Supplement to:

APOL1 renal-risk variants and cardiovascular disease: An individual participant meta-analysis

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Appendix 1. Genotyping and ancestry methods

Study	Risk allele genotyping method	Ancestry method
AA-DHS	Custom assay designed in the Wake Forest School of Medicine Center for Genomics and Personalized Medicine Research on the Sequenom platform (San Diego, CA)	African ancestry proportion was computed based on the ancestry informative markers available on the Illumina OMNI 5 chip genome-wide association study data
AASK	ABI Taqman (Applied Biosystems, Foster City, California)	Percentage of European ancestry was estimated using 140 ancestry informative markers and the software ANCESTRYMAP
ARIC	Taqman	The global percentage of European ancestry for each participant was estimated using ANCESTRYMAP based on approximately 1350 ancestry informative markers
CHS	TaqMan assays (ABI, Foster City, California)	N/A
JHS	Coding exons of the *APOL1* gene were sequenced using a custom hybrid capture array	Principal component analysis was performed using PLINK and EIGENSTRAT
MESA	TaqMan assays (Applied Biosystems 7900) and DNA samples (extracted from buffy coat) collected at the baseline examination	Global African ancestry proportion was estimated using 406 ancestry informative markers from the Affymetrix 6.0 array, and 4 ancestral populations in ADMIXMAP software (http://www.homepages.ed.ac.uk/pmckeigu/software/admixmap/manual_desc.html)
REGARDS	*APOL1* risk variants were obtained using TaqMan SNP Genotyping Assays (Applied Biosystems/Thermo Fisher Scientific).	A subset of participants had available genomic array data (Illumina exome chip) to estimate population substructure (n=6,714).
SPRINT	Custom assay designed in the Wake Forest School of Medicine Center for Genomics and Personalized Medicine Research on the Sequenom platform (San Diego, CA).	The maximum likelihood approach of Tang *et al.*[1] as coded in the package FRAPPE (frequentist estimation of individual ancestry proportion) was used to obtain the proportion of African and European ancestry for each individual. Genotype data at these markers were obtained from 44 HapMap Yoruba individuals (YRI) and 39 European American controls as anchors and provided starting values for the expectation maximization algorithm used in FRAPPE.

Appendix 2. Cardiovascular disease definitions; coronary heart disease (includes myocardial infarction), stroke, and heart failure

Study	**Definition of Coronary Heart Disease (includes Myocardial Infarction)** • Death due to coronary heart disease such as myocardial infarction • Incidence of myocardial infarction • Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)	**Definition of Stroke** • Death due to stroke • Incidence of ischemic stroke • Incidence of hemorrhagic stroke (preferably **without subarachnoid hemorrhage**)	**Definition of Heart Failure** Hospitalization or death due to heart failure
AA-DHS	• N/A	• N/A	N/A
AASK	• Nonfatal myocardial infarction was defined by a clinical report of myocardial infarction supported by changes in serum cardiac enzymes (creatine kinase, MB fraction, or troponin I) or on electrocardiogram (new pathologic Q-waves, appearance of a R wave in lead V1, or loss of progression of R waves in leads V2 to V5). Probable myocardial infarctions were defined by clinical reports of each but without supporting documentation. • Cardiac revascularization procedures included coronary artery bypass graft surgery, angioplasty, and percutaneous stent placement.	• Stroke was defined as a neurologic deficit persisting beyond 24 hours attributed to stroke and verified by imaging. Probable strokes were defined by clinical reports of each but without supporting documentation.	Heart failure was defined as a hospitalization for congestive heart failure with need for inotropic, vasodilator, or angiotensin-receptor inhibitor therapy, escalation of diuretic therapy, ultrafiltration, or dialysis.
ARIC	• Definite coronary death based on medical chart review by adjudication committee • Definite or probable myocardial infarction based on medical chart review by adjudication committee • ICD-9-CM codes 36.0, 36.1 or 36.2	• Stroke death was not adjudicated. Thus, we defined fatal stroke as adjudicated cases who died during hospitalization for adjudicated stroke event. • Definite or probable ischemic or hemorrhagic stroke cases, defined as sudden or rapid onset of neurological symptoms that lasted for 24 hours or led to death in the absence of another	Hospitalization or death with ICD code 428 (for ICD 9-CM) or I 50 (ICD 10)

		cause (subarachnoid hemorrhage was not included)	
CHS	• Cardiovascular events in CHS are adjudicated by central committees. Details of the protocols and algorithms for confirmation of these events have been published.2 • In brief, participants were questioned regarding hospitalizations and other acute events every six months. Discharge summaries and diagnoses were obtained for all hospitalizations. For all potential incident events, additional information, such as cardiac enzyme levels, serial electrocardiograms, and cranial imaging studies, was collected.	• To be categorized as a stroke, a new neurologic deficit had to persist for 24 hours, or if less than 24 hours, a lesion appropriate to the clinical deficit must have been detected on brain imaging studies.	Congestive heart failure required a physician diagnosis along with treatment with a diuretic and vasodilator or diagnostic radiographic findings.
JHS	• Cardiovascular illnesses and deaths among the JHS cohort are identified by monitoring and surveillance of a combination of hospitalizations and deaths. Final event classification is completed by a carefully developed process of computer-generated diagnosis with follow-up review and adjudication by trained medical personnel, if necessary. • CHD events based on ICD 9 and ICD 10 codes and medical record review including clinical information and cardiac biomarker levels.	• Trained and certified stroke abstractors review the cohort eligibility forms and identify participants with a stroke ICD 9 or ICD 10 codes; discharge summaries are reviewed for key words.	Incident HF hospitalizations were identified through annual follow-up telephone interviews and hospital discharge lists and confirmed with reviews and abstractions of HF hospitalization records. The HF hospitalization adjudication was performed by trained medical personnel using abstracted information from hospital records. The formal adjudication of HF events in the JHS started in January 2005 and events before that were self-reported.
MESA	• Classified as definite, possible, or absent. Definite fatal CHD required a documented MI within the previous 28 days, chest pain within the 72 hours before death, or a history of CHD, and required the absence of a known non-atherosclerotic or non-cardiac cause of death. If the definite fatal CHD criteria were not met, possible fatal CHD could be	• Classified as present or absent and consisted of rapid onset of a documented focal neurologic deficit lasting 24 hours or until death, or if < 24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits	Reviewers classified CHF as definite, probable, or absent. Definite or probable CHF required heart failure symptoms, such as shortness of breath or edema, as asymptomatic disease is not a MESA endpoint. In addition to symptoms, probable

	assigned with an underlying cause of death consistent with fatal CHD and required the absence of a known non-atherosclerotic or non-cardiac cause of death. • Reviewers classified MI as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. In most cases, definite or probable MI required either abnormal cardiac biomarkers (2 times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels 1-2 times upper limits of normal. • Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)	secondary to brain trauma, tumor, infection, or other non-vascular cause were excluded. Strokes were subclassified on the basis of neuroimaging or other tests into subarachnoid hemorrhage, intraparenchymal hemorrhage, other hemorrhage, brain infarction, or other stroke. Infarcts were also subtyped.	CHF required CHF diagnosed by a physician and patient receiving medical treatment for CHF. Definite CHF required one or more other criteria, such as pulmonary edema/congestion by chest X-ray; dilated ventricle or poor LV function by echocardiography or ventriculography; or evidence of left ventricular diastolic dysfunction. We considered participants not meeting any criteria, including just a physician diagnosis of CHF without any other evidence, as having no CHF.
REGARDS	• Total CHD including revascularization: first event of definite/probable MI OR revascularization OR definite/probable acute CHD death on/before 12/31/2010. After report of a CHD-related hospitalization or death, medical records were retrieved and the event was adjudicated by trained clinicians following published guidelines. CHD was confirmed by presence of signs or symptoms suggestive of ischemia; a rising and/or falling pattern in cardiac troponin or creatine phosphokinase-MB over 6 or more hours with a peak value greater than or equal to twice the upper limit of normal (diagnostic cardiac enzymes); and ECG changes consistent with ischemia or MI, guided by the Minnesota code. Additionally, medical records in the last year of life, death certificates and autopsy reports were collected and	• Death due to stroke • Incidence of ischemic stroke • Incidence of hemorrhagic stroke (preferably without subarachnoid hemorrhage). Incident ischemic stroke was investigated by retrieval of hospital records upon self-report of a possible stroke/transient ischemic attack and/or a positive response to the Questionnaire for Verifying Stroke-Free Status during follow-up telephone contact, or report by a proxy of death related to stroke. Stroke was then confirmed by a panel of neurologists according to the World Health Organization (WHO) definition. Events not meeting the WHO definition but characterized by symptoms lasting <24	Incident HF hospitalizations were detected via telephone follow-up with participants every 6 months through December 31st, 2015. Adjudication of HF hospitalizations was performed independently by two clinician investigators with disagreements resolved by discussion. If agreement fell below 80%, adjudicators were retrained. Heart failure events were based on signs and symptoms, laboratory studies (troponin-I, troponin-T, creatinine kinase-MB fraction, B-type natriuretic peptide), electrocardiogram, chest x-ray, and assessments of left ventricular function. Signs and symptoms of HF

	reviewed to determine if the death was a CHD death following published guidelines.	hours with neuroimaging consistent with acute infarct or hemorrhage were classified as clinical strokes. Additionally, medical records, death certificates and autopsy reports were retrieved and reviewed to determine if a participant death was stroke-related following guidelines described. Stroke subtype classifications were based upon the stroke etiology as determined during adjudication. [3-5]	included paroxysmal nocturnal dyspnea, orthopnea, abnormal jugular vein distension, pulmonary rales, cardiomegaly, central venous pressure >16 mm Hg, edema, nocturnal cough, exertional dyspnea, hepatomegaly, pleural effusion, heart rate >120/minute, and ≥ 4.5 kilogram weight loss in 5 days with diuresis. Heart failure with reduced ejection fraction (HFrEF) was defined as EF <50% or qualitative report of reduced EF. Heart failure with preserved ejection fraction (HFpEF) was defined as EF ≥50% or qualitative report of preserved EF. Heart failure events that were not able to be categorized as reduced or preserved ejection fraction were classified as unspecified. In order to focus on incident HF hospitalizations, we excluded individuals with suspected HF at baseline, determined by current use of HF-related medications at the baseline visit. Heart failure-related medications included use of carvedilol, any loop diuretic, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers plus beta blockers in the absence of hypertension, or digoxin in the absence of atrial fibrillation.

SPRINT	• Cardiovascular events were ascertained via surveillance for self-reported events, review of pertinent medical records, and ECG collection. • The algorithm for classifying myocardial infarction has been published previously.[6] In brief, the definition includes myocardial infarction that occurred during surgery or a procedure and myocardial infarction aborted by thrombolytic therapy or procedure. Silent myocardial infarction, determined using 12-lead ECG at years 2 and 4 and the close-out visit compared to baseline, was determined centrally in the absence of clinically detected myocardial infarction using the Minnesota ECG classification • Diagnosis of non-myocardial infarction acute coronary syndrome required hospitalization for evaluation, with documented new or changing cardiac ischemic symptoms. Furthermore, confirmatory evidence of coronary artery disease was required.	• Stroke was defined as the rapid onset of focal neurologic symptoms, headache, or meningismus not due to other conditions (e.g. central nervous system infection), plus a lesion on brain imaging consistent with symptoms except when death occurs within 24 h without resolution of symptoms.	Diagnosis of heart failure required a hospitalization or emergency department visit requiring treatment with infusion therapy for a clinical syndrome that presents with multiple signs and symptoms consistent with cardiac decompensation or inadequate cardiac pump function. This outcome includes heart failure with preserved or reduced left ventricular ejection fraction.

Appendix 3. Acronyms or abbreviations for studies included in the current report and their key references.

AA-DHS:	African American-Diabetes Heart Study[7]
AASK:	African American Study of Kidney Disease and Hypertension
ARIC:	Atherosclerosis Risk in Communities Study
CHS:	Cardiovascular Health Study[8]
JHS:	Jackson Heart Study
MESA:	Multi-Ethnic Study of Atherosclerosis[9]
REGARDS:	Reasons for Geographic and Racial Differences in Stroke[10]
SPRINT:	Systolic Blood Pressure Intervention Trial[11]

Appendix 4. Acknowledgements and funding for collaborating studies.

Study	
AA-DHS	The African American-Diabetes Heart Study is supported by the National Institutes of Health (R01 DK071891 and R01 NS075107).
AASK	The authors thank the staff and participants of the African American Study of Kidney Disease and Hypertension for important contributions. AASK was supported by grants to each clinical center and the coordinating center from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Office of Research in Minority Health (now the National Center on Minority Health and Health Disparities), and institutional grants from the National Institutes of Health (NIH) (M01 RR-00080, M01 RR- 00071, M0100032, P20-RR11145, M01 RR00827, M01 RR00052, 2P20 RR11104, RR029887, and DK 2818-02); King Pharmaceuticals provided monetary support and antihypertensive medications to each clinical center; Pfizer, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Forest Laboratories, Pharmacia, and Upjohn also donated antihypertensive medications.
ARIC	The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). R01HL087641, R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C.The authors thank the staff and participants of the ARIC study for their important contributions.
CHS	This research was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org
JHS	The Jackson Heart Study (JHS) is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), the Mississippi State Department of Health (HHSN268201800015I/HHSN26800001) and the University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Minority Health and Health Disparities (NIMHD). The authors also wish to thank the staffs and participants of the JHS.
MESA	MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-000040, UL1-TR-001079, UL1-TR-001420, UL1-TR-001881, and DK063491. Funding for SHARe genotyping was provided by NHLBI contract N02-HL-64278. Genotyping was performed at Affymetrix (Santa Clara, California, USA) and the Broad Institute of Harvard and MIT

	(Boston, Massachusetts, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.
REGARDS	The authors thank the other investigators, the staff and the participants of the REGARDS Study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org. This study was supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke, the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes of Health.
SPRINT	The authors thank the study participants and study coordinators in SPRINT. The Systolic Blood Pressure Intervention Trial is funded with Federal funds from the National Institutes of Health (NIH), including the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS), under Contract Numbers HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, HHSN268200900049C, and Inter-Agency Agreement Number A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. The SPRINT investigators acknowledge the contribution of study medications (azilsartan and azilsartan combined with chlorthalidone) from Takeda Pharmaceuticals International, Inc. All components of the SPRINT study protocol were designed and implemented by the investigators. The investigative team collected, analyzed, and interpreted the data. All aspects of manuscript writing and revision were carried out by the coauthors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government. For a full list of contributors to SPRINT, please see the supplementary acknowledgement list. We also acknowledge the support from the following CTSAs funded by NCATS: CWRU: UL1TR000439, OSU: UL1RR025755, U Penn: UL1RR024134& UL1TR000003, Boston: UL1RR025771, Stanford: UL1TR000093, Tufts: UL1RR025752, UL1TR000073 & UL1TR001064, University of Illinois: UL1TR000050, University of Pittsburgh: UL1TR000005, UT Southwestern: 9U54TR000017-06, University of Utah: UL1TR000105-05, Vanderbilt University: UL1 TR000445, George Washington University: UL1TR000075, University of CA, Davis: UL1 TR000002, University of Florida: UL1 TR000064, University of Michigan: UL1TR000433, Tulane University: P30GM103337 COBRE Award NIGMS. ClinicalTrials.gov Identifier NCT0120602.

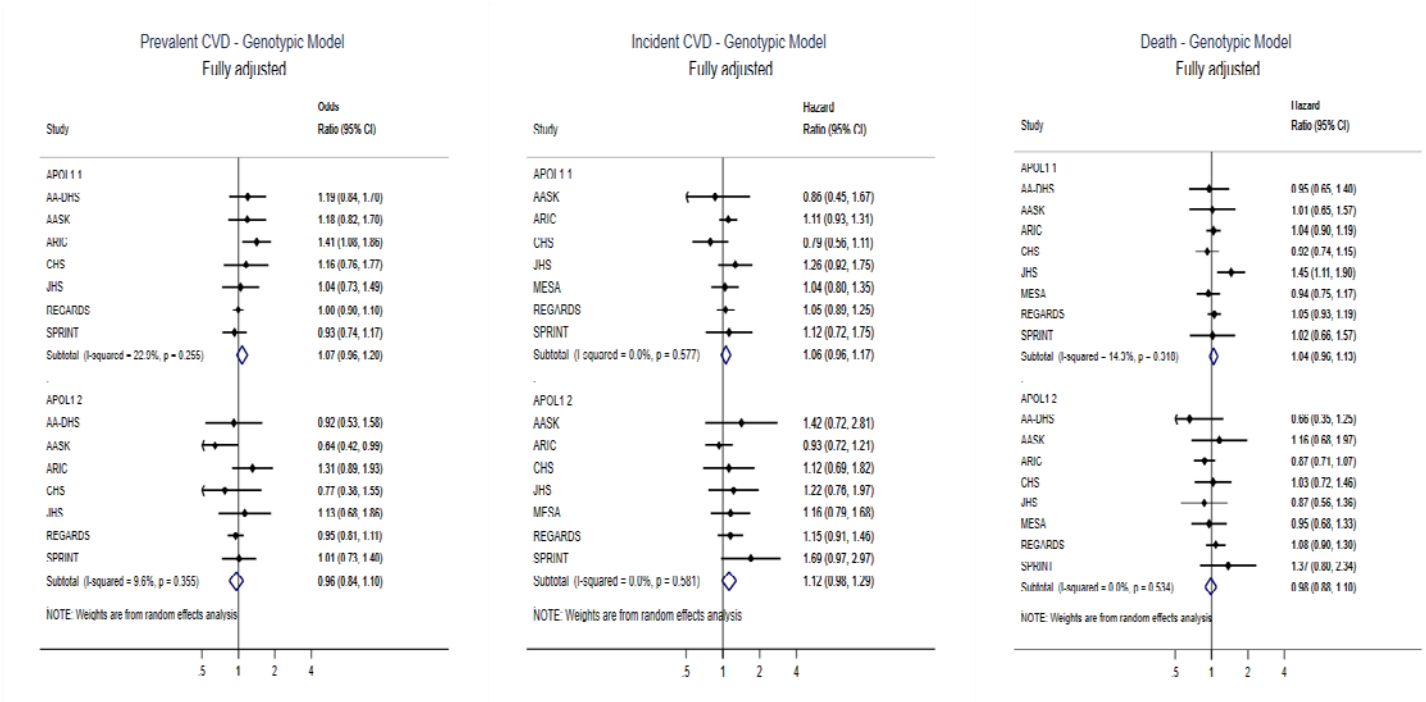
Supplemental Table 1. Percent with missing data.

Study	Ancestry	Current Smoking	AntiHTN	Statin	BMI	Cholesterol	HDLC	Albuminuria	Diabetes	History of CVD
AA-DHS	0	0	100	0	0	1	1	2	0	0
AASK	0	0	0	100	0	1	1	0	0	0
ARIC	11	2	0	1	0	0	0	2	2	2
CHS	100	4	0	0	2	0	100	9	0	0
JHS	1	1	1	1	0	7	7	41	0	0
MESA	8	1	0	0	0	0	0	1	0	0
REGARDS	100	0	0	0	0	0	1	4	0	2
SPRINT	0	0	0	1	0	0	0	3	0	0

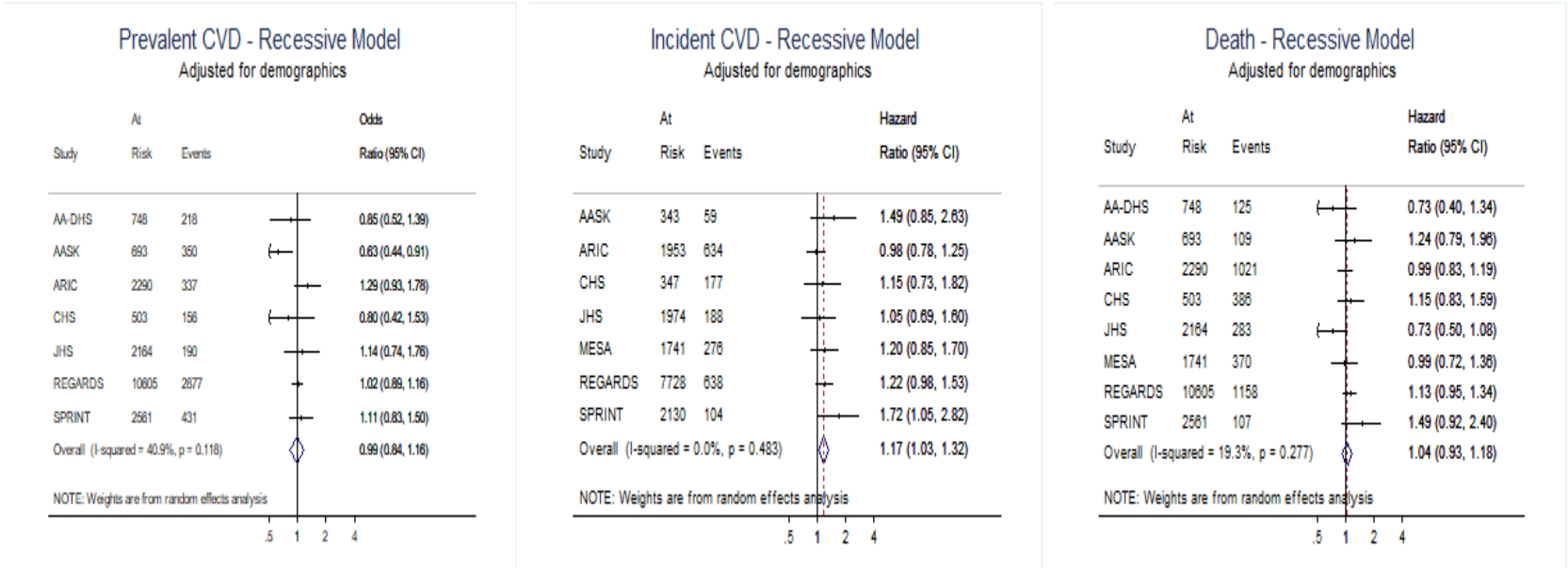
AntiHTN: hypertension medications; HDLC: high density lipoprotein cholesterol; CVD: cardiovascular disease

*ARIC visit 4 is baseline; CHS visit 9 is baseline; all other studies use visit 1 as baseline

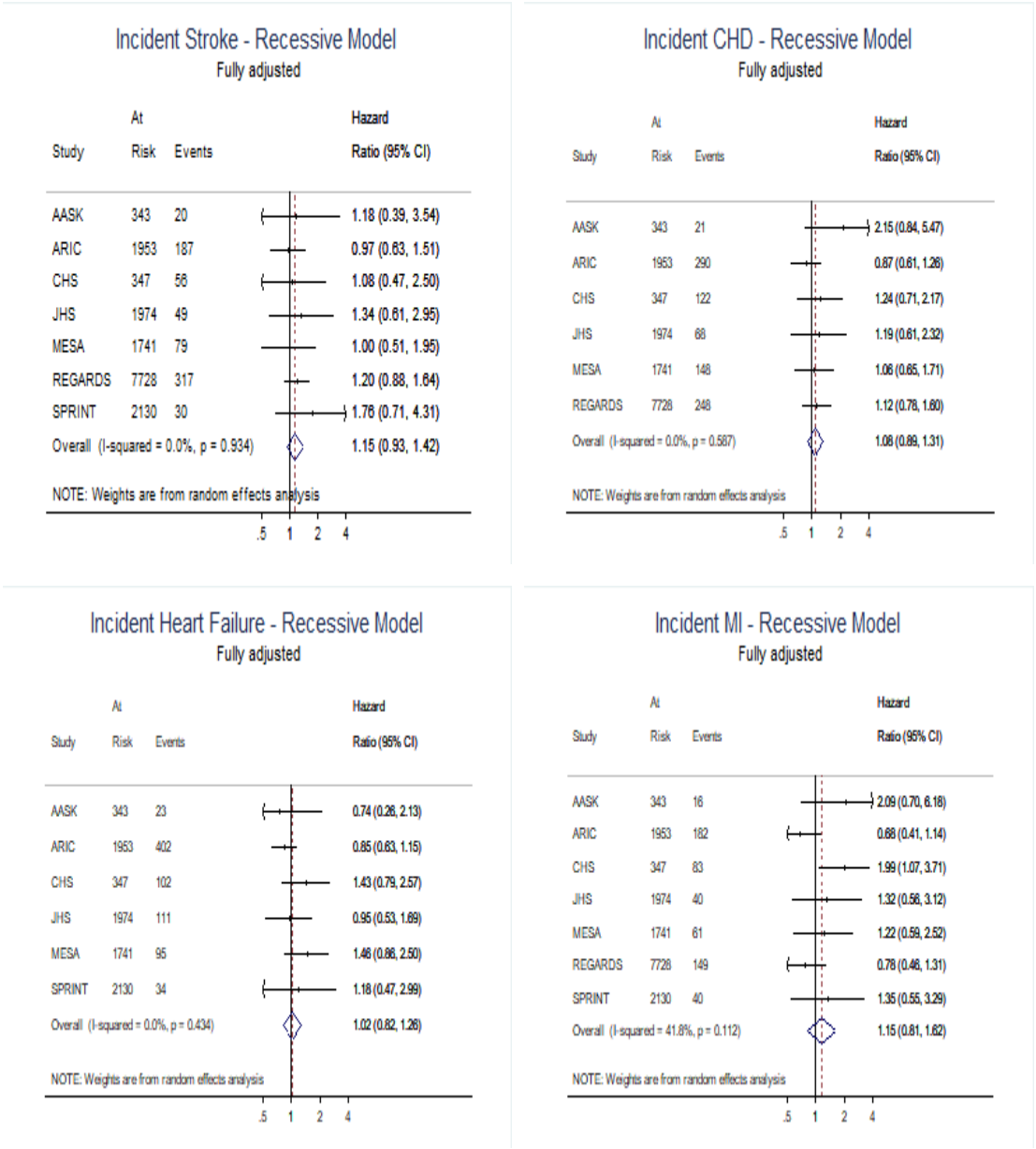
Supplemental Figure 1. Association of APOL1 risk alleles with prevalent cardiovascular disease, incident cardiovascular disease, and death, in a fully-adjusted genotypic model, for 1 (top forest plot) and 2 (bottom forest plot) *APOL1* risk alleles with a reference of 0 *APOL1* risk alleles.



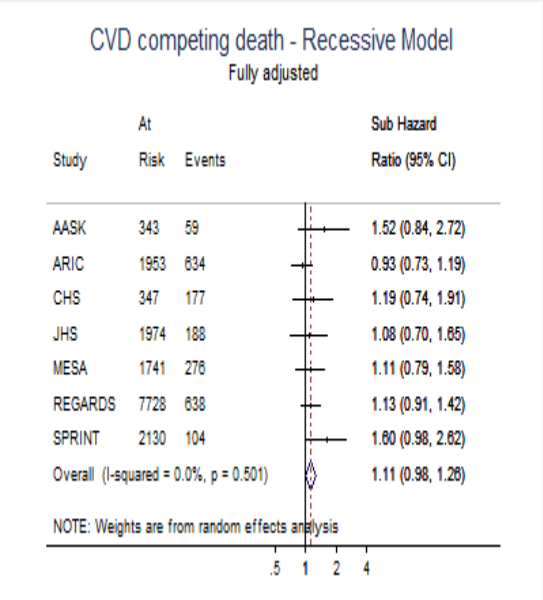
Supplemental Figure 2. Association of APOL1 high-risk genotype with prevalent cardiovascular disease, incident cardiovascular disease, and death, in a minimally adjusted model.

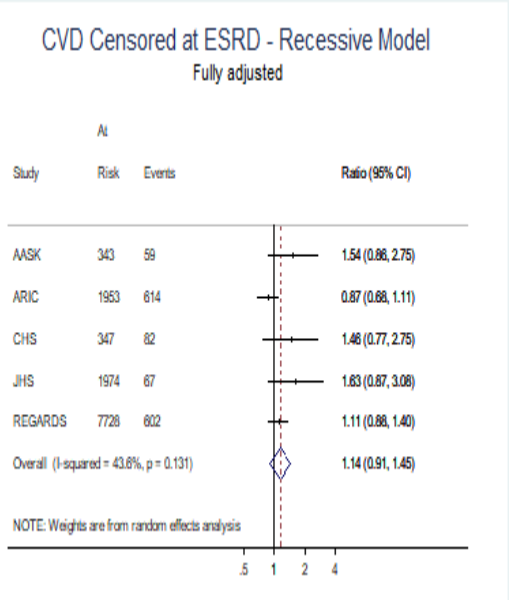


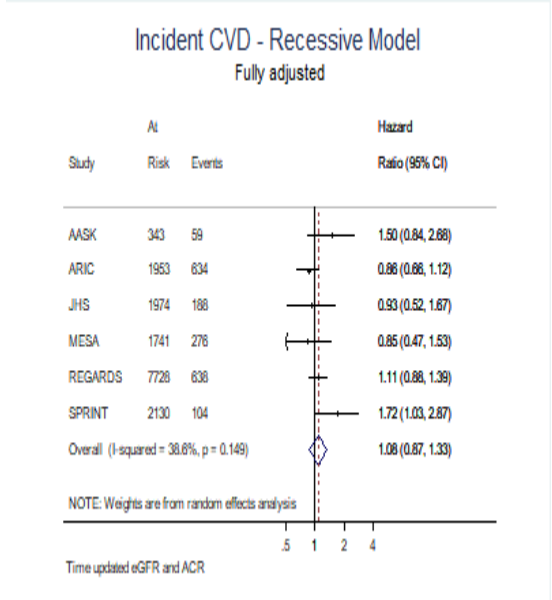
Supplemental Figure 3. Association of APOL1 high-risk genotype (2 risk alleles) with individual components of cardiovascular disease, with a reference group of 0 or 1 risk allele.



Supplemental Figure 4. Association of APOL1 high-risk genotype with incident cardiovascular disease when accounting for death as a competing event, when censoring at end-stage kidney disease, and when adjusting for time-varying kidney measures.







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