the following 12 characteristics, as assessed by food frequency questionnaire: 1. Fruits: ≥ 3 servings/day 2. Nuts: ≥ 1 serving/week 3. Vegetables: ≥ 3 servings/day 4. Whole grains: ≥ 3 servings/day 5. Fish: ≥ 2 servings/week; 6. Dairy: ≥ 2.5 servings/day 7. Refined grains: ≤ 1.5 servings/day 8. Processed meats: ≤ 1 serving/week 9. Unprocessed red meats ≤ 1.5 servings/week 10. Trans fat: ≤ cohort median 11. Sugar-sweetened beverages: ≤ 1 serving/week 12. Sodium: ≤ 2000 mg	At least 5 of the following 10 characteristics, as assessed by food frequency questionnaire, diet record, and structured interview: 1. Fruits: ≥ 3 servings/day 2. Nuts: ≥ 1 serving/week 3. Vegetables: ≥ 3 servings/day 4. Whole grains: ≥ 3 servings/day 5. Fish: ≥ 2 servings/week; 6. Dairy: ≥ 2.5 servings/day 7. Refined grains: ≤ 1.5 servings/day 8. Processed meats: ≤ 1 serving/week 9. Unprocessed red meats ≤ 1.5 servings/week 10. Sugar-sweetened beverages: ≤ 1 serving/week	At least 2 of the following three characteristics, assessed by baseline survey: 1. Fruits: ≥ 3 servings/day 2. Vegetables: ≥ 5 times/week 3. Fish: ≥ 3 times/week



**Table S4.** Number of Each Component of the Composite Coronary Endpoint within the Prospective Cohorts.

	<b>Atherosclerosis Risk in Communities</b>	<b>Women's Genome Health Study</b>	<b>Malmö Diet and Cancer Study</b>
<b>Composite Coronary Endpoint</b>	1,230	971	2,902
<b>Myocardial Infarction</b>	602	368	1,444
<b>Coronary Revascularization</b>	568	589	1,226
<b>Death From Coronary Causes</b>	60	14	232

**Table S5.** Risk of Coronary Events According to Genetic Risk Score Quintiles

	<b>Atherosclerosis Risk in Communities</b>	<b>Women's Genome Health Study</b>	<b>Malmö Diet and Cancer Study</b>	<b>Combined</b>
<b>Genetic Risk Category</b>				
<b>Quintile 1</b>	Reference	Reference	Reference	Reference
<b>Quintile 2</b>	1.16 (0.96 – 1.40)	1.20 (0.83 – 0.96)	1.26 (1.11 – 1.43)	1.22 (1.11 – 1.34)
<b>Quintile 3</b>	1.26 (1.04 – 1.52)	1.40 (1.13 – 1.74)	1.28 (1.13 – 1.45)	1.30 (1.18 – 1.42)
<b>Quintile 4</b>	1.41 (1.17 – 1.69)	1.53 (1.23 – 1.89)	1.53 (1.35 – 1.73)	1.50 (1.36 – 1.64)
<b>Quintile 5</b>	1.75 (1.46 – 2.10)	1.94 (1.58 – 2.39)	1.98 (1.76 – 2.23)	1.91 (1.75 – 2.09)
<b>P-Trend</b>	$8.1 \times 10^{-11}$	$7.4 \times 10^{-12}$	$3.2 \times 10^{-33}$	

Cox regression models were adjusted for age, gender (in ARIC and MDCS), randomization to Vitamin E or aspirin (in WGHS), education level, and principal components of ancestry (in ARIC and WGHS). Cohort-specific findings were combined using random effects meta-analysis. Those in the lowest quintile of genetic risk serve as the reference group. Values displayed represent hazard ratios and 95% confidence intervals.

**Table S6.** Baseline Characteristics by Genetic Risk Category, ARIC

	<b>Low Risk N = 1,563</b>	<b>Intermediate Risk N = 4,688</b>	<b>High Risk N = 1,563</b>	<b>P-value</b>
<b>Age, years</b>	54 (5.7)	54 (5.6)	54 (5.7)	0.09
<b>Male Gender</b>	739 (47%)	2,105 (45%)	711 (45%)	0.26
<b>History of Hypertension</b>	405 (26%)	1,218 (26%)	397 (25%)	0.88
<b>History of Diabetes Mellitus</b>	140 (9%)	349 (7%)	143 (9%)	0.04
<b>Family History of Premature CAD</b>	143 (11%)	439 (11%)	169 (13%)	0.14
<b>Body-mass Index, kg/m<sup>2</sup></b>	27 (5.0)	27 (4.8)	27 (4.8)	0.21
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	134 (37)	137 (38)	139 (37)	<0.001
<b>HDL Cholesterol, mg/dl</b>	38 (11)	37 (11)	37 (10)	0.07
<b>Triglycerides, mg/dl</b>	112 (80 – 159)	113 (81 – 162)	117 (82 – 165)	0.11
<b>Lipid-lowering Medication</b>	6 (0.4%)	26 (0.6%)	13 (0.8%)	0.24
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	1,156 (74%)	3,554 (76%)	1,163 (74%)	0.25
<b>Nonobese</b>	1,198 (77%)	3,665 (78%)	1,230 (79%)	0.33
<b>Regular Physical Activity</b>	547 (35%)	1,659 (35%)	537 (34%)	0.76
<b>Healthy Diet</b>	303 (19%)	901 (19%)	311 (20%)	0.84
<b>Lifestyle Risk Category</b>				
<b>3-4 Healthy Lifestyle Factors</b>	484 (31%)	1,480 (32%)	495 (32%)	
<b>2 Healthy Lifestyle Factors</b>	613 (39%)	1,926 (41%)	623 (40%)	0.41
<b>0-1 Healthy Lifestyle Factors</b>	466 (30%)	1,282 (27%)	445 (28%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of premature coronary artery disease refers to self-reported parental history of myocardial infarction prior to age 60 years.

**Table S7.** Baseline Characteristics by Genetic Risk Category, WGHS

	<b>Low Risk N = 4,280</b>	<b>Intermediate Risk N = 12,716</b>	<b>High Risk N = 4,226</b>	<b>P-value</b>
<b>Age, years</b>	54.2 (7.2)	54.2 (7.1)	54.1 (6.9)	0.25
<b>History of Hypertension</b>	1,038 (24%)	3,080 (24)	1,046 (25%)	0.78
<b>History of Diabetes Mellitus</b>	105 (3%)	313 (3%)	101 (2%)	0.97
<b>FH of Premature CAD</b>	420 (11%)	1,472 (13%)	584 (16%)	< 0.001
<b>Body-mass Index, kg/m<sup>2</sup></b>	25.9 (4.8)	25.9 (5)	25.9 (5)	0.83
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	121 (34)	124 (34)	126 (34)	< 0.001
<b>HDL Cholesterol, mg/dl</b>	54 (15)	54 (15)	54 (15)	0.45
<b>Triglycerides, mg/dl</b>	118 (84 – 172)	120 (84 – 176)	119 (84 – 177)	0.85
<b>Lipid-lowering Medication</b>	129 (3%)	406 (3%)	155 (3.7%)	0.21
<b>C-Reactive Protein</b>	2.0 (0.8 – 4.4)	2.0 (0.8 – 4.4)	1.9 (0.8 – 4.3)	0.37
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	3,751 (88%)	11,298 (89%)	3,735 (88%)	0.10
<b>Nonobese</b>	3,551 (83%)	10,535 (83%)	3,480 (82%)	0.70
<b>Regular Physical Activity</b>	1,872 (44%)	5,556 (44%)	1,828 (43%)	0.87
<b>Healthy Diet</b>	1,460 (34%)	4,328 (34%)	1,463 (35%)	0.78
<b>Lifestyle Risk Category</b>				
<b>3-4 Healthy Lifestyle Factors</b>	2,103 (49%)	6,319 (50%)	2,094 (50%)	
<b>2 Healthy Lifestyle Factors</b>	1,509 (35%)	4,414 (35%)	1,462 (35%)	0.95
<b>0-1 Healthy Lifestyle Factors</b>	668 (16%)	1,983 (16%)	670 (16%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG and CRP modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of premature coronary artery disease refers to self-reported parental history of myocardial infarction prior to age 60 years.

**Table S8.** Baseline Characteristics by Genetic Risk Category, MDCS

	<b>Low Risk N = 4,478</b>	<b>Intermediate Risk N = 13,434</b>	<b>High Risk N = 4,477</b>	<b>P-value</b>
<b>Age, years</b>	58.2 (7.8)	58.0 (7.7)	57.8 (7.7)	0.11
<b>Male gender</b>	1,733 (39%)	5,061 (38%)	1,721 (38%)	0.39
<b>History of Hypertension</b>	2,732 (61%)	8,018(60%)	2,803 (63%)	0.002*
<b>History of Diabetes Mellitus</b>	175 (4%)	557 (4%)	172 (4%)	0.59
<b>FH of CAD</b>	1,267 (28%)	4,352 (32%)	1,606 (36%)	<0.0001
<b>Body-mass Index, kg/m<sup>2</sup></b>	25.7 (3.9)	25.7 (3.9)	25.7 (4.0)	0.70
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	157 (38)	161 (38)	167 (39)	<0.0001
<b>HDL Cholesterol, mg/dl</b>	54 (15)	54 (15)	53 (15)	0.84
<b>Triglycerides, mg/dl</b>	101 (76 – 143)	102 (75 – 139)	105 (79 – 152)	0.08
<b>Lipid-lowering Medication</b>	79 (2%)	290 (2%)	119 (3%)	0.02
<b>C-Reactive Protein, mg/L</b>	1.4 (0.7-2.8)	1.4 (0.6-2.7)	1.3 (0.6-2.6)	0.17
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	3,214 (72%)	9,703 (72%)	3,245 (72%)	0.75
<b>Nonobese</b>	3,891 (87%)	11,716 (87%)	3,900 (87%)	0.86
<b>Regular Physical Activity</b>	1,861 (42%)	5,470 (41%)	1,762 (39%)	0.10
<b>Healthy Diet</b>	578 (13%)	1,660 (12%)	557 (12%)	0.62
<b>Lifestyle Risk Category</b>				
<b>3-4 Healthy Lifestyle Factors</b>	1,444 (32%)	4,336 (32%)	1,430 (32%)	
<b>2 Healthy Lifestyle Factors</b>	2,060 (46%)	6,145 (46%)	2,029 (45%)	0.82
<b>0-1 Healthy Lifestyle Factors</b>	974 (22%)	2,953 (22%)	1,018 (23%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG and CRP modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of coronary artery disease refers to self-reported parental history of myocardial infarction.

\*P-value for test of linear trend = 0.12.

**Table S9.** ACC/AHA 2013 Atherosclerotic Cardiovascular Disease Risk Score According to Genetic Risk Categories.

	<b>Atherosclerosis Risk in Communities</b>	<b>Women’s Genome Health Study</b>	<b>Malmö Diet and Cancer Study</b>	<b>BiImage Study</b>
<b>Genetic Risk Category</b>				
<b>Low Risk</b>	9.9 (10.8)	3.5 (4.2)	9.8 (8.4)	17.6 (11.7)
<b>Intermediate Risk</b>	9.2 (10.6)	3.6 (4.4)	9.5 (8.0)	18.7 (12.3)
<b>High Risk</b>	9.8 (11.6)	3.5 (4.2)	10.2 (8.6)	17.7 (10.9)
<b>P-Trend</b>	0.62	0.91	0.12	0.91

Ten-year predicted risk according to the ACC/AHA Pooled Cohorts Equation was determined within each category of genetic risk. Individuals reporting baseline use of lipid-lowering therapy were excluded from this analysis. The Malmö Diet and Cancer Study calculations were restricted to individuals with baseline total and HDL cholesterol values available (N = 4,172). Values displayed represent mean (standard deviation).

**Table S10.** Association of Healthy Lifestyle Factors with Incident Coronary Events

Healthy Lifestyle Factor	Atherosclerosis Risk in Communities	Women's Genome Health Study	Malmö Diet and Cancer Study	Combined
<b>No Current Smoking</b>	0.64 (0.57 – 0.73) < 0.001	0.45 (0.38 – 0.53) < 0.001	0.58 (0.53 – 0.62) < 0.001	0.56 (0.47 – 0.66) < 0.001
<b>Non-obese</b>	0.67 (0.59 – 0.76) < 0.001	0.58 (0.50 – 0.68) < 0.001	0.74 (0.67 – 0.81) < 0.001	0.66 (0.58 – 0.76) < 0.001
<b>Regular Physical Activity</b>	0.91 (0.80 – 1.03) 0.12	0.78 (0.69 – 0.89) < 0.001	0.92 (0.86 – 0.99) 0.035	0.88 (0.80 – 0.97) 0.007
<b>Healthy Diet</b>	0.93 (0.79 – 1.08) 0.34	0.83 (0.73 – 0.95) 0.008	0.96 (0.86 – 1.08) 0.54	0.91 (0.83 – 0.99) 0.036

Cox regression models were adjusted for age, gender (in ARIC and MDCS), randomization to Vitamin E or aspirin (in WGHS), education level, and principal components of ancestry (in ARIC and WGHS). Cohort-specific findings were combined using random effects meta-analysis. Hazard ratios, 95% confidence intervals and P-values are displayed within each cell.

**Table S11.** Risk of Coronary Events According to Number of Healthy Lifestyle Factors

	<b>Atherosclerosis Risk in Communities</b>	<b>Women's Genome Health Study</b>	<b>Malmö Diet and Cancer Study</b>	<b>Combined</b>
<b>Lifestyle Risk Category</b>				
<b>4 Healthy Lifestyle Factors</b>	Reference	Reference	Reference	Reference
<b>3 Healthy Lifestyle Factors</b>	1.42 (1.05 – 1.90)	1.07 (0.86 – 1.33)	0.96 (0.78-1.18)	1.11 (0.78 – 1.18)
<b>2 Healthy Lifestyle Factors</b>	1.56 (1.17 – 2.08)	1.39 (1.13 – 1.71)	1.05 (0.86-1.29)	1.29 (1.03 – 1.63)
<b>1 Healthy Lifestyle Factor</b>	2.17 (1.62 – 2.90)	2.17 (1.73 – 2.72)	1.62 (1.32-2.00)	1.93 (1.57 – 2.38)
<b>0 Healthy Lifestyle Factors</b>	3.30 (2.25 – 4.82)	5.32 (3.66 – 7.72)	3.00 (2.25-4.00)	3.40 (2.62 – 4.42)
<b>P-Trend</b>	7.6 x 10 <sup>-15</sup>	6.7 x 10 <sup>-21</sup>	3.0 x 10 <sup>-29</sup>	

Cox regression models were adjusted for age, gender (in ARIC and MDCS), randomization to Vitamin E or aspirin (in WGHS), education level, principal components of ancestry (in ARIC and WGHS). Cohort-specific findings were combined using random effects meta-analysis. Those adherent to all four healthy lifestyle factors serve as the reference group. Values displayed represent hazard ratios and 95% confidence intervals.



**Table S12.** Baseline Characteristics by Lifestyle Risk Category, ARIC

	<b>Favorable Lifestyle N = 2,459</b>	<b>Intermediate Lifestyle N = 3,162</b>	<b>Unfavorable Lifestyle N = 2,193</b>	<b>P-value</b>
<b>Age, years</b>	55 (5.8)	54 (5.6)	54 (5.6)	<0.001
<b>Male Sex</b>	1,100 (45%)	1,453 (46%)	1,002 (46%)	0.65
<b>History of Hypertension</b>	548 (22%)	822 (26%)	650 (30%)	<0.001
<b>History of Diabetes Mellitus</b>	148 (6%)	241 (8%)	243 (11%)	<0.001
<b>Family History of Premature CAD</b>	228 (11%)	296 (11%)	227 (12%)	0.23
<b>Body-mass Index, kg/m<sup>2</sup></b>	25.3 (3.2)	26.6 (4.3)	29.3 (6.0)	<0.001
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	134 (37)	136 (37)	140 (38)	<0.001
<b>HDL Cholesterol, mg/dl</b>	39 (11)	37 (11)	34 (10)	<0.001
<b>Triglycerides, mg/dl</b>	102 (73 – 147)	112 (81 – 160)	129 (95 – 177)	<0.001
<b>Lipid-lowering Medication</b>	17 (0.7%)	18 (0.6%)	10 (0.5%)	0.57
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	2,384 (97%)	2,661 (84%)	828 (38%)	<0.001
<b>Non-obese</b>	2,364 (96%)	2,657 (84%)	1,072 (49%)	<0.001
<b>Regular Physical Activity</b>	2,003 (81%)	691 (22%)	49 (2%)	<0.001
<b>Healthy Diet</b>	1,166 (47%)	315 (10%)	34 (2%)	<0.001
<b>Genetic Risk Category</b>				
<b>Low Genetic Risk</b>	484 (20%)	613 (19%)	466 (21%)	
<b>Intermediate Genetic Risk</b>	1,480 (60%)	1,926 (61%)	1,282 (58%)	0.41
<b>High Genetic Risk</b>	495 (20%)	623 (20%)	445 (20%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of premature coronary artery disease refers to self-reported parental history of myocardial infarction prior to age 60 years.

**Table S13.** Baseline Characteristics by Lifestyle Risk Category, WGHS

	<b>Favorable Lifestyle N = 10,516</b>	<b>Intermediate Lifestyle N = 7,385</b>	<b>Unfavorable Lifestyle N = 3,321</b>	<b>P-value</b>
<b>Age, years</b>	54.5 (7.3)	54.1 (7.1)	53.4 (6.5%)	< 0.001
<b>History of Hypertension</b>	2150 (20%)	1,850 (25%)	1,164 (35%)	< 0.001
<b>History of Diabetes Mellitus</b>	178 (2%)	168 (2%)	173 (5%)	< 0.001
<b>FH of Premature CAD</b>	1194 (13%)	852 (13%)	430 (15%)	0.02
<b>Body-mass Index, kg/m<sup>2</sup></b>	24.3 (3.3)	25.9 (4.6)	30.8 (6.4)	< 0.001
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	122 (34)	125 (34)	129 (35)	< 0.001
<b>HDL Cholesterol, mg/dl</b>	57 (15)	53 (15)	47 (13)	< 0.001
<b>Triglycerides, mg/dl</b>	111 (78 – 161)	123 (85 - 178)	147 (102 – 212)	< 0.001
<b>Lipid-lowering Medication</b>	354 (3%)	232 (3%)	104 (3%)	0.63
<b>C-Reactive Protein</b>	1.6 (0.6 – 3.4)	2.1 (0.9 – 4.4)	3.8 (1.8 – 6.8)	< 0.001
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	10,309 (98%)	6,674 (90%)	1,801 (54%)	< 0.001
<b>Nonobese</b>	10,164 (97%)	6,230 (84%)	1,172 (35%)	< 0.001
<b>Regular Physical Activity</b>	8,148 (78%)	1,058 (14%)	50 (2%)	< 0.001
<b>Healthy Diet</b>	6,410 (61%)	808 (11%)	33 (1%)	< 0.001
<b>Genetic Risk Category</b>				
<b>Low Genetic Risk</b>	2,103 (20%)	1,509 (20%)	668 (20%)	
<b>Intermediate Genetic Risk</b>	6,319 (60%)	4,414 (60%)	1,983 (60%)	0.95
<b>High Genetic Risk</b>	2,094 (20%)	1,462 (20%)	670 (20%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG and CRP modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of premature coronary artery disease refers to self-reported parental history of myocardial infarction prior to age 60 years.

**Table S14.** Baseline Characteristics by Lifestyle Risk Category, MDCS

	<b>Favorable Lifestyle N = 7,210</b>	<b>Intermediate Lifestyle N = 10,234</b>	<b>Unfavorable Lifestyle N = 4,945</b>	<b>P-value</b>
<b>Age, years</b>	58.2 (7.7)	58.1 (7.8)	57.4 (7.5)	<0.0001
<b>Male Gender</b>	3,065 (43%)	3,722 (36%)	1,728 (35%)	<0.0001
<b>History of Hypertension</b>	4,212 (58%)	6,149 (60%)	3,192 (65%)	<0.0001
<b>History of Diabetes Mellitus</b>	279 (4%)	371 (4%)	254 (5%)	<0.0001
<b>FH of CAD</b>	2,322 (32%)	3,350(33%)	1,553(31%)	0.26
<b>Body-mass Index, kg/m<sup>2</sup></b>	24.9 (2.9)	25.4 (3.6)	27.4 (5.2)	<0.0001
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	160 (38)	161 (38)	164 (40)	0.06
<b>HDL Cholesterol, mg/dl</b>	55 (15)	54 (15)	50 (13)	<0.0001
<b>Triglycerides, mg/dl</b>	97 (72-134)	102 (76-141)	117 (86-162)	0.0001
<b>Lipid-lowering Medication</b>	147 (2.0%)	227 (2.2%)	114 (2.3%)	0.58
<b>C-Reactive Protein, mg/L</b>	1.1 (0.6-2.2)	1.3 (0.6-2.7)	2.0 (0.9-4.2)	0.0001
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	6,981 (97%)	7,924 (77%)	1,257 (25%)	<0.0001
<b>Nonobese</b>	7,094 (98%)	9,316 (91%)	3,097 (63%)	<0.0001
<b>Regular Physical Activity</b>	6,146 (85%)	2,747 (27%)	200 (4%)	<0.0001
<b>Healthy Diet</b>	2,279 (32%)	481 (5%)	35 (1%)	<0.0001
<b>Genetic Risk Category</b>				
<b>Low Genetic Risk</b>	1,444 (20%)	2,060 (20%)	974 (20%)	
<b>Intermediate Genetic Risk</b>	4,336 (60%)	6,145 (60%)	2,953 (60%)	0.82
<b>High Genetic Risk</b>	1,430 (20%)	2,029 (20%)	1,018 (21%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG and CRP modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of coronary artery disease refers to self-reported parental history of myocardial infarction.

**Table S15.** Risk of Coronary Events According to Genetic and Lifestyle Categories Adjusted for Traditional Risk Factors

	<b>Atherosclerosis Risk in Communities</b>	<b>Women’s Genome Health Study</b>	<b>Malmö Diet and Cancer Study</b>	<b>Combined</b>
<b>Genetic Risk Category</b>				
<b>Low Risk</b>	Reference	Reference	Reference	Reference
<b>Intermediate Risk</b>	1.19 (1.00 – 1.41)	1.25 (1.03 – 1.53)	1.33 (1.20-1.48)	1.28 (1.18 – 1.39)
<b>High Risk</b>	1.70 (1.40 – 2.06)	1.67 (1.35 – 2.08)	1.88 (1.67-2.11)	1.80 (1.64 – 1.97)
<b>P-Trend</b>	$3.4 \times 10^{-8}$	$1.6 \times 10^{-6}$	$6.4 \times 10^{-27}$	
<b>Lifestyle Risk Category</b>				
<b>Favorable</b>	Reference	Reference	Reference	Reference
<b>Intermediate</b>	1.10 (0.94 – 1.28)	1.17 (0.99 – 1.37)	1.04 (0.96-1.14)	1.08 (1.01 – 1.15)
<b>Unfavorable</b>	1.46 (1.24 – 1.72)	1.40 (1.17 – 1.69)	1.52 (1.38-1.68)	1.49 (1.38 – 1.61)
<b>P-Trend</b>	$4.1 \times 10^{-6}$	0.0004	$4.9 \times 10^{-15}$	

Cox regression models were adjusted for age, gender (in ARIC and MDCS), randomization to Vitamin E or aspirin (in WGHS), education level, principal components of ancestry (in ARIC and WGHS), presence of diabetes mellitus, hypertension, family history of coronary artery disease, LDL cholesterol levels (apolipoprotein B in MDCS), and HDL cholesterol levels (apolipoprotein A-I in MDCS). Cohort-specific findings were combined using random effects meta-analysis. Values displayed represent hazard ratios and 95% confidence intervals.

**Table S16.** Baseline Characteristics by Genetic Risk Category, BiImage Study

	<b>Low Risk N = 846</b>	<b>Intermediate Risk N = 2,557</b>	<b>High Risk N = 857</b>	<b>P-value</b>
<b>Age, years</b>	68.9 (6.1)	69.1 (6.1)	69.1 (5.7)	0.69
<b>Male Gender</b>	405 (48%)	1,132 (44%)	341 (40%)	0.003
<b>History of Hypertension</b>	507 (60%)	1,553 (61%)	516 (60%)	0.90
<b>History of Diabetes Mellitus</b>	101 (12%)	329 (13%)	92 (11%)	0.25
<b>Family History of CAD</b>	312 (37%)	1,037 (41%)	368 (43%)	0.11
<b>Body-mass Index, kg/m<sup>2</sup></b>	29.0 (5.4)	28.9 (5.5)	28.3 (5.2)	0.02
<b>Lipid Levels</b>				
<b>LDL Cholesterol, mg/dl</b>	111 (33)	114 (33)	114 (32)	0.08
<b>HDL Cholesterol, mg/dl</b>	57 (16)	56 (16)	56 (15)	0.29
<b>Triglycerides, mg/dl</b>	145 (105 – 210)	150 (108 – 211)	145 (104 – 204)	0.19
<b>Lipid-lowering Medication</b>	264 (31%)	893 (35%)	310 (36%)	0.07
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	767 (91%)	2,333 (91%)	787 (92%)	0.69
<b>Non-obese</b>	518 (61%)	1,629 (64%)	582 (68%)	0.01
<b>Regular Physical Activity</b>	406 (48%)	1,188 (47%)	373 (44%)	0.16
<b>Healthy Diet</b>	109 (13%)	377 (15%)	124 (15%)	0.40
<b>Lifestyle Risk Category</b>				
<b>3-4 Healthy Lifestyle Factors</b>	293 (35%)	955 (37%)	316 (37%)	
<b>2 Healthy Lifestyle Factors</b>	329 (39%)	932 (36%)	337 (39%)	0.30
<b>0-1 Healthy Lifestyle Factors</b>	224 (27%)	670 (26%)	204 (34%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of coronary artery disease refers to self-reported parental history of myocardial infarction.

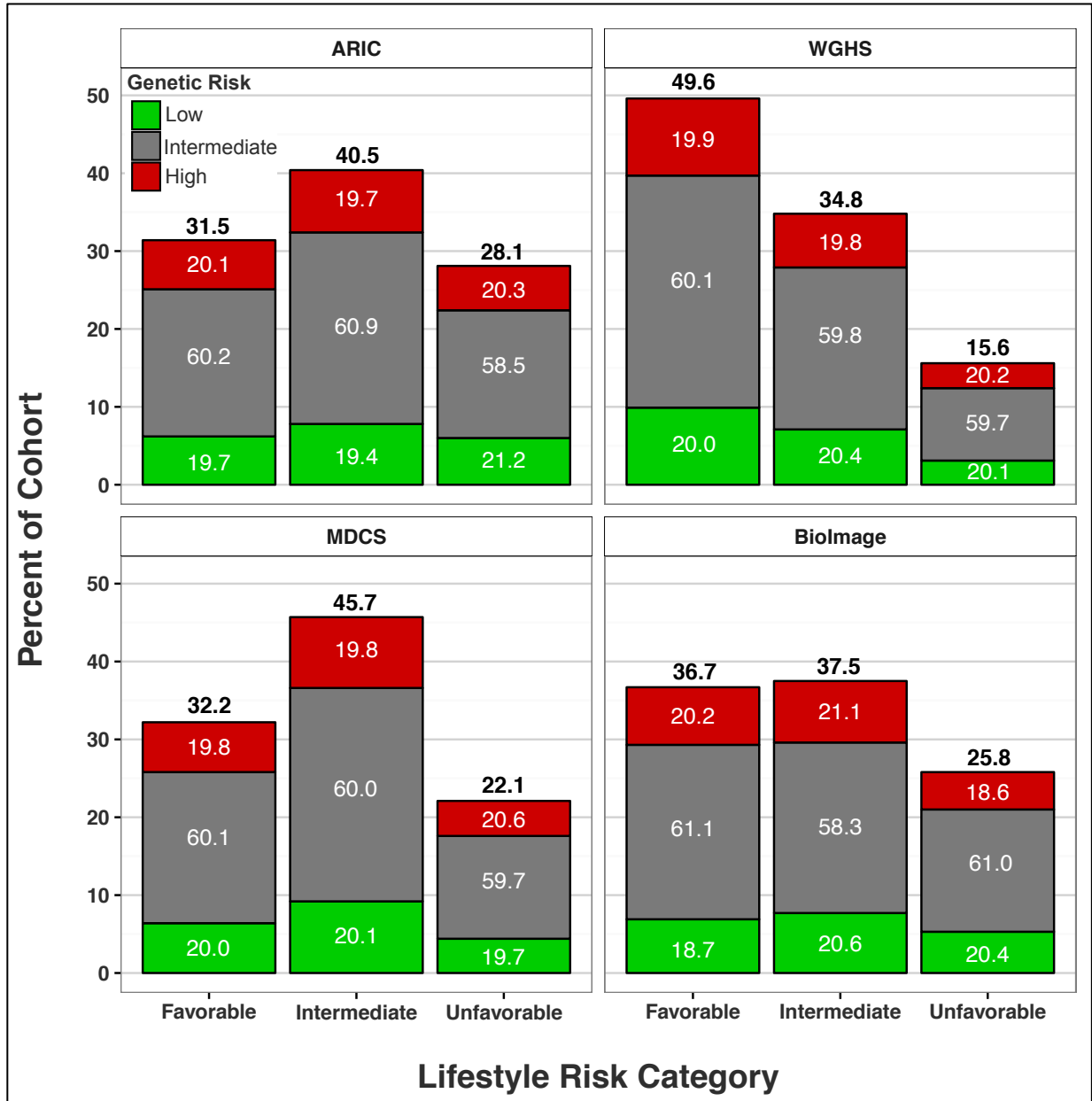
**Table S17.** Baseline Characteristics by Lifestyle Risk Category, Biolmage Study

	<b>Favorable Lifestyle N = 1,564</b>	<b>Intermediate Lifestyle N = 1,598</b>	<b>Unfavorable Lifestyle N = 1,098</b>	<b>P-value</b>
<b>Age, years</b>	69.7 (5.9)	69.2 (6.1)	68.0 (5.9)	< 0.001
<b>Male Gender</b>	683 (44%)	687 (43%)	507 (46%)	0.17
<b>History of Hypertension</b>	870 (56%)	976 (61%)	730 (67%)	< 0.001
<b>History of Diabetes Mellitus</b>	107 (7%)	190 (12%)	225 (21%)	< 0.001
<b>Family History of CAD</b>	608 (39%)	652 (41%)	457 (41%)	0.11
<b>Body-mass Index, kg/m<sup>2</sup></b>	26.0 (3.3)	28.5 (5.1)	33.2 (5.6)	< 0.001
<b>Lipid Levels</b>				
<b>LDL cholesterol, mg/dl</b>	115 (31)	114 (33)	110 (34%)	< 0.001
<b>HDL cholesterol, mg/dl</b>	60 (16)	56 (15)	51 (14)	< 0.001
<b>Triglycerides, mg/dl</b>	133 (98 – 187)	149 (108 – 208)	173 (123 – 238)	< 0.001
<b>Lipid-lowering Medication</b>	467 (30%)	550 (34%)	450 (41%)	< 0.001
<b>Healthy Lifestyle Factors</b>				
<b>No Current Smoking</b>	1,558 (99.6%)	1,497 (94%)	832 (76%)	< 0.001
<b>Non-obese</b>	1477 (94%)	1,080 (68%)	172 (16%)	< 0.001
<b>Regular Physical Activity</b>	1,423 (91%)	523 (33%)	21 (2%)	< 0.001
<b>Healthy Diet</b>	511 (33%)	96 (6%)	3 (0.3%)	< 0.001
<b>Genetic Risk Category</b>				
<b>Low Genetic Risk</b>	293 (19%)	329 (21%)	224 (20%)	
<b>Intermediate Genetic Risk</b>	955 (61%)	932 (58%)	670 (61%)	0.30
<b>High Genetic Risk</b>	316 (20%)	337 (21%)	204 (19%)	

Values represent N (% with recorded values), mean (SD), or median (IQR). P-values computed via ANOVA for continuous variables (TG modeled using Kruskal-Wallis test) and chi-square test for categorical variables. FH (family history); CAD (coronary artery disease). Family history of coronary artery disease refers to self-reported parental history of myocardial infarction.

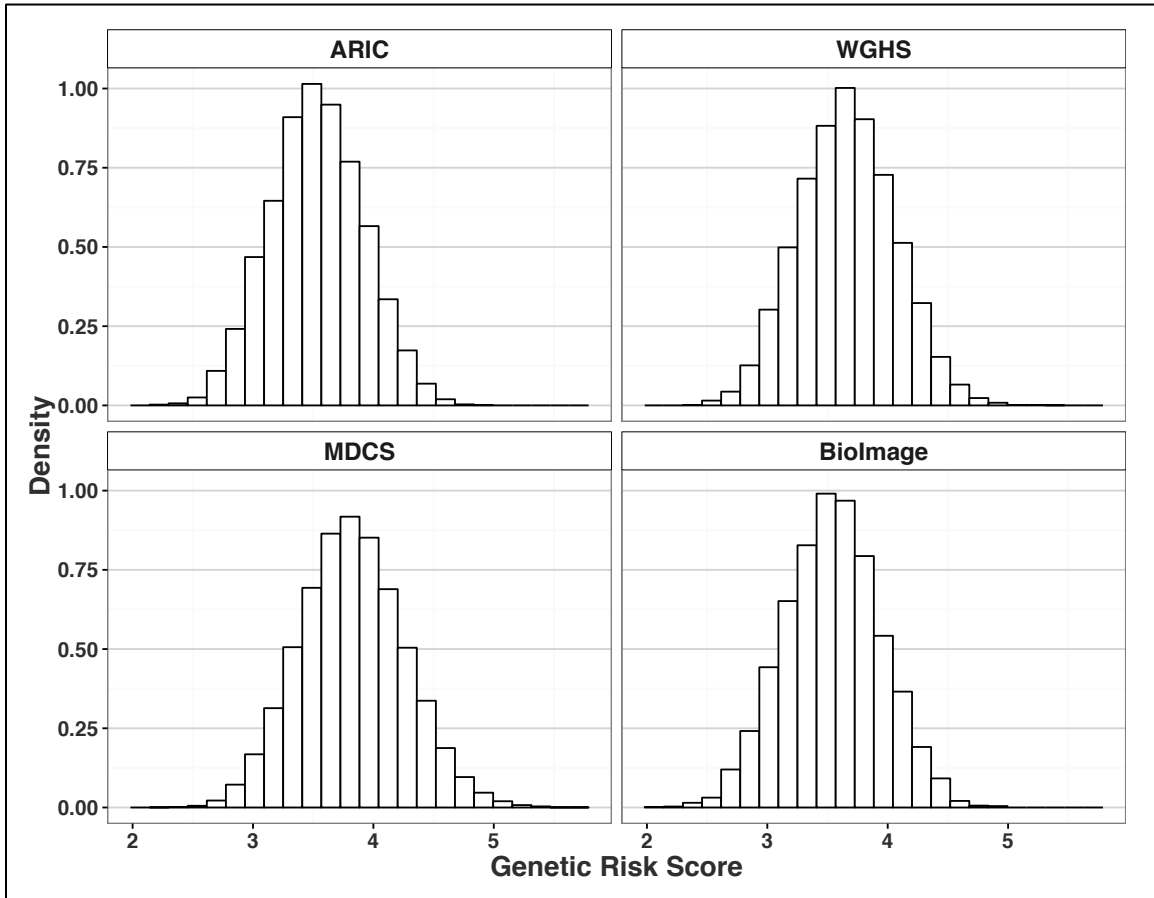
**Figure S1.** Distribution of Lifestyle and Genetic Risk by Cohort

Within each cohort, the percentages in black font refer to the number of individuals in each category of lifestyle risk. For each lifestyle risk category, the percentage of individuals in each genetic risk category is displayed in white font. P-values for association between genetic and lifestyle risk categories 0.41, 0.95, 0.82, and 0.30 in ARIC, WGHS, MDCS, and Biolmage cohorts respectively.



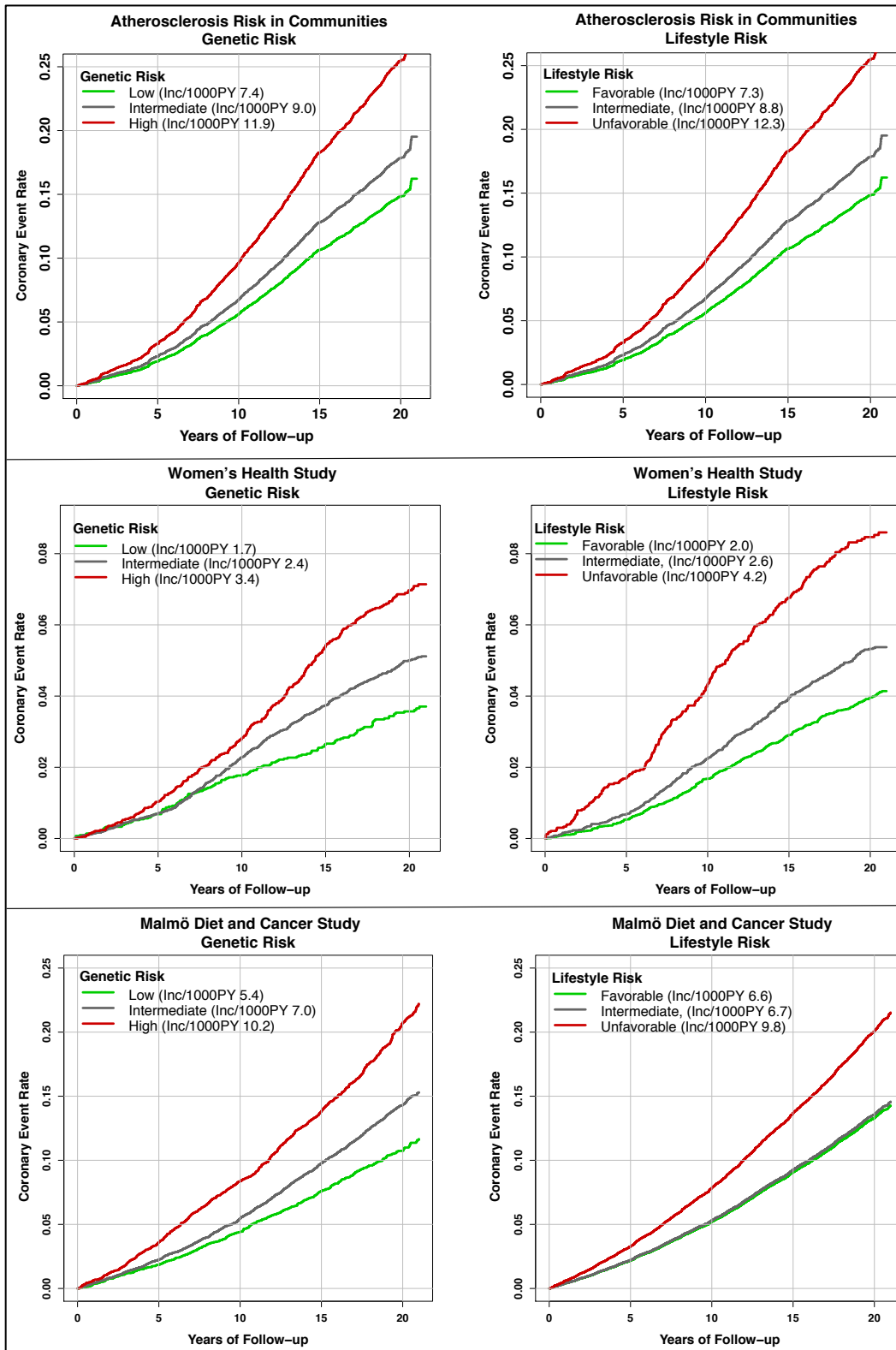
**Figure S2.** Distribution of Genetic Risk Score by Cohort

Average (Range) genetic risk scores were 3.53 (2.15 – 4.87) in ARIC, 3.66 (2.33 – 5.41) in WGHS, 3.82 (2.20 – 5.71) in MDCS and 3.54 (2.07 – 4.90) in the Biolmage Study. Variation in scores across cohorts was related to slight differences in number of available component SNPs as noted in Table S1.



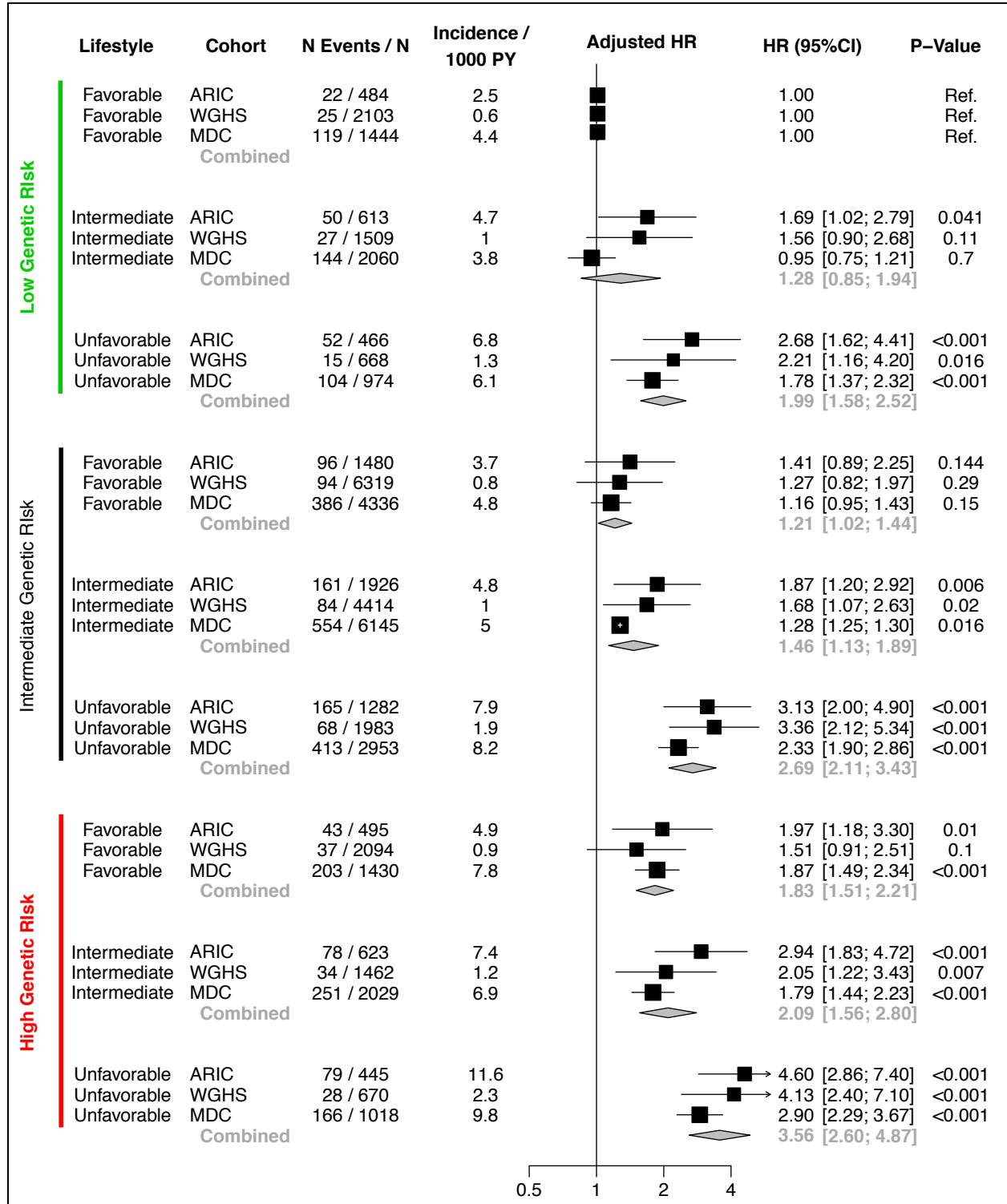


**Figure S3.** Unadjusted Cumulative Hazard Plots by Genetic and Lifestyle Risk Category  
 Unadjusted incidence rates per 1000 person-years of follow-up are displayed for each category of genetic and lifestyle risk.



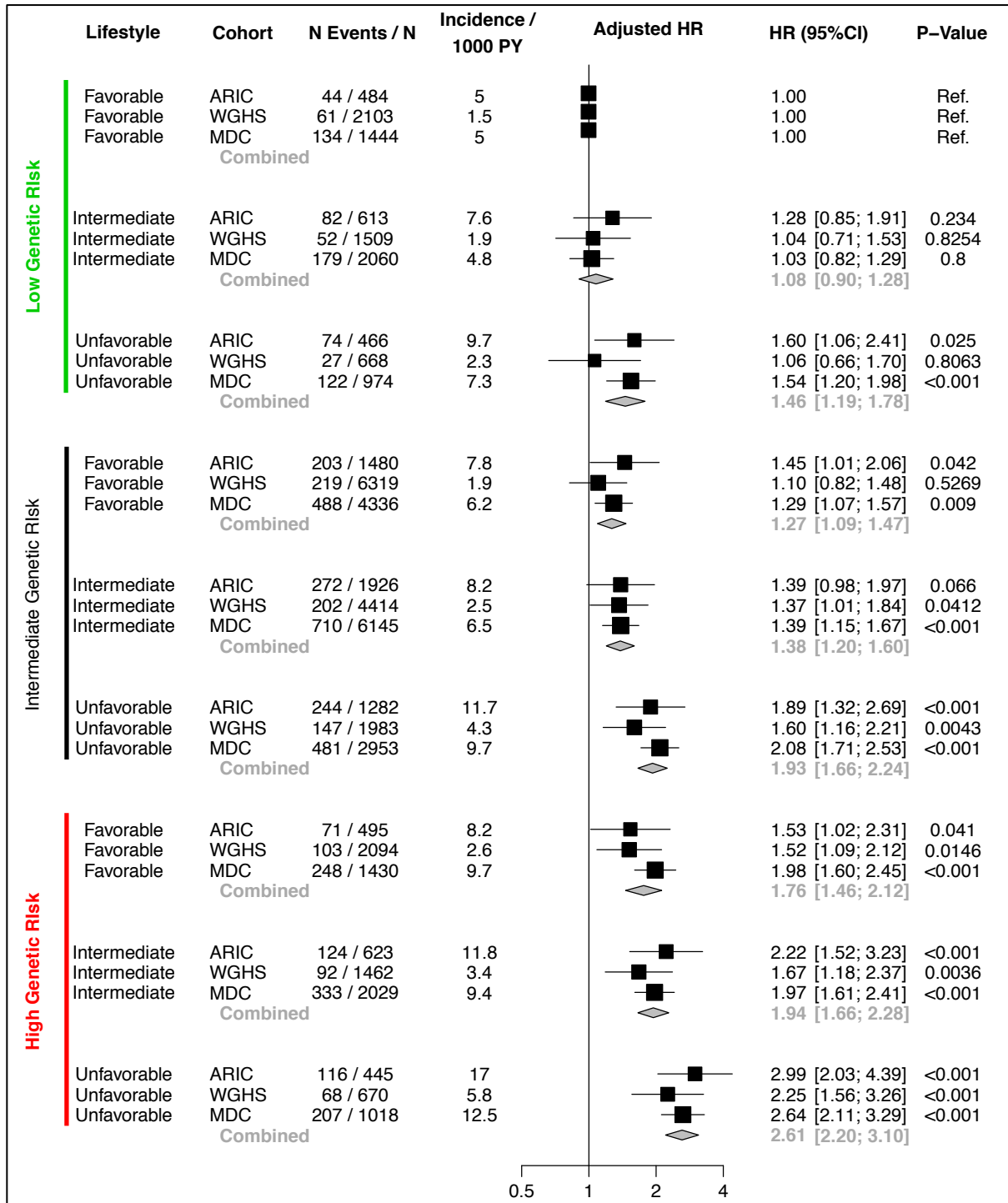
**Figure S4.** Sensitivity Analysis: Risk of Myocardial Infarction or Death from Coronary Causes According to Genetic and Lifestyle Category in Prospective Cohorts

Cox regression models were adjusted for age, gender (in ARIC and MDCS), randomization to Vitamin E or aspirin (in WGHS), education level, and principal components of ancestry (in ARIC and WGHS).



**Figure S5.** Sensitivity Analysis: Risk of Coronary Events According to Genetic and Lifestyle Category Adjusted for Traditional Risk Factors.

Cox regression models were adjusted for age, gender (in ARIC and MDCS), randomization to Vitamin E or aspirin (in WGHS), education level, principal components of ancestry (in ARIC and WGHS), presence of diabetes mellitus, hypertension, family history of coronary artery disease, LDL cholesterol levels (apolipoprotein B in MDCS), and HDL cholesterol levels (apolipoprotein A-I in MDCS).



**Figure S6:** Risk of Coronary Events According to Genetic and Lifestyle Category Among Black Participants  
 Cox regression model was adjusted for age, gender, education level, and principal components of ancestry. 2,269 black participants of the ARIC study had genotype and covariate data available for analysis. 350 incident coronary events were observed during follow-up. Those at high genetic risk were at increased risk of coronary events (HR 1.65; 95%CI 1.16 – 1.34; p= 0.006) compared to those at low genetic risk. Furthermore, an unfavorable lifestyle was associated with a 70% increased coronary risk (HR 1.70; 95%CI 1,20 – 2.39; p= 0.003). As with white participants, risk of coronary events tended to decrease with adherence to a more favorable lifestyle within categories of low and intermediate genetic risk. This pattern was not apparent among those with a high genetic risk, potentially related to decreased power due to a small number of incident events.

