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Supplemental Methods

1.1 Cohort description and protocols for covariate assessment

AGES

The Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik) cohort is a prospective, community-based cohort study previously described in detail.[1] AGES was designed to examine risk factors, genetic susceptibility and gene-environment interaction in relation to disease in the elderly. The AGES cohort was drawn from an established population-based cohort (Reykjavik Study) that has been followed since 1967 by the Icelandic Heart Association. Enrollment in the AGES-Reykjavik study occurred between 2002-2006, and follow-up continued until 2012 for this study. The AGES study was approved by the National Bioethics Committee in Iceland, the National Institute on Aging Intramural Institutional Review Board, and the Data Protection Authority in Iceland. Informed consent was obtained from all study participants.

Standard examination protocols and questionnaires were completed in the AGES study. Clinic visits included anthropometry, blood pressure measurement (defined as the mean value of two consecutive blood pressure measurements), electrocardiogram (ECG), and measures of different physical and cognitive function domains. Diabetes was defined from a self-report of a physician diagnosis, use of oral hypoglycemic agents or insulin, or a fasting blood glucose ≥126 mg/dL. Diagnoses of myocardial infarction and heart failure were based on hospital discharge records.[1]

ARIC

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort study of 15,792 men and women aged 45–64, recruited from four communities in the US (Washington County, MD; suburbs of Minneapolis, MN; Jackson, MS; Forsyth County, NC) in 1987–89. Participants were mostly white in the Washington County and Minneapolis centers, only African-American in the Jackson center, and included both races in Forsyth County. After the initial assessment, study participants were examined four additional times (1990–92, 1993–95, 1996–98, 2011–13). Follow-up for this analysis was through 2010. The University of Minnesota Institutional Review Board approved the present ARIC study, and all participants enlisted in the ARIC study have given their written informed consent.

Study participants were asked to fast before the clinic visit, during which a blood sample was obtained and a physical examination performed. Race, education and smoking status were determined by participant self-report. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Blood pressure was measured 3 times with the subject in the sitting position after 5 minutes of rest using a random-zero sphygmomanometer, and the last 2 measurements were averaged. Participants were asked to bring all medications with them to the clinic visits. A prescription bottle or self-report was used to determine cholesterol and blood pressure medication use. A 12-lead ECG at rest was used to define the presence of left ventricular hypertrophy (LVH). Diabetes was categorized as a fasting glucose of ≥126 mg/dl or non-fasting glucose level of ≥200 mg/dl, a reported a physician diagnosis of diabetes, or currently taking medication for diabetes. Prevalent coronary heart disease at baseline included a history of myocardial infarction, myocardial infarction adjudicated from the baseline ECG, or a history of coronary bypass or angioplasty. Prevalent heart failure at study enrollment was defined based on the Gothenburg criteria.[2]

FHS

The Original Cohort of the Framingham Heart Study (FHS) was initiated in 1948 with 5,209 participants from the town of Framingham. The 5,124 Offspring participants (children of the Original Cohort, and the children's spouses) were beginning in the early 1970s. The participants were largely of European ancestry and have been systematically examined every two to eight years since enrollment. The index examinations for the present analysis were completed between 1987-2007 with follow-up through 2011. The study protocol was approved by the Boston University Medical Center Institutional Review Board and all participants signed written informed consent.

In the FHS, for this study, baseline was defined as the date of DNA collection. Medication, alcohol use and smoking were ascertained by self-report. BMI was as weight (in kilograms) divided by height (in meters) squared and covariate values. Current smoking was defined as regular use of one or more cigarettes/day within the year prior to the Framingham clinic visit. Glucose was measured after an overnight fast in the Framingham Study laboratory. Diabetes was diagnosed as fasting glucose ≥126 mg/dL, or use of hypoglycemic medications. Blood pressure was determined in seated participants as the average of two Framingham Study physician systolic and diastolic blood

pressure measurements in mm Hg. Cardiovascular events were adjudicated by a panel of 3 physicians, examining participant hospitalization and outpatient records. Heart failure was diagnosed based on major and minor clinical criteria that have been used for all heart failure cases of FHS participants. Myocardial infarction was diagnosed based on the presence of clinical history, electrocardiographic signs, and biomarkers.

PREVEND

The Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort study was founded in 1997 and is an ongoing community-based cohort study including 8,592 inhabitants of the city of Groningen, The Netherlands.[3] PREVEND is investigating the natural course of microalbuminaria and its relation to renal and cardiovascular disease. Details of the protocol and covariate definitions have been described elsewhere (www.prevend.org). Follow-up for this study was through 2008. The PREVEND study was approved by the institutional medical ethics committee and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Covariates were assessed during study visits including 2 baseline visits to assess demographic, anthropometric, cardiovascular and metabolic risk factors. BMI was calculated as the ratio of weight to height squared. Systolic and diastolic blood pressure were calculated as the mean of two measurements. Anti-hypertensive medications were self-reported and included angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or calcium channel antagonists. Diabetes was defined as a fasting plasma glucose $\geq$ 7.0 mmol/L, or a non-fasting glucose $\geq$ 11.1 mmol/L, or use of anti-diabetic drugs. Smoking was defined as nicotine use in the 5 years prior to study entry. Previous myocardial infarction was defined using self-reported hospitalization of at least 3 days. Heart failure was assessed by an expert panel assessing hospitalization or outpatient records.

RS

The Rotterdam Study (RS-I, RS-II) is a prospective, community-based cohort study of 7,983 subjects aged 55 years or older, designed to assess risk factors of morbidity (eg. coronary heart disease, heart failure, atrial fibrillation (AF), diabetes mellitus) in the elderly.[4] Study participants were recruited from the Ommoord district in the city of Rotterdam, Netherlands. Enrollment for RS-I accrued from 1990-1993. In 2000, participants who had become 55 years of age or moved into the study district since the start of the study were added to the cohort (RS-II). Follow-up for this analysis was through 2010. The Medical Ethics Committee of the Erasmus Medical Center approved the study, and written consent was obtained from all participants.

Information on current health status, medical history, and smoking was obtained using a computerized questionnaire. Participants were classified as current or non-smokers. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice at the right upper arm with a random zero mercury sphygmomanometer in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the two consecutive measurements. A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. Diabetes was defined as the use of anti-diabetic medication or a random or post-load serum glucose level of 200 mg/dL or more. Diagnosis of heart failure was based on a score of heart failure symptoms, on medication prescribed with the indication of heart failure, on hospital discharge diagnoses, and on the information available in general practitioner files.

WGHS

The Women's Genome Health Study (WGHS) is a prospective cohort comprised of over 25,000 initially healthy female health professionals enrolled in the Women's Health Study (WHS). The WHS cohort, a completed randomized trial of vitamin E and low-dose aspirin for the primary prevention of cancer and cardiovascular disease, began in 1993 in women aged 45 years or older and free of cardiovascular disease (including prior myocardial infarction or heart failure) and cancer. After the end of randomized treatment on March 31, 2004, all participants were invited to participate in continued observational follow-up which extended until 2011 for this study. The study was approved by the institutional review board of the Brigham and Women's Hospital (Boston, Massachusetts), and written informed consent was obtained from all participants.

All participants in WGHS provided baseline blood samples and extensive survey data collated from questionnaires obtained every 6 months for the first year and every 12 months thereafter.[5] Covariates of interest assessed at study enrollment included age, height, weight, smoking status, hypertension (including anti-hypertensive medication use), and alcohol consumption.

1.2 Cohort-specific ascertainment of atrial fibrillation

AGES

AF or atrial flutter was diagnosed from Minnesota-coded ECG recorded at AGES study exams and from ICD-9 427.3 or ICD-10 I48 codes from hospital discharges in the National Hospital of Iceland database through April 2010.[1]

ARIC

AF in ARIC was identified from 3 sources: ECG conducted at each study visit, hospital discharge codes (ICD-9CM 427.31, AF, or 427.32, atrial flutter), and death certificates (ICD-9 427.3 or ICD-10 I48). AF cases occurring during the same hospitalization as open cardiac surgery were not included as events.[6, 7]

FHS

Participants were classified as having AF if AF or atrial flutter was present on an ECG derived from a Framingham Study clinic tracing, on an ECG during an encounter with an external clinician, or by Holter monitoring, or if it was noted in hospital records. All incident AF cases were reviewed and adjudicated by one of two Framingham cardiologists.[8, 9]

RS

AF cases were ascertained at baseline and during follow-up as described previously.[10] Briefly, ECGs were recorded and stored digitally, and analyzed by the Modular ECG Analysis System. Two research physicians and a cardiologist verified AF diagnoses. Additional information was obtained from general practitioner records, from outpatient clinics, and from a national database of hospitalizations, which records all hospitalization discharge diagnoses occurring in the Netherlands. AF cases occurring during a serious disease resulting in death, or during myocardial infarction or cardiac operative procedures who recovered during the hospital admission were not included.

PREVEND

Participants were classified as having AF if either atrial flutter or AF was present on a 12-lead ECG at (a) one of three follow-up visits, (b) an outpatient visit, or (c) hospital admission to one of two hospitals in the city of Groningen (University Medical Center Groningen and martini Hospital).[11]

WGHS

Women were asked to report diagnoses of AF at baseline, 48 months, and then annually thereafter. Beginning on September 19, 2006, women enrolled in the continued observational follow-up who reported an incident AF event on at least one yearly questionnaire were sent an additional questionnaire to confirm the episode and to collect additional information. They were also asked for permission to review their medical records, particularly available ECGs, rhythm strips, 24-hour ECGs, and information on cardiac structure and function. For all deceased participants who reported AF during the trial and extended follow-up period, family members were contacted to obtain consent and additional relevant information. An end-point committee of physicians reviewed medical records for reported events according to predefined criteria. An AF event was confirmed if there was ECG evidence, or if a medical report clearly indicated a personal history of AF. The earliest date in the medical records when documentation was believed to have occurred was set as the date of onset of AF. Only confirmed events are included in this analysis.[5]

Supplementary Tables and Figures

2.1. Supplemental Tables

Supplemental Table 1. Characteristics of genotyping methodology, per cohort

	AGES	ARIC	FHS	PREVEND	RS-I	RS-II	WGHS
Study	Age, Gene/ Environment Susceptibility Study	Atherosclerosis Risk in Communities Study	Framingham Heart Study	Prevention of Renal and Vascular End-Stage Disease	Rotterdam Study		Women's Genome Health Study
Array	Illumina HumanCNV370-Duo BeadChip	Affymetrix 6.0	Affymetrix Gene Chip® 500K Array Set & 50K Human Gene Focused Panel	Illumina Cyto SNP12 v2 array	Illumina Infinium HumanHap550-chip v3.0		Illumina HumanHap300 Duo+
Calling Algorithm	BeadStudio	Birdseed	BRLMM	Genomestudio	BeadStudio		BeadStudio
Per SNP Call rate	<98%	<95%	<97%	95%	<98%		<90%
HWE p-value	$<10^{-5}$	$<10^{-5}$	$<10^{-6}$	$<10^{-5}$	$<10^{-6}$		$<10^{-6}$
Excess heterozygosity	NA	NA	subject heterozygosity >5 SD away from the mean	NA	>0.336; n=21		NA
MAF	<1%	<1%	<1%	<1%	<1%		<1%
Selection criteria for PCs	Association with AF (p<0.05)	Eigenstrat: anyone >8 SD from top 10 PCs was removed	Association with AF (p<0.05)	Top 10 PCs	Outliers as identified by IBS clustering were excluded		Top 10 PCs
Number of PCs in the model	0	0	0	10	0		10
Number of SNPs used for imputation	308,340	711,589	385,958	232,571	530,683		331959
Imputation software	Mach1 v 1.0.16	Shapelt(v1.r532) + IMPUTE 2.1.0	Mach1 v 1.0.15	Shapeit v2.790 + Impute2	Mach1 v 1.0.15		Mach1 v. 1.0.16 HapMap II CEU r22

	AGES	ARIC	FHS	PREVEND	RS-I	RS-II
Imputation Reference Panel	1000 Genomes phase I v3, March 2012	1000 Genomes phase I v3, March 2012	1000 Genomes phase I v3, March 2012	1000 Genomes phase I v3, March 2012	1000 Genomes phase I v3, March 2012	1000 Genomes phase I v3, March 2012
SNP position from NCBI build	Build 36	Build 37	Build 36	Build 37	Build 36	Build 36
GWAS Statistical Analysis	ProbABEL, R	FAST	R packages kinship, GEE, COXPH	NA	Mach2QTL GenABEL + PLINK, R, GRIMP	ProbABEL, R
Total number of SNPs used in the analysis (MAF>0.005)	2,408,991	2,512,759	2501666	NA	2,502,002	2,608,508

AGES, indicates the Age, Gene/Environment Susceptibility—Reykjavik study; ARIC, Atherosclerosis Risk in Communities; FHS, Framingham Heart Study; PREVEND, Prevention of Renal and Vascular End-Stage Disease; RS, Rotterdam Study; WGHS, Women's Genome Health Study; SNP, single nucleotide polymorphism; HWE, Hardy Weinberg equilibrium; MAF, minor allele frequency; NCBI, National Center for Biotechnology Information; GWAS, genome wide association study; NA, not available; PCs, principal components; BRLMM, Bayesian Robust Linear Modeling.
PLINK, http://pngu.mgh.harvard.edu/purcell/PLINK/
Eigenstrat, http://genepath.med.harvard.edu/~reich/Software.htm
MACH, http://www.sph.umich.edu/csg/abecasis/MaCH/index.html
BIMBAM, http://stephenslab.uchicago.edu/software.html

Supplemental Table 2. Characteristics of the 39 established SNPs for BMI

SNP	Nearest gene	Alleles		Frequency Effect Allele	Per allele change in BMI	Explained variance	P
		Effect	Other				
rs1558902	*FTO*	A	T	0.42	0.39 (0.02)	0.34%	$4.8x10^{-120}$
rs2867125	*TMEM18*	C	T	0.83	0.31 (0.03)	0.15%	$2.77x10^{-49}$
rs571312	*MC4R*	A	C	0.24	0.23 (0.03)	0.10%	6.43x10-^{42}
rs10938397	*GNPDA2*	G	A	0.43	0.18 (0.02)	0.08%	$3.78x10^{-31}$
rs10767664	*BDNF*	A	T	0.78	0.19 (0.03)	0.07%	$4.69x10^{-26}$
rs2815752	*NEGR1*	A	G	0.61	0.13 (0.02)	0.04%	$1.16x10^{-22}$
rs7359397	*SH2B1*	T	C	0.4	0.15 (0.02)	0.05%	$1.88\text{-}10^{-20}$
rs9816226	*ETV5*	T	A	0.82	0.14 (0.03)	0.03%	$1.69x10^{-18}$
rs3817334	*MTCH2*	T	C	0.41	0.06 (0.02)	0.01%	$1.59x10^{-12}$
rs29941	*KCTD15*	G	A	0.67	0.06 (0.02)	0.00%	$3.01x10^{-9}$
rs543874	*SEC16B*	G	A	0.19	0.22 (0.03)	0.07%	$3.56x10^{-23}$
rs987237	*TFAP2B*	G	A	0.18	0.13 (0.03)	0.03%	$2.90x10^{-20}$
rs7138803	*FAIM2*	A	G	0.38	0.12 (0.02)	0.04%	$1.82x10^{-17}$
rs10150332	*NRXN3*	C	T	0.21	0.13 (0.03)	0.02%	$2.75x10^{-11}$
rs713586	*RBJ*	C	T	0.47	0.14 (0.02)	0.06%	$6.17x10^{-22}$
rs12444979	*GPRC5B*	C	T	0.87	0.17 (0.03)	0.04%	$2.91x10^{-21}$
rs2241423	*MAP2K5*	G	A	0.78	0.13 (0.02)	0.03%	$1.19x10^{-18}$
rs2287019	*QPCTL*	C	T	0.8	0.15 (0.03)	0.04%	$1.88x10^{-16}$
rs1514175	*TNNI3K*	A	G	0.43	0.07 (0.02)	0.02%	$8.16x10^{-14}$
rs13107325	*SLC39A8*	T	C	0.07	0.19 (0.04)	0.03%	$1.50x10^{-13}$
rs2112347	*FLJ35779*	T	G	0.63	0.10 (0.02)	0.02%	$2.17x10^{-13}$
rs10968576	*LRRN6C*	G	A	0.31	0.11 (0.02)	0.02%	$2.65x10^{-13}$
rs3810291	*TMEM160*	A	G	0.67	0.09 (0.02)	0.02%	$1.64x10^{-12}$
rs887912	*FANCL*	T	C	0.29	0.10 (0.02)	0.03%	$1.79x10^{-12}$
rs13078807	*CADM2*	G	A	0.2	0.10 (0.02)	0.02%	$3.94x10^{-11}$
rs11847697	*PRKD1*	T	C	0.04	0.17 (0.05)	0.01%	$5.76x10^{-11}$
rs2890652	*LRP1B*	C	T	0.18	0.09 (0.03)	0.02%	$1.35x10^{-10}$
rs1555543	*PTBP2*	C	A	0.59	0.06 (0.02)	0.01%	$3.68x10^{-10}$
rs4771122	*MTIF3*	G	A	0.24	0.09 (0.03)	0.02%	$9.48x10^{-10}$
rs4836133	*ZNF608*	A	C	0.48	0.07 (0.02)	0.01%	$1.97x10^{-9}$
rs4929949	*RPL27A*	C	T	0.52	0.06 (0.02)	0.01%	$2.80x10^{-9}$
rs206936	*NUDT3*	G	A	0.21	0.06 (0.02)	0.01%	$3.02x10^{-8}$

SNP	Nearest gene	Alleles		Frequency Effect Allele	Per allele change in BMI	Explained variance	P
rs7989336	*HS6ST3*	A	G	0.47	0.016	-	8.80×10^{-6}
rs17381664	*ZZZ3*	C	T	0.39	0.022	-	2.50×10^{-11}
rs17024258	*GNAT2*	T	C	0.04	0.067	-	4.34×10^{-14}
rs4735692	*HNF4G*	A	G	0.58	0.019	-	9.94×10^{-10}
rs13041126	*MRPS33P4*	T	C	0.72	0.017	-	8.52×10^{-7}
rs2531995	*ADCY9*	T	C	0.61	0.021	-	6.58×10^{-8}
rs7503807	*RPTOR*	A	C	0.57	0.02	-	3.00×10^{-10}

SNPs, single nucleotide polymorphisms; BMI, body mass index. Data are taken from Speliotes et al.[12] and Berndt et al.[13] Percent of BMI variance explained by given SNP is reported when available.

Supplemental Table 3. Heterogeneity of meta-analyzed genetic instrument association with BMI and AF: meta-regression analysis

Association	Primary Analysis				Meta-Regression (Mean Age)				Meta-Regression (Mean Age, Mean Height, % Men)			
	FTO		*Gene Score*		*FTO*		*Gene Score*		*FTO*		*Gene Score*	
	I^2 (%)	Qp	I^2 (%)	Qp	I^2 (%)	Qp	I^2 (%)	Qp	I^2 (%)	Qp	I^2 (%)	Qp
Instrument-BMI												
Model 1	67.9	<0.01	72.3	<0.01	37.5	0.17	37.5	0.16	31.3	0.25	9.5	0.37
Model 2	59.8	0.02	76.2	<0.01	29.5	0.22	47.2	0.10	11.8	0.36	27.5	0.27
Model 3	47.9	0.09	64.9	0.01	0	0.57	0	0.50	0	0.46	0	0.42
Model 4	49.7	0.08	64.3	0.01	0	0.58	0	0.30	0	0.49	26.6	0.24
Instrument-AF												
Model 1	0	0.83	0	0.73								
Model 2	0	0.84	0	0.68	-	-	-	-	-	-	-	-
Model 3	0	0.80	0	0.87								
Model 4	0	0.82	0	0.89								
Instrument-AF + BMI												
Model 1	0	0.83	0	0.88								
Model 2	0	0.83	0	0.91	-	-	-	-	-	-	-	-
Model 3	0	0.82	0	0.94								
Model 4	0	0.81	0	0.95								

Shown are heterogeneity estimates for the meta-analyzed associations of each genetic instrument (FTO, gene score) with BMI and AF. Instrument-AF models were further adjusted for BMI in mediation analysis. I^2 reflects heterogeneity across studies with greater values reflecting greater heterogeneity. Qp reflects Cochran's Q statistic, a test for heterogeneity. Given evidence of moderate heterogeneity of the instrument-BMI associations, additional meta-regression was performed to assess for sources of heterogeneity. Shown are residual heterogeneity estimates of the meta-analyzed instrument-BMI associations after accounting for (a) mean age of each cohort as well as (b) proportion of men and mean height. Model 1: adjustment for age and sex. Model 2: Model 1 + smoking status and alcohol intake. Model 3: Model 2 + potential mediators of BMI-AF association (systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, previous coronary heart disease and previous heart failure). Model 4: Model 3 + height. BMI, body mass index. AF, atrial fibrillation.

Supplemental Table 4: Meta-analyzed instrumental variable estimates of BMI-AF: sensitivity analysis

Methodology	IV Estimate Method 1				IV Estimate Method 2			
	FTO		*Gene Score*		*FTO*		*Gene Score*	
	HR [95% CI]	**P-value**	**HR [95% CI]**	**P-value**	**HR [95% CI]**	**P-value**	**HR [95% CI]**	**P-value**
Model 1	1.15 (1.05-1.27)	0.0040.0	1.11 (1.05-1.17)	<0.001	1.17 (1.05-1.31)	0.006	1.11 (1.05-1.17)	< 0.001
Model 2	1.15 (1.05-1.27)	03	1.10 (1.05-1.16)	<0.001	1.16 (1.04-1.30)	0.006	1.11 (1.04-1.17)	<
Model 3	1.14 (1.02-1.28)	0.02	1.09 (1.03-1.15)	0.004	1.15 (1.02-1.30)	0.027	1.09 (1.02-1.16)	0.0010.0
Model 4	1.15 (1.03-1.29)	0.02	1.09 (1.03-1.15)	0.005	1.16 (1.02-1.32)	0.019	1.09 (1.02-1.16)	08
								0.008
	FTO		*Gene Score*		*FTO*		*Gene Score*	
	I^2 (%)	**Qp**	**I^2 (%)**	**Qp**	**I^2 (%)**	**Qp**	**I^2 (%)**	**Qp**
Model 1	0	0.91	0	0.91				
Model 2	0	0.95	0	0.89	-	-	-	-
Model 3	0	0.87	0	0.96				
Model 4	0	0.88	0	0.96				

Shown are the meta-analyzed instrumental variable (IV) risk estimates of body mass index (BMI; per kg/m^2) for incident AF in adjusted models (1-4). IV estimates were derived using two methods. Method 1 refers to estimation of cohort-specific IV estimates followed by meta-analysis (presented in manuscript Table 3). Method 2 utilized study-combined estimates of the genetic instrument (FTO, gene score) associations with BMI and AF. The inferred causal effect of BMI on AF was then derived as the ratio of these estimates (see Methods). I^2 reflects heterogeneity across studies with greater values reflecting greater heterogeneity. Qp reflects Cochran's Q statistic, a test for heterogeneity. As Method 2 employs study-combined estimates, the relevant heterogeneity statistics for instrument-BMI and instrument-AF associations are reported elsewhere (see Supplementary Table 3). Model 1: adjustment for age and sex. Model 2: Model 1 + smoking status and alcohol intake. Model 3: Model 2 + potential mediators of BMI-AF association (systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, diabetes, previous coronary heart disease and previous heart failure). Model 4: Model 3 + height. BMI, body mass index. AF, atrial fibrillation. HR, hazard ratio; CI, confidence interval.

2.2. Supplementary Figures

Supplementary Figure Legends

Supplemental Figure 1: Meta-regression plot of genetic instrument effect size and mean cohort age

Shown is a meta-regression plot of the instrument-BMI effect size (adjusted for age, age-squared, and sex) against mean age at time of cohort enrollment. The regression equation for each genetic instrument (*FTO*, BMI gene score) is shown inclusive of the slope (i.e. Δ effect size per year of mean cohort age). Mean cohort age demonstrated significant inverse association with instrument-AF effect size (*FTO*, p-value = 0.01; BMI gene score, p=0.004). BMI, body mass index.

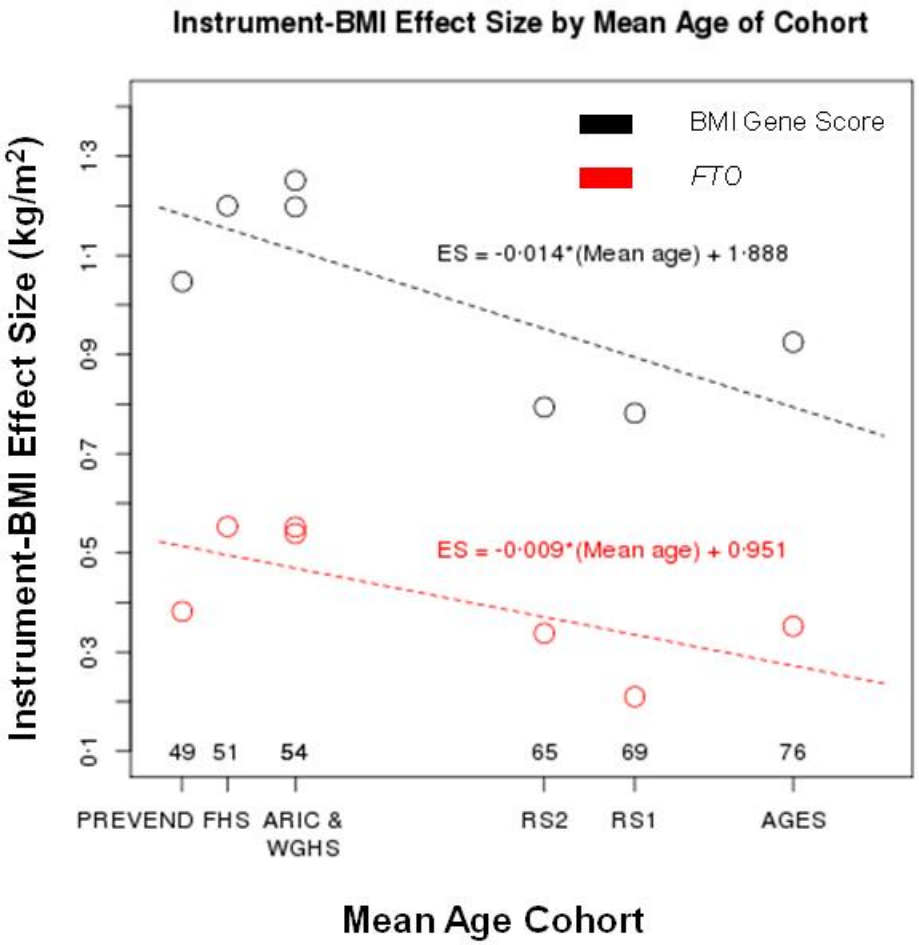
Supplemental Figure 2: Genetic instruments and body mass index

Study-specific and meta-analyzed pooled associations between each genetic instrument (*FTO*, BMI gene score) and BMI are shown with multivariable adjustment (Models 2-4; see Methods). (A) Model 1 is adjusted for age, age-squared, and sex. Multivariable adjustment include (B) Model 2: Model 1 + smoking status, alcohol intake, (C) Model 3: Model 2 + known mediators of the BMI-AF association (systolic and diastolic blood pressure, anti-hypertensive medication use, diabetes mellitus, previous heart failure or coronary heart disease), and (D) Model 4: Model 3 + height. There was moderate heterogeneity in the meta-analyzed instrument-BMI association across studies in each model which was substantially attenuated in meta-regression accounting for mean age in each cohort (Supplementary Table 3 for heterogeneity statistics for each model). Gene score estimate are shown per 1-unit change as well as per 1 standard deviation (SD) change. BMI; body mass index; AF, atrial fibrillation.

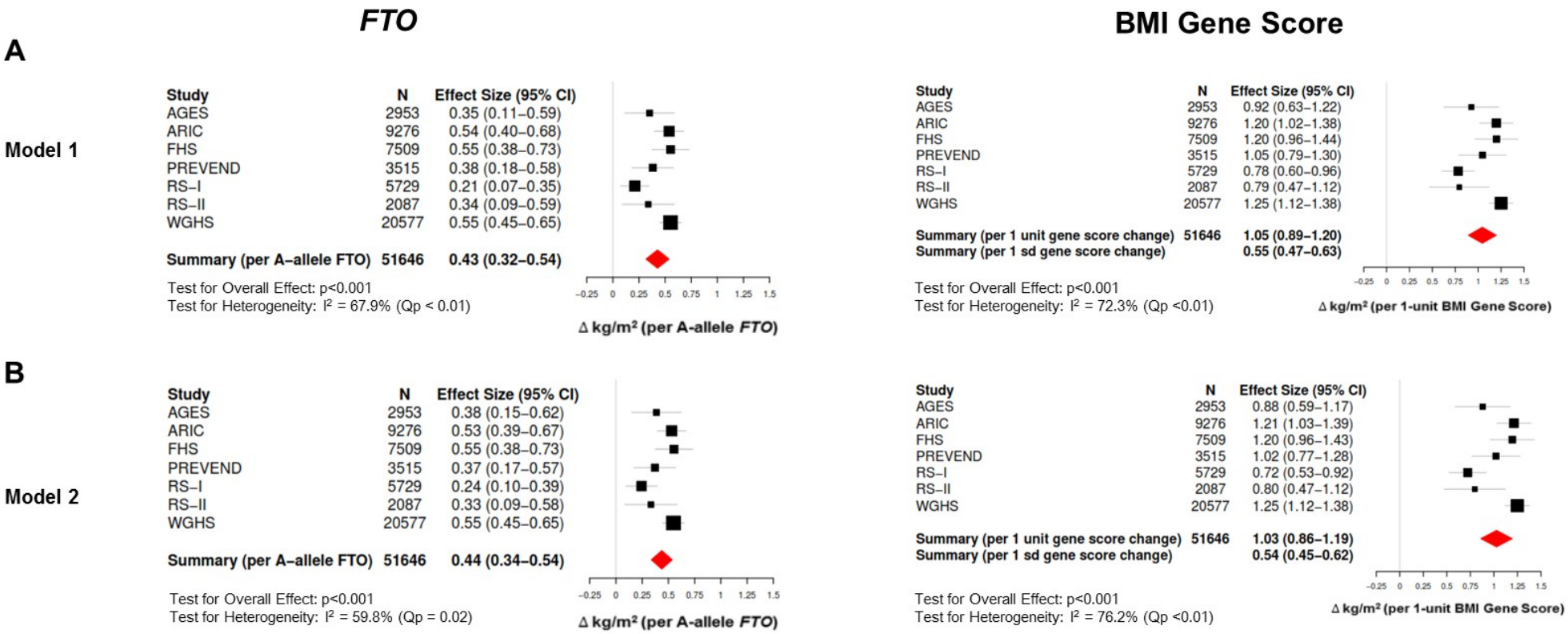
Supplemental Figure 3: Genetic instruments and atrial fibrillation: adjustment for BMI

To assess whether the observed association between genetic instruments (*FTO*, BMI gene score) and incident AF was mediated by BMI, instrument-AF models were adjusted for BMI measured at study enrollment. Shown are study-specific and meta-analyzed pooled estimates for the associations between each genetic instrument (*FTO*, gene score) and risk of incident AF. Models shown are (A) Model 1: age, sex + BMI, (B) Model 2: Model 1 + smoking status, alcohol intake, (C) Model 3: Model 2 + known mediators of the BMI-AF association (systolic and diastolic blood pressure, anti-hypertensive medication use, diabetes mellitus, previous heart failure or coronary heart disease) and (D) Model 4: Model 3 + height. BMI; body mass index. There was minimal heterogeneity of meta-analyzed estimates in all BMI-adjusted models (I^2 = 0% for all models; see Supplementary Table 3 for heterogeneity statistics). Gene score estimate are shown per 1-unit change as well as per 1 standard deviation (SD) change. BMI; body mass index; AF, atrial fibrillation.

Supplemental Figure 1: Meta-regression plot of genetic instrument effect size and mean cohort age



Supplemental Figure 2: Genetic instruments and body mass index

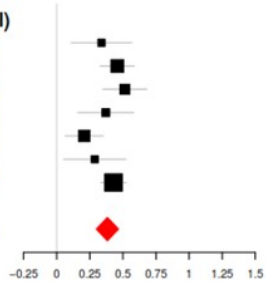


C

Model 3

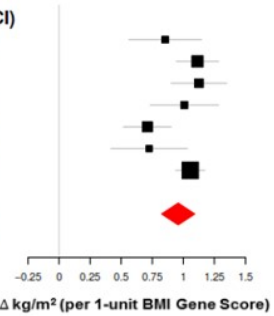
Study	N	Effect Size (95% CI)
AGES	2953	0.34 (0.11–0.57)
ARIC	9276	0.46 (0.33–0.59)
FHS	7509	0.52 (0.35–0.68)
PREVEND	3515	0.37 (0.16–0.58)
RS–I	5729	0.21 (0.06–0.35)
RS–II	2087	0.29 (0.05–0.52)
WGHS	20577	0.43 (0.33–0.52)
Summary (per A–allele FTO)	**51646**	**0.38 (0.30–0.47)**

Test for Overall Effect: p<0.001
Test for Heterogeneity: I^2 = 47.9% (Qp = 0.09)



Study	N	Effect Size (95% CI)
AGES	2953	0.85 (0.56–1.15)
ARIC	9276	1.11 (0.94–1.28)
FHS	7509	1.13 (0.90–1.35)
PREVEND	3515	1.01 (0.73–1.28)
RS–I	5729	0.71 (0.52–0.90)
RS–II	2087	0.72 (0.42–1.03)
WGHS	20577	1.06 (0.94–1.17)
Summary (per 1 unit gene score change)	**51646**	**0.96 (0.83–1.09)**
Summary (per 1 sd gene score change)		**0.50 (0.43–0.57)**

Test for Overall Effect: p<0.001
Test for Heterogeneity: I^2 = 64.9% (Qp =0.01)

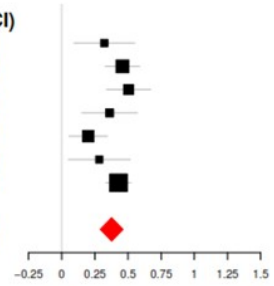


D

Model 4

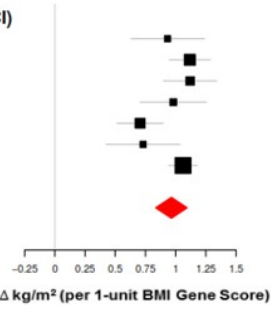
Study	N	Effect Size (95% CI)
AGES	2953	0.32 (0.09–0.55)
ARIC	9276	0.46 (0.33–0.59)
FHS	7509	0.50 (0.34–0.67)
PREVEND	3515	0.36 (0.15–0.57)
RS–I	5729	0.20 (0.05–0.35)
RS–II	2087	0.28 (0.05–0.52)
WGHS	20577	0.43 (0.33–0.52)
Summary (per A–allele FTO)	**51646**	**0.38 (0.29–0.46)**

Test for Overall Effect: p<0.001
Test for Heterogeneity: I^2 = 49.7% (Qp = 0.08)

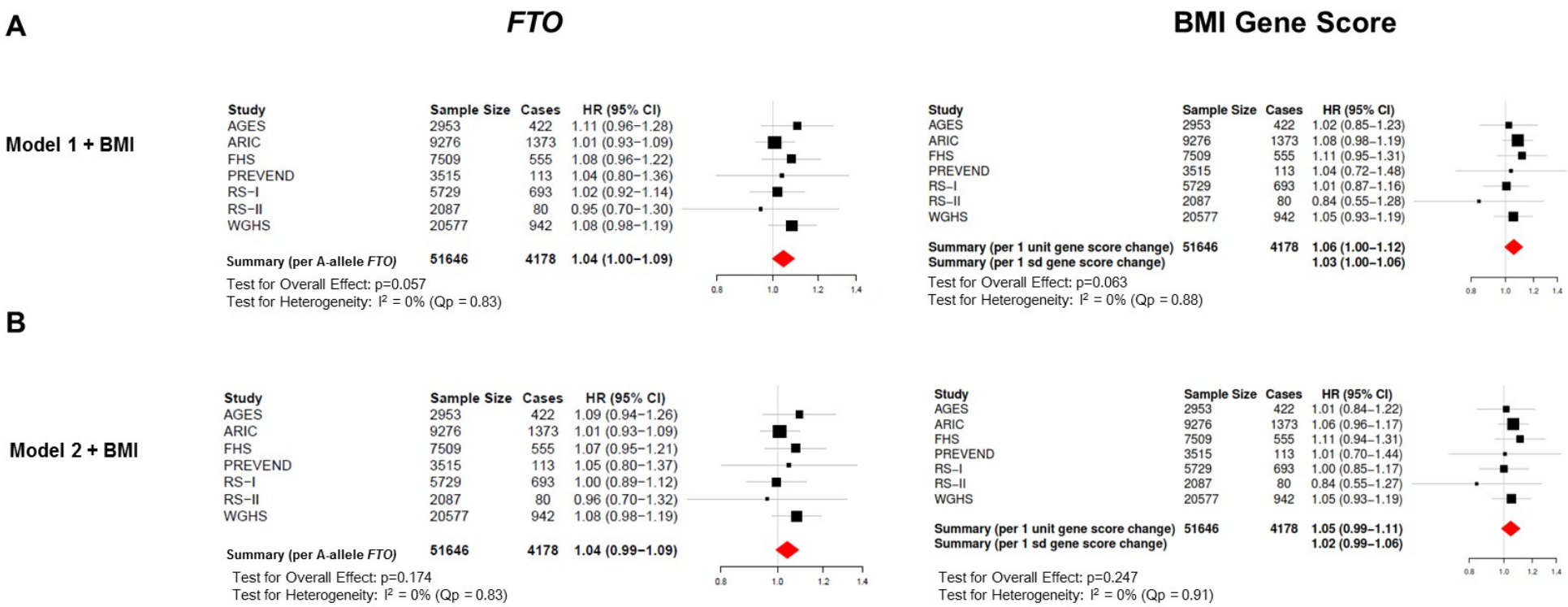


Study	N	Effect Size (95% CI)
AGES	2953	0.93 (0.63–1.24)
ARIC	9276	1.12 (0.95–1.29)
FHS	7509	1.12 (0.90–1.34)
PREVEND	3515	0.98 (0.71–1.25)
RS–I	5729	0.71 (0.52–0.90)
RS–II	2087	0.73 (0.42–1.04)
WGHS	20577	1.06 (0.94–1.18)
Summary (per 1 unit gene score change)	**51646**	**0.96 (0.83–1.10)**
Summary (per 1 sd gene score change)		**0.50 (0.43–0.57)**

Test for Overall Effect: p<0.001
Test for Heterogeneity: I^2 = 64.3% (Qp =0.01)



Supplemental Figure 3: Genetic instruments and atrial fibrillation: adjustment for BMI

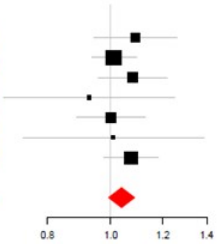


C

Model 3 + BMI

Study	Sample Size	Cases	HR (95% CI)
AGES	2953	422	1.09 (0.94–1.26)
ARIC	9276	1373	1.01 (0.93–1.09)
FHS	7509	555	1.08 (0.96–1.22)
PREVEND	3515	113	0.93 (0.69–1.25)
RS–I	5729	693	1.00 (0.89–1.13)
RS–II	2087	80	1.01 (0.73–1.38)
WGHS	20577	942	1.07 (0.97–1.18)
Summary (per A-allele *FTO*)	**51646**	**4178**	**1.04 (0.99–1.09)**

Test for Overall Effect: p=0.107
Test for Heterogeneity: I^2 = 0% (Qp = 0.82)



Study	Sample Size	Cases	HR (95% CI)
AGES	2953	422	1.03 (0.86–1.25)
ARIC	9276	1373	1.06 (0.96–1.17)
FHS	7509	555	1.11 (0.94–1.30)
PREVEND	3515	113	1.03 (0.69–1.53)
RS–I	5729	693	1.00 (0.85–1.17)
RS–II	2087	80	0.86 (0.56–1.31)
WGHS	20577	942	1.04 (0.92–1.18)
Summary (per 1 unit gene score change)	**51646**	**4178**	**1.05 (0.99–1.11)**
Summary (per 1 sd gene score change)			**1.02 (0.99–1.06)**

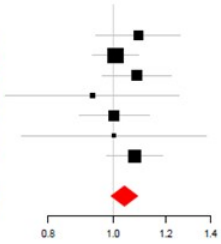
Test for Overall Effect: p=0.118
Test for Heterogeneity: I^2 = 0% (Qp = 0.94)

D

Model 4 + BMI

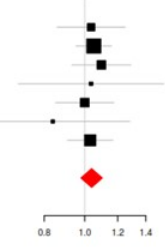
Study	Sample Size	Cases	HR (95% CI)
AGES	2953	422	1.09 (0.94–1.26)
ARIC	9276	1373	1.01 (0.93–1.09)
FHS	7509	555	1.09 (0.96–1.22)
PREVEND	3515	113	0.93 (0.69–1.26)
RS–I	5729	693	1.01 (0.89–1.13)
RS–II	2087	80	1.00 (0.73–1.38)
WGHS	20577	942	1.08 (0.98–1.19)
Summary (per A-allele *FTO*)	**51646**	**4178**	**1.04 (0.99–1.09)**

Test for Overall Effect: p=0.088
Test for Heterogeneity: I^2 = 0% (Qp = 0.81)



Study	Sample Size	Cases	HR (95% CI)
AGES	2953	422	1.04 (0.86–1.25)
ARIC	9276	1373	1.05 (0.95–1.16)
FHS	7509	555	1.10 (0.93–1.29)
PREVEND	3515	113	1.04 (0.69–1.55)
RS–I	5729	693	1.00 (0.85–1.17)
RS–II	2087	80	0.84 (0.55–1.28)
WGHS	20577	942	1.03 (0.91–1.17)
Summary (per 1 unit gene score change)	**51646**	**4178**	**1.04 (0.98–1.10)**
Summary (per 1 sd gene score change)			**1.02 (0.99–1.05)**

Test for Overall Effect: p=0.199
Test for Heterogeneity: I^2 = 0% (Qp = 0.95)



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