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Supplemental Data

Association of Low-Frequency and Rare Coding-Sequence Variants with Blood Lipids and Coronary Heart Disease in 56,000 Whites and Blacks

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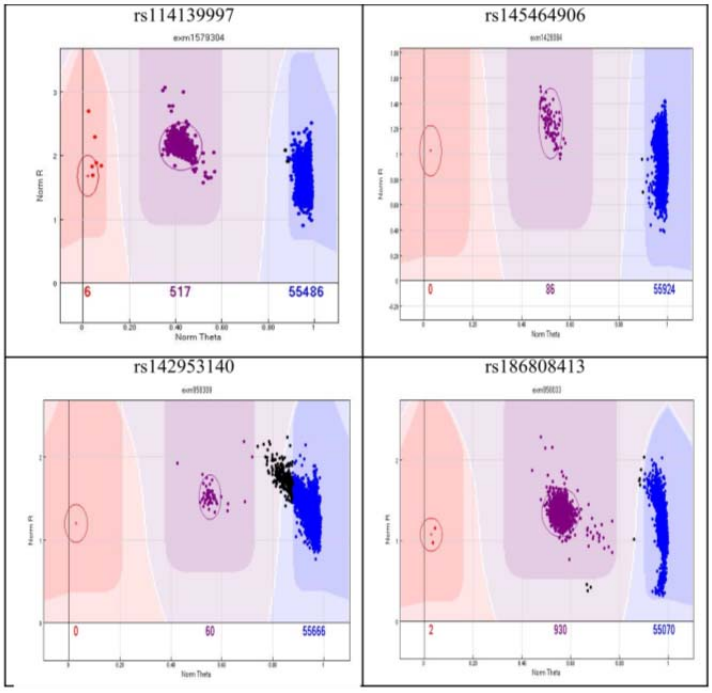
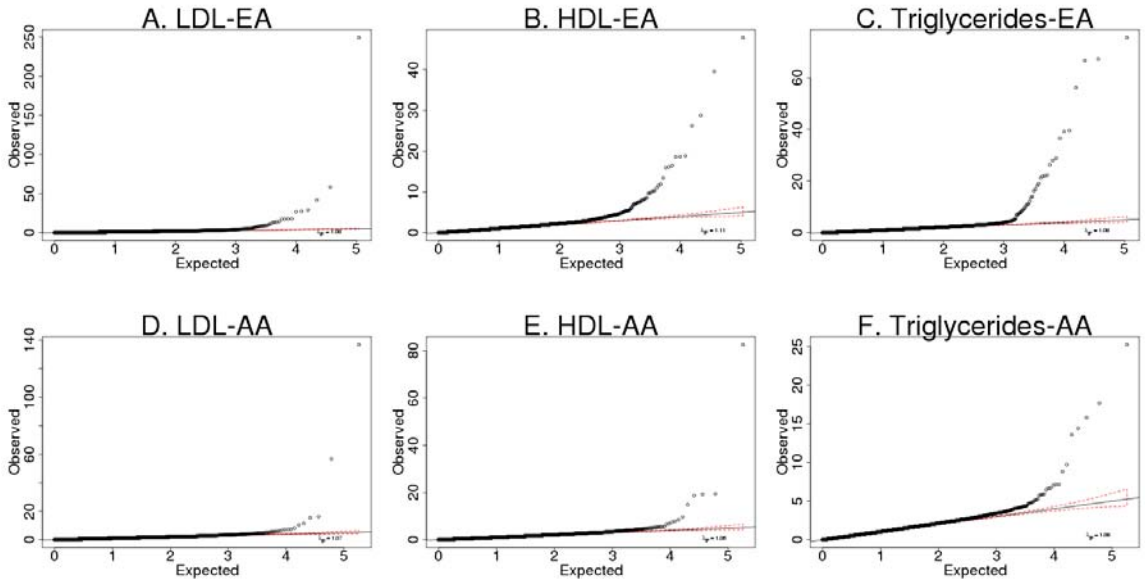
Figure S1. Cluster plots from the CHARGE joint calling for the 4 reported variants show that the minor alleles were appropriately called.



Genotypes of black dots were set to missing.

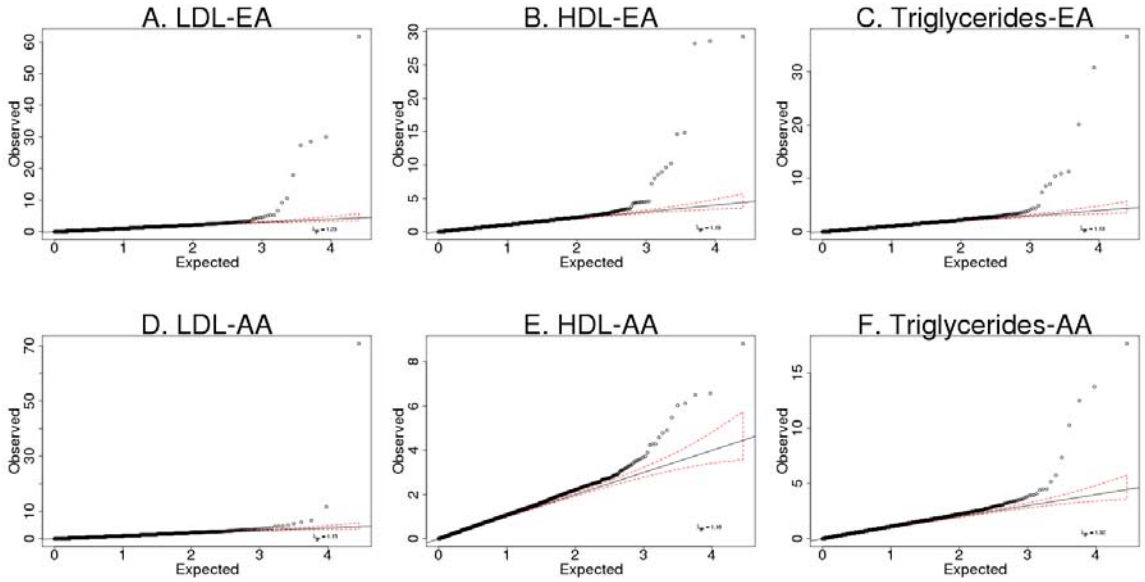
Figure S2. Quantile-quantile (Q-Q) plots from single variant association meta-analysis.



Plotted are distributions are based on nonsynonymous, nonsense, and splice site variants with a MAF > 0.02% in EA individuals and a MAF > 0.07% in AA individuals.

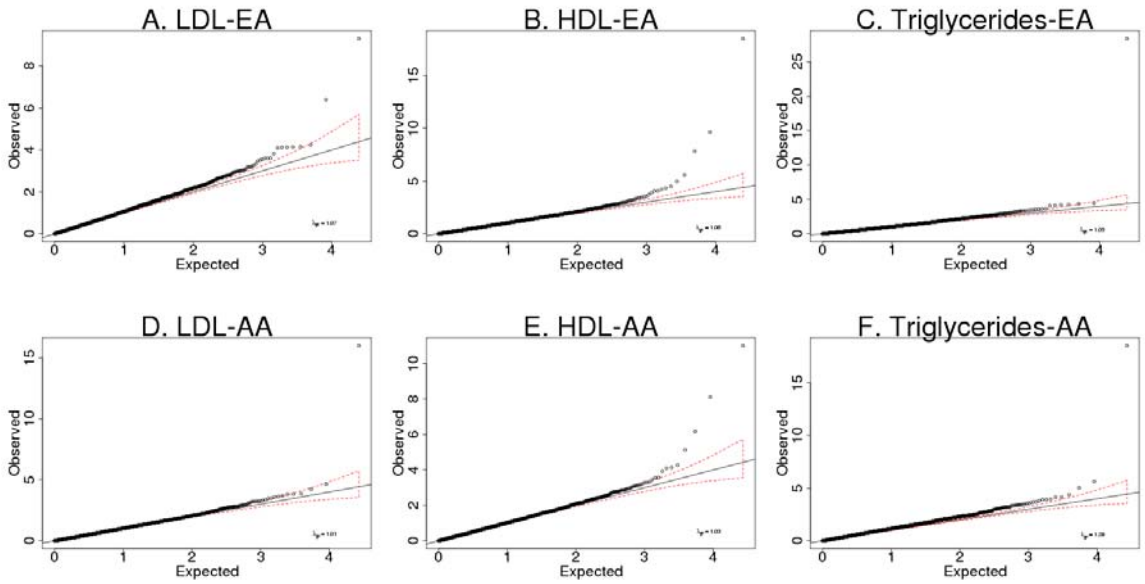
Figure S3. Gene-based association quantile-quantile plots.

A. Q-Q plots from SKAT



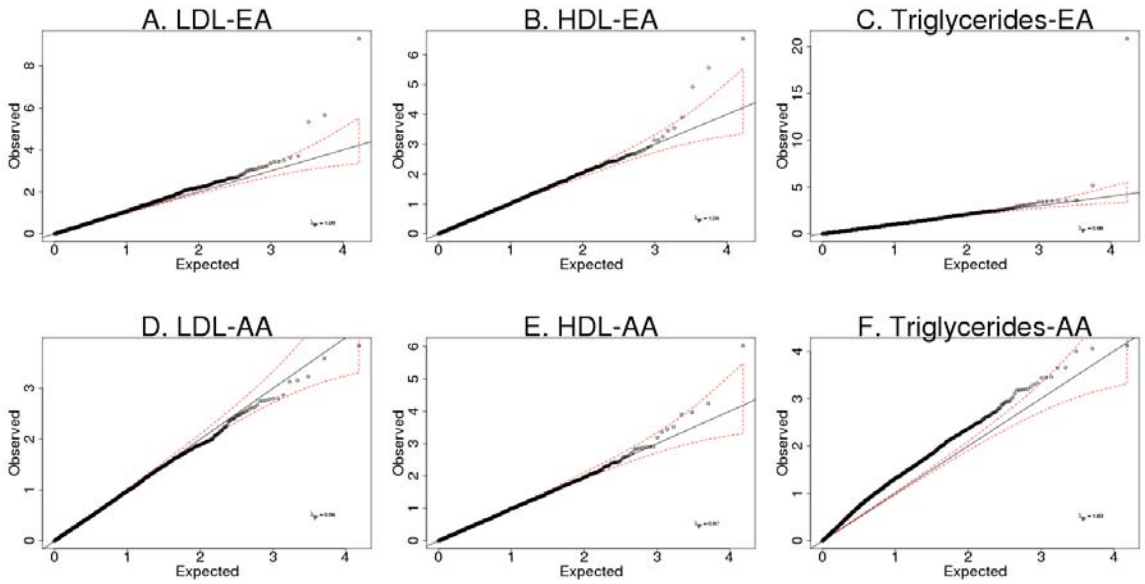
A. SKAT was performed for each gene using nonsynonymous, nonsense, and splice site variants with a MAF < 5%. Genes with at least 2 variants and a cumulative minor allele frequency > 0.05% in EA individuals and > 0.14% in AA individuals are displayed in the distribution plots.

B. Q-Q plots from T1



B. T1 was performed for each gene using nonsynonymous, nonsense, and splice site variants with a MAF < 1%. Genes with at least 2 variants and a cumulative minor allele frequency > 0.04% in EA individuals and > 0.11% in AA individuals are displayed in the distribution plots.

C. Q-Q plots from T0.1



C. T0.1 was performed for each gene using nonsynonymous, nonsense, and splice site variants with a MAF < 0.1%. Genes with at least 2 variants and a cumulative minor allele frequency > 0.04% in EA individuals and > 0.11% in AA individuals are displayed in the distribution plots.

Table S1. Characteristics of study participants analyzed.

	N	Age, years mean	% Female	% on lipid lowering treatment	LDL-c, mg/dL mean (SE)	HDL-c, mg/dL mean (SE)	Triglycerides (TG), mg/dL mean (SE)
European Ancestry							
AGES	2,983	76	58 (1723)	22 (666)	145.6 (35.9)	61.1 (17.2)	107.0 (59.0)
ARIC	10,634	54	53.3 (5671)	3.5 (367)	137.6 (37.6)	50.6 (16.7)	137.1 (90.7)
CHS	4,122	73	56 (2306)	2 (94)	131.2 (36.9)*	53.9 (15.9)	143.9 (79.7)
CARDIA	2,143	25	53 (1129)	NA	108.7 (29.6)	51.9 (13.1)	79.9 (58.5)
FAMHS	1,865	54	56 (1047)	10 (186)	130.8 (40.8)	50.4 (14.6)	151.9 (100.6)
FHS	7,034	38	53 (3754)	4 (186)	118.9 (34.3)	53.0 (15.5)	102.7 (82.4)
Health ABC	1,619	74	47 (766)	14 (234)	126.4 (35.4)	51.9 (16.3)	153.1 (88.3)
Korcula	855	56	64 (545)	4 (34)	150.1 (40.8)	56.7 (13.7)	132.6 (114.2)
LBC1936	910	70	50 (453)	29 (262)	NA	58.6 (16.9)	NA
MESA	2,490	63	52 (1291)	18.8 (468)	125.2 (32.2)	52.5 (15.7)	123.1 (88.7)
RS1	3,092	70	54 (1658)	3 (89)	150.7 (36.7)	51.0 (13.4)	133.5 (59.3)
WHI	4,342	67	100 (4342)	10 (452)	155.3 (39.7)	51.8 (13.8)	161.2 (91.2)
African Ancestry							
ARIC	2,975	54	62.0 (1843)	1.5 (44)	138.1 (43.1)	54.9 (17.5)	111.6 (76.5)
CHS	781	73	62 (484)	4 (38)	131.9 (40.0)*	58.1 (15.6)	115.6 (63.7)
CARDIA	1,888	24	57 (1076)	NA	110.5 (32.3)	54.3 (13.0)	66.4 (37.7)
Health ABC	1,062	73	57 (609)	11 (113)	129.7 (40.9)	57.1 (17.7)	119.8 (73.1)
FAMHS	598	53	66 (392)	18 (108)	123.2 (42.6)	53.5 (15.5)	112.3 (80.7)
JHS	2,154	53	63 (1352)	11 (219)	133.8 (39.0)	51.6 (14.6)	103.2 (78.0)
MESA	2,496	61	56 (1406)	18.6 (463)	124.9 (37.0)	52.7 (15.0)	103.0 (66.3)
WHI	2,158	67	100 (2158)	11 (240)	153.9 (42.7)	57.0 (14.5)	113.2 (69.6)

Values are reported as mean (standard deviation) for continuous measures and as percent (n) for dichotomous measures.

Table S2. Definition of coronary heart disease across studies.

Study	N Total	N Cases	Design	Definition of CHD	Ascertainment of controls	Refs
AGES (EA)	2,290	307	Prospective, cohort	Incident event (MI, PTCA, CABC event or death from CHD) after entry to AGES study, according to hospital records. Follow-up time up to 7 years.	Participants free of CHD on follow-up	
ARIC (EA, AA)	EA: 10,314 AA: 3,225	EA: 1,092 AA: 447	Prospective, cohort	Incident definite or probable MI, fatal CHD, or ECG MI by December 31, 2009. Individuals with prevalent CHD at the baseline exam were excluded	Participants free of CHD on follow-up	[1]
CHS (EA, AA)	EA: 3,735 AA: 732	EA: 1,114 AA:204	Prospective, cohort	Incident fatal and non-fatal MI, fatal CHD (possible and definite), or sudden death within 1 hour of onset of symptoms.	Participants free of CHD on follow-up	[2]
FHS (EA)	3,608	126	Prospective, cohort	Recognized myocardial infarction detected through ECG or enzymes or autopsy, or death due to CHD as a first event	Participants free of CHD on follow-up	[3]
MESA (EA, AA)	EA: 2,347 AA:1,558	EA: 77 AA: 46	Prospective, cohort	Incident fatal or non-fatal MI, fatal CHD due to atherosclerotic coronary heart disease or other cardiovascular disease (not including stroke)	Participants free of CHD on follow-up	
Health ABC (EA, AA)	EA: 1,299 AA:872	EA:286 AA:187	Prospective, cohort	Incident definite or probable MI, definite CHD death, or coronary revascularization	Participants free of CHD on follow-up	[4]
RS1 (EA)	2,919	356	Prospective, cohort	Incident MI, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft.	Participants free of CHD on follow-up	[5; 6]
WHI (EA, AA)	EA: 18,057 AA: 2,065	EA: 3,156 AA: 211	Prospective, cohort	WHI participants included in this study were 50-79 years of age at enrollment in 1993-1998. These women were followed for development of clinical CHD until 2012. A CHD event was defined as a definite or probable myocardial infarction, silent myocardial infarction, coronary revascularization, hospitalized angina, or death due to CHD.	Participants free of CHD on follow-up	[7]
MDC-CVA (EA)	6,794	2,283	Prospective, cohort	Incident nonfatal or fatal MI	Participants free of CHD on follow-up	[8]
IPM (EA, AA)	EA: 2,433 AA: 3,797	EA: 704 AA: 556	Case-control	CAD cases were ascertained from Institute for Personalized Medicine Biobank; CAD was defined using the electronic	Controls were individuals in biobank who did not meet case	NIH dbGaP Study Accession: phs000388.v1.p1

				health record. Cases were documented ICD9 codes 410.xx to 414.xx and (abnormal stress test or abnormal coronary angiography)	criteria	
ATVB/VHS (EA)	2,837	1,604	Case-control	ATVB: MI in men or women ≤ 45 yo VHS: Documented diagnosis of MI, coronary artery bypass grafting (CABG), CAD (by angiography) in males ≤ 50 yo for males and in females ≤ 60 yo	ATVB: No history of thromboembolic disease VHS: Coronary angiography normal	[9,10]
Ottawa (EA)	3,291	1,024	Case-control	Angiography (>1 coronary vessel with >50% stenosis); ≤ 50 yo for males and ≤ 60 yo for females; without type 2 diabetes	Asymptomatic, males >65, females >70	[11]
PROCARDIS (EA)	1,536	728	Case-control	Symptomatic CAD before age 66 years and 80% of cases also had a sibling in whom CAD had been diagnosed before age 66 years. CAD was defined as clinically documented evidence of myocardial infarction (80%), coronary artery bypass graft (10%), acute coronary syndrome (6%), coronary angioplasty (1%) or stable angina (hospitalization for angina or documented obstructive coronary disease) (3%)	No personal or sibling history of CAD before age 66 years.	[12]
DUKE (AA)	1216	653	Case-control	MI; coronary stenosis >= 50%	Patients > 50 yo; no coronary stenosis greater than 30%. No history of ICC/PCI, CABG, MI or transplant.	[13]
PENN (EA)	921	459	Case-control	Angiography (>1 coronary vessel with > 50% stenosis); < 55 yo for males and < 60 yo for females	Angiography normal, men > 40 yo / women > 45 yo	[14]

AGES, Age, Gene/Environment Susceptibility Study; ARIC, Atherosclerosis Risk in Communities Study; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; Health ABC, Health Aging, and Body Composition Study; RS1, Rotterdam Baseline Study; WHI, Women's Health Initiative; MDC-CVA, Malmo Diet and Cancer Study-Cardiovascular Arm; IPM, Mt. Sinai Institute for Personalized Medicine Biobank; ATVB, Italian Atherosclerosis, Thrombosis, and Vascular Biology Study; VHS, Verona Heart Study; Ottawa, Ottawa Heart Study; PROCARDIS, Precocious Coronary Artery Disease Study; MI denotes myocardial infarction; CAD, coronary artery disease.

I. Individual cohort descriptions

Age, Gene/Environment Susceptibility (AGES) Study

The AGES study has been described previously[15]. The study was initiated in 2002 to examine genetic susceptibility and gene/environment interactions related to disease and disability in old age. The AGES study is comprised of 5,764 individuals drawn from the Reykjavik Study, a population-based cohort comprised of individuals born between 1907 and 1935 and followed since 1967 by the Icelandic Heart Association. 2983 European individuals have both ExomeChip genotypes and lipid levels measured.

Atherosclerosis Risk in Communities Study (ARIC)

The ARIC study has been described in detail previously[1]. Men and women aged 45-64 years at baseline were recruited from four communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals, predominantly White and African American, participated in the baseline examination in 1987-1989, with three triennial follow-up examinations. 3,364 African-American and 10,893 European-American individuals were genotyped using the Illumina HumanExome BeadChip array. Individuals that overlapped with JHS were randomly split between the two cohorts, except individuals in a known JHS family were kept in JHS.

Cardiovascular Health Study (CHS)

The CHS has been described in detail Previously[16]. The CHS is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥65 years conducted across four field centers. The original predominantly Caucasian cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists, and an additional 687 African-Americans were enrolled subsequently for a total sample of 5,888. DNA was extracted from blood samples drawn on all participants at their baseline examination in 1989-90. 750 African-American and 4,021 European-American individuals were genotyped using the Illumina HumanExome BeadChip array.

The Coronary Artery Risk Development in Young Adults (CARDIA) Study

The CARDIA Study is a prospective multicenter study with 5115 Caucasian and African American participants ages 18-30 years at baseline, recruited from four centers. The recruitment was done from the total community in Birmingham, AL, from selected census tracts in Chicago, IL and Minneapolis, MN; and from the Kaiser Permanente health plan membership in Oakland, CA. The details of the study design for the CARDIA study have been published before[17]. Eight examinations have been completed since the baseline examination in 1985–1986, with follow-up examinations 2, 5, 7, 10, 15, 20, and 25 years after baseline. Written informed consent was obtained from participants at each examination and all study protocols were approved by the institutional review boards of the participating institutions. 1,886 African-American and 2,131 European-American individuals were genotyped using the Illumina HumanExome BeadChip array.

Family Heart Study (FamHS)
The FamHS (https://dsgweb.wustl.edu/fhscc/) began in 1992 with the ascertainment of 1,200 families, half randomly sampled and half selected because of an excess of CHD or risk factor abnormalities as compared with age- and sex-specific population rates[18]. The families, with approximately 6,000 subjects, were sampled from four population-based parent studies: the Framingham Heart Study, the Utah Family Tree Study, and two centers for the Atherosclerosis Risk in Communities study (ARIC: Minneapolis, and Forsyth County, NC). The participants attended a clinic visit between the years 1994-1996 and a broad range of phenotypes was assessed in the general domains of CHD, atherosclerosis, cardiac and vascular function, inflammation and hemostasis, lipids and lipoproteins, blood pressure, diabetes and insulin resistance, pulmonary function, diet, habitual physical activity, anthropometry, medical history and medication use. Approximately 8 years later, 2,756 European American (EA) subjects belonging to the 510 of the largest and most informative pedigrees were invited for a second clinical exam (2002-04). The most important CHD risk factors were measured again, including lipids, parameters of glucose metabolism, blood pressure, anthropometry, and several biochemical and hematologic markers. Medical history and medication use was updated. A total of 1,865 key EA subjects within this group of families were genotyped using the Illumina Infinium HumanExome v1.0 BeadChip. Informed consent was obtained from all participants, and this project was approved by the Institutional Review Boards of all participating institutions. In addition, a sample of African-American (AA) families was recruited at an additional ARIC field center at the University of Alabama in Birmingham. Measurements of the most important CHD risk factors in the lipid, glucose metabolism, blood pressure, and anthropometry domains were assessed, along with medical history and medication use. A total of 598 AA subjects were genotyped using the Illumina Infinium HumanExome v1.0 BeadChip.

Framingham Heart Study (FHS)
The FHS is a three generational prospective cohort that has been described in detail previously[19]. Individuals were initially recruited in 1948 in Framingham, USA to evaluate cardiovascular disease risk factors. The second generation cohort (5,124 offspring of the original cohort) was recruited between 1971 and 1975. The third generation cohort (4,095 grandchildren of the original cohort) was collected between 2002 and 2005. Fasting lipid levels were measured at exam 1 of the Offspring (1971-1975) and third generation (2002-2005) cohorts, using standard LRC protocols. 8,153 European-American individuals were genotyped using the Illumina HumanExome BeadChip array.

Health, Aging, and Body Composition Study (Health ABC)
The Health ABC study is a prospective cohort study investigating the associations between body composition, weight-related health conditions, and incident functional limitation in older adults. Health ABC enrolled well-functioning, community-dwelling black (n=1281) and white (n=1794) men and women aged 70-79 years between April 1997 and June 1998. Participants were recruited from a random sample of white and all black Medicare eligible residents in the Pittsburgh, PA, and Memphis, TN, metropolitan areas. Participants have undergone annual exams and semi-annual phone interviews. The

current study sample consists of 1619 white participants and 1,062 black participants who attended the second exam in 1998-1999 with available genotyping data.

Jackson Heart Study (JHS)

The JHS is a large, population-based observational study evaluating the etiology of cardiovascular, renal, and respiratory diseases among African Americans residing in the three counties (Hinds, Madison, and Rankin) that make up the Jackson, Mississippi metropolitan area[20]. Data and biologic materials have been collected from 5301 participants, including a nested family cohort of 1,498 members of 264 families. The age at enrollment for the unrelated cohort was 35-84 years; the family cohort included related individuals >21 years old. Participants provided extensive medical and social history, had an array of physical and biochemical measurements and diagnostic procedures, and provided genomic DNA during a baseline examination (2000-2004) and two follow-up examinations (2005-2008 and 2009-2012). The study population is characterized by a high prevalence of diabetes, hypertension, obesity, and related disorders. Annual follow-up interviews and cohort surveillance are ongoing. 2,139 African-American individuals were genotyped using the Illumina HumanExome BeadChip array. Individuals that overlapped with ARIC were randomly split between the two cohorts, except individuals in a known JHS family were kept in JHS.

CROATIA-Korcula study (Korcula)

The CROATIA-Korcula study[21] includes 969 Croatians between the ages of 18 and 98. The field work was performed in 2007 and 2008 in the eastern part of the island, targeting healthy volunteers from the town of Korcula and the villages of Lumbarda, Zrnovo and Racisce. Ethical approval was obtained from appropriate regulatory bodies in both Scotland and Croatia and participants gave informed consent prior to joining the study. After all quality control measures, 855 European individuals were successfully genotyped using the Illumina HumanExome BeadChip array.

Lothian Birth Cohort 1936 (LBC1936)

The LBC1936 consists of 1,091 relatively healthy individuals assessed on cognitive and medical traits at about 70 years of age. They were all born in 1936 and most took part in the Scottish Mental Survey of 1947. At baseline the sample of 548 men and 543 women had a mean age 69.6 years (SD = 0.8). They were all Caucasian, community-dwelling, and almost all lived in the Lothian region (Edinburgh city and surrounding area) of Scotland. A full description of participant recruitment and testing can be found elsewhere[22; 23]. 988 individuals were genotyped using the Illumina HumanExome BeadChip at the Wellcome Trust Clinical Research Facility, Edinburgh.

Multi-Ethnic Study of Atherosclerosis (MESA)

The Multi-Ethnic Study of Atherosclerosis[24] is a National Heart, Lung and Blood Institute-sponsored, population-based investigation of subclinical cardiovascular disease and its progression. A total of 6,814 individuals, aged 45 to 84 years, were recruited from six US communities (Baltimore City and County, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN) between July 2000 and August 2002. Participants were excluded if they had physician-diagnosed cardiovascular

disease prior to enrollment, including angina, myocardial infarction, heart failure, stroke or TIA, resuscitated cardiac arrest or a cardiovascular intervention (e.g., CABG, angioplasty, valve replacement, or pacemaker/defibrillator placement). Pre-specified recruitment plans identified four racial/ethnic groups (White European-American, African-American, Hispanic-American, and Chinese-American) for enrollment, with targeted oversampling of minority groups to enhance statistical power.

Rotterdam Baseline Study (RS)

The Rotterdam Study is an ongoing prospective population-based cohort study, focused on chronic disabling conditions of the elderly. The study comprises an outbred ethnically homogenous population of Dutch Caucasian origin. The rationale of the study has been described in detail elsewhere[5]. In summary, 7,983 men and women aged 55 years or older, living in Ommoord, a suburb of Rotterdam, the Netherlands, were invited to participate. 3163 European individuals were genotyped using the Illumina HumanExome BeadChip array.

Women's Health Initiative (WHI)

WHI[7] is one of the largest (n=161,808) studies of women's health ever undertaken in the U.S. There are two major components of WHI: (1) a Clinical Trial (CT) that enrolled and randomized 68,132 women ages 50 – 79 into at least one of three placebo-control clinical trials (hormone therapy, dietary modification, and calcium/vitamin D); and (2) an Observational Study (OS) that enrolled 93,676 women of the same age range into a parallel prospective cohort study. A diverse population including 26,045 (17%) women from minority groups were recruited from 1993-1998 at 40 clinical centers across the U.S. The design has been published[25; 26]. For the CT and OS participants enrolled in WHI and who had consented to genetic research, DNA was extracted by the Specimen Processing Laboratory at the Fred Hutchinson Cancer Research Center (FHCRC) using specimens that were collected at the time of enrollment in to the study (between 1993 and 1998). 2,142 African-American and 4,005 European-American individuals were genotyped using the Illumina HumanExome BeadChip array.

II. Cohort Acknowledgments

Age, Gene/Environment Susceptibility (AGES) Study
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Atherosclerosis Risk in Communities Study (ARIC)
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Cardiovascular Health Study (CHS)
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The Coronary Artery Risk Development in Young Adults (CARDIA) Study
The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the University of Alabama at Birmingham (HHSN268201300025C & HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging. Genotyping and data analyses were funded in part by grants U01-HG004729, R01-HL093029, and R01-HL084099 from the National Institutes of Health to MF. This manuscript has been reviewed by CARDIA for scientific content.

Family Heart Study (FamHS)
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Framingham Heart Study (FHS)
Genotyping, quality control and calling of the Illumina HumanExome BeadChip in the Framingham Heart Study was supported by funding from the National Heart, Lung and Blood Institute Division of Intramural Research (Daniel Levy and Christopher J. O'Donnell, Principle Investigators). Support for the centralized genotype calling was provided by Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium through the National Institutes of Health (NIH) American Recovery and Reinvestment Act of 2009 (5RC2HL102419). The NHLBI's Framingham Heart Study is a joint project of the National Institutes of Health and Boston University School of Medicine and was supported by contract N01-HC-25195. A portion of this research was conducted using the Linux Clusters for Genetic Analysis (LinGA) computing resources at Boston University Medical Campus.

Health, Aging, and Body Composition Study (Health ABC)
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Jackson Heart Study (JHS)
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CROATIA-Korcula study (Korcula)
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Multi-Ethnic Study of Atherosclerosis (MESA)
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[1]Anthropometry Project Team, [2]Blood Count/Hematology Project Team, [3]Blood Pressure Project Team, [4]Data Flow Working Group, [5]Early MI Project Team, [6]ELSI Working Group, [7]Executive Committee, [8]Family Study Project Team, [9]Lipids Project Team, [10]Lung Project Team, [11]Personal Genomics Project Team, [12]Phenotype and Harmonization Working Group, [13]Population Genetics and Statistical Analysis Working Group, [14]Publications and Presentations Working Group, [15]Quantitative Analysis Ad Hoc Task Group, [16]Sequencing and Genotyping Working Group, [17]Steering Committee, [18]Stroke Project Team, [19]Structural Variation Working Group, [20]Subclinical/Quantitative Project Team

ESP Cohorts
[21]Acute Lung Injury (ALI), [22]Atherosclerosis Risk in Communities (ARIC), [23]Cardiovascular Health Study (CHS), [24]Chronic Obstructive Pulmonary Disease (COPDGene), [25]Coronary Artery Risk Development in Young Adults (CARDIA), [26]Cystic Fibrosis (CF), [27]Early Pseudomonas Infection Control (EPIC), [28]Framingham Heart Study (FHS), [29]Jackson Heart Study (JHS), [30]Lung Health Study (LHS), [31]Multi-Ethnic Study of Atherosclerosis (MESA), [32]Pulmonary Arterial Hypertension (PAH), [33]Severe Asthma Research Program (SARP), [34]Women's Health Initiative (WHI)

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