

Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk

The International Consortium for Blood Pressure Genome-Wide Association Studies

Blood pressure is a heritable trait¹ influenced by several biological pathways and responsive to environmental stimuli. Over one billion people worldwide have hypertension (≥ 140 mm Hg systolic blood pressure or ≥ 90 mm Hg diastolic blood pressure)². Even small increments in blood pressure are associated with an increased risk of cardiovascular events³. This genome-wide association study of systolic and diastolic blood pressure, which used a multi-stage design in 200,000 individuals of European descent, identified sixteen novel loci: six of these loci contain genes previously known or suspected to regulate blood pressure (*GUCY1A3–GUCY1B3*, *NPR3–C5orf23*, *ADM*, *FURIN–FES*, *GOSR2*, *GNAS–EDN3*); the other ten provide new clues to blood pressure physiology. A genetic risk score based on 29 genome-wide significant variants was associated with hypertension, left ventricular wall thickness, stroke and coronary artery disease, but not kidney disease or kidney function. We also observed associations with blood pressure in East Asian, South Asian and African ancestry individuals. Our findings provide new insights into the genetics and biology of blood pressure, and suggest potential novel therapeutic pathways for cardiovascular disease prevention.

Genetic approaches have advanced the understanding of biological pathways underlying inter-individual variation in blood pressure. For example, studies of rare Mendelian blood pressure disorders have identified multiple defects in renal sodium handling pathways⁴. More recently two genome-wide association studies (GWAS), each of >25,000 individuals of European ancestry, identified 13 loci associated with systolic blood pressure (SBP), diastolic blood pressure (DBP) and hypertension^{5,6}. We now report results of a new meta-analysis of GWAS data that includes staged follow-up genotyping to identify additional blood pressure loci.

Primary analyses evaluated associations between 2.5 million genotyped or imputed single nucleotide polymorphisms (SNPs) and SBP and DBP in 69,395 individuals of European ancestry from 29 studies (Supplementary Materials sections 1–3 and Supplementary Tables 1 and 2). Following GWAS meta-analysis, we conducted a three-stage validation experiment that made efficient use of available genotyping resources, to follow up top signals in up to 133,661 additional individuals of European descent (Supplementary Fig. 1 and Supplementary Materials section 4). Twenty-nine independent SNPs at 28 loci were significantly associated with SBP, DBP, or both in the meta-analysis combining discovery and follow-up data (Fig. 1, Table 1, Supplementary Figs 2, 3 and Supplementary Tables 3–5). All 29 SNPs attained association $P < 5 \times 10^{-9}$, an order of magnitude beyond the standard genome-wide significance level for a single-stage experiment (Table 1).

Sixteen of these 29 associations were novel (Table 1). Two associations were near the *FURIN* and *GOSR2* genes; prior targeted analyses of variants in these genes suggested they may be blood pressure loci^{7,8}. At the *CACNB2* locus we validated association for a previously reported⁶ SNP, rs4373814, and detected a novel independent association for rs1813353 (pairwise $r^2 = 0.015$ in HapMap CEU). Of our 13 previously reported associations^{5,6}, only the association at *PLCD3*

was not supported by the current results (Supplementary Table 4). Some of the associations are in or near genes involved in pathways known to influence blood pressure (*NPR3*, *GUCY1A3–GUCY1B3*, *ADM*, *GNAS–EDN3*, *NPPA–NPPB* and *CYP17A1*; Supplementary Fig. 4). Twenty-two of the 28 loci did not contain genes that were a priori strong biological candidates.

As expected from prior blood pressure GWAS results, the effects of the novel variants on SBP and DBP were small (Fig. 1 and Table 1). For all variants, the observed directions of effects were concordant for SBP, DBP and hypertension (Fig. 1, Table 1 and Supplementary Fig. 3). Among the genes at the genome-wide significant loci, only *CYP17A1*, previously implicated in Mendelian congenital adrenal hyperplasia and hypertension, is known to harbour rare variants that have large effects on blood pressure⁹.

We performed several analyses to identify potential causal alleles and mechanisms. First, we looked up the 29 genome-wide significant index SNPs and their close proxies ($r^2 > 0.8$) among *cis*-acting expression SNP (eSNP) results from multiple tissues (Supplementary Materials section 5). For 13/29 index SNPs, we found an association between nearby eSNP variants and the expression levels of at least one gene transcript ($10^{-4} > P > 10^{-51}$; Supplementary Table 6). In five cases, the index blood pressure SNP and the best eSNP from a genome-wide survey were identical, highlighting potential mediators of the SNP–blood pressure associations.

Second, because changes in protein sequence are a priori strong functional candidates, we sought non-synonymous coding SNPs that were in high linkage disequilibrium ($r^2 > 0.8$) with the 29 index SNPs. We identified such SNPs at eight loci (Table 1, Supplementary Materials section 6 and Supplementary Table 7). In addition we performed analyses testing for differences in genetic effect according to body mass index (BMI) or sex, and analyses of copy number variants, pathway enrichment and metabolomic data, but we did not find any statistically significant results (Supplementary Materials sections 7–9 and Supplementary Tables 8–10).

We evaluated whether the blood pressure variants we identified in individuals of European ancestry were associated with blood pressure in individuals of East Asian ($N = 29,719$), South Asian ($N = 23,977$) and African ($N = 19,775$) ancestries (Table 1 and Supplementary Tables 11–13). We found significant associations in individuals of East Asian ancestry for SNPs at nine loci and in individuals of South Asian ancestry for SNPs at six loci; some have been reported previously (Supplementary Tables 12 and 15). The lack of significant association for individual SNPs may reflect small sample sizes, differences in allele frequencies or linkage disequilibrium patterns, imprecise imputation for some ancestries using existing reference samples, or a genuinely different underlying genetic architecture. Because of limited power to detect effects of individual variants in the smaller non-European samples, we created genetic risk scores for SBP and DBP incorporating all 29 blood pressure variants weighted according to effect sizes observed in the European samples. In each non-European ancestry group, risk scores were strongly associated with SBP ($P = 1.1 \times 10^{-40}$ in East Asian, $P = 2.9 \times 10^{-13}$ in South Asian, $P = 9.8 \times 10^{-4}$ in African

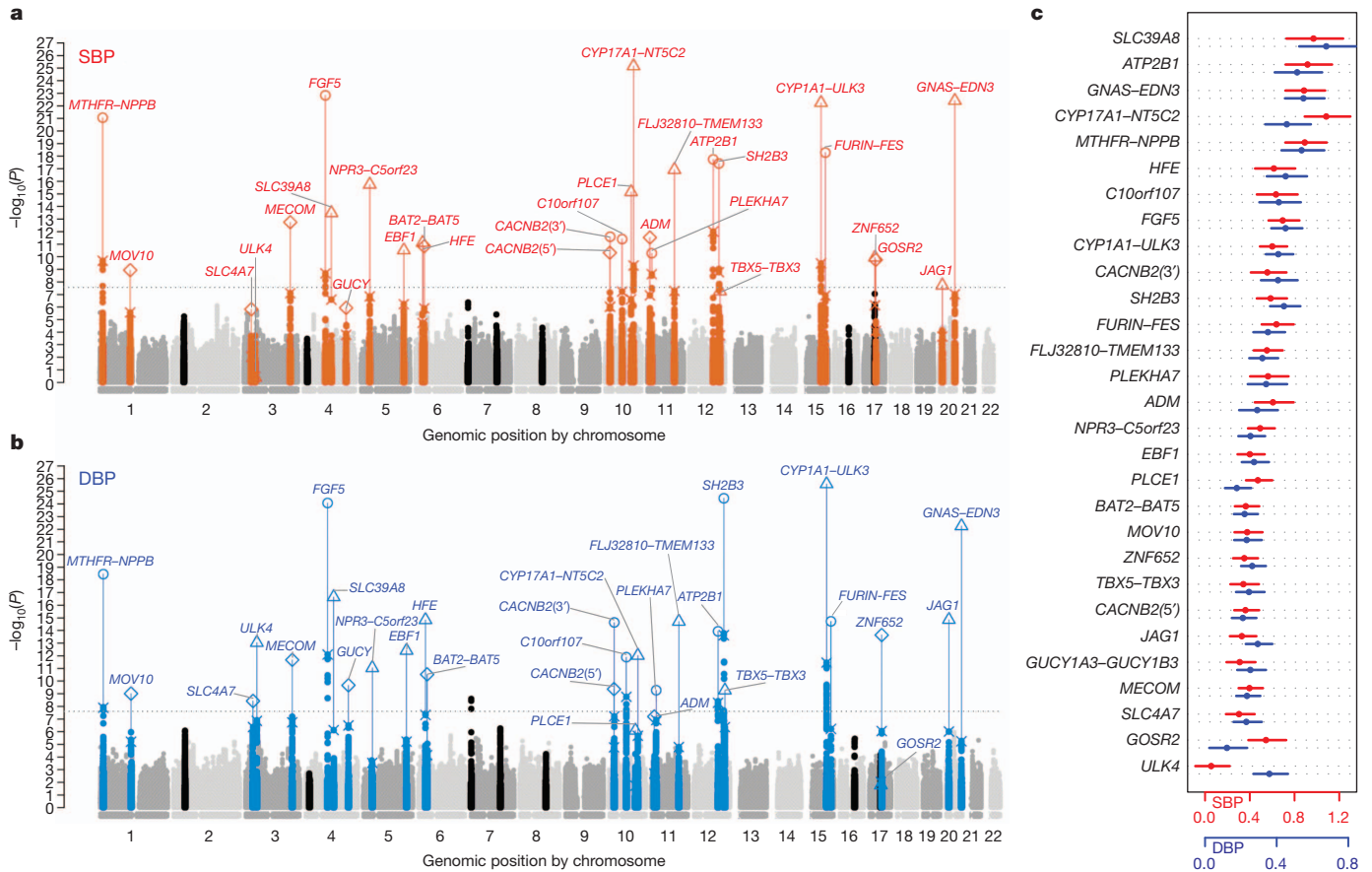


Figure 1 | Genome-wide $-\log_{10} P$ -value plots and effects for significant loci. a, b, Genome-wide $-\log_{10} P$ -value plots are shown for SBP (a) and DBP (b). SNPs within loci reaching genome-wide significance are labelled in red for SBP and blue for DBP (± 2.5 Mb of lowest P value) and lowest P values in the initial genome-wide analysis as well as the results of analysis including validation data are labelled separately. The lowest P values in the initial GWAS are denoted with a X. The range of different sample sizes in the final meta-

ancestry individuals) and DBP ($P = 2.9 \times 10^{-48}$, $P = 9.5 \times 10^{-15}$ and $P = 5.3 \times 10^{-5}$, respectively; Supplementary Table 13).

We also created a genetic risk score to assess association of the variants in aggregate with hypertension and with clinical measures of hypertensive complications including left ventricular mass, left ventricular wall thickness, incident heart failure, incident and prevalent stroke, prevalent coronary artery disease (CAD), kidney disease and measures of kidney function, using results from other GWAS consortia (Table 2, Supplementary Materials sections 10, 11 and Supplementary Table 14). The risk score was weighted using the average of SBP and DBP effects for the 29 SNPs. In an independent sample of 23,294 women¹⁰, an increase of one standard deviation in the genetic risk score was associated with a 23% increase in the odds of hypertension (95% confidence interval 19–28%; Table 2 and Supplementary Table 14). Among individuals in the top decile of the risk score, the prevalence of hypertension was 29% compared with 16% in the bottom decile (odds ratio 2.09, 95% confidence interval 1.86–2.36). Similar results were observed in an independent hypertension case-control sample (Table 2). In our study, individuals in the top compared to bottom quintiles of genetic risk score differed by 4.6 mm Hg SBP and 3.0 mm Hg DBP, differences that approach population-averaged blood pressure treatment effects for a single antihypertensive agent¹¹. Epidemiological data have shown that differences in SBP and DBP of this magnitude, across the population range of blood pressure, are associated with an increase in cardiovascular disease risk³. Consistent with this and in line with findings from randomized trials

analysis including the validation data are indicated as: circle (96,000–140,000), triangle ($>140,000$ –180,000) and diamond ($>180,000$ –220,000). SNPs near unconfirmed loci are in black. The horizontal dotted line is $P = 2.5 \times 10^{-8}$. GUCY denotes GUCY1A3–GUCY1B3. c, Effect size estimates and 95% confidence bars per blood-pressure-increasing allele of the 29 significant variants for SBP (red) and DBP (blue). Effect sizes are expressed in mm Hg per allele.

of blood-pressure-lowering medication in hypertensive patients^{12,13}, the genetic risk score was positively associated with left ventricular wall thickness ($P = 6.0 \times 10^{-6}$), occurrence of stroke ($P = 3.3 \times 10^{-5}$) and CAD ($P = 8.1 \times 10^{-29}$). The same genetic risk score was not, however, significantly associated with chronic kidney disease or measures of kidney function, even though these renal outcomes were available in a similar sample size as for the other outcomes (Table 2). The absence of association with kidney phenotypes could be explained by a weaker causal relationship between blood pressure and kidney phenotypes than with CAD and stroke. This finding is consistent with the mismatch between observational data that show a positive association of blood pressure with kidney disease, and clinical trial data that show inconsistent evidence of a benefit from blood pressure lowering on kidney disease prevention in patients with hypertension¹⁴. Thus, several lines of evidence converge to indicate that blood pressure elevation may in part be a consequence rather than a cause of sub-clinical kidney disease.

Our discovery meta-analysis (Supplementary Fig. 2) suggests an excess of modestly significant ($10^{-5} < P < 10^{-2}$) associations probably arising from common blood pressure variants of small effect. By dividing our principal GWAS data set into non-overlapping discovery ($N \approx 56,000$) and validation ($N \approx 14,000$) subsets, we found robust evidence for the existence of such undetected common variants (Supplementary Fig. 5 and Supplementary Materials section 12). We estimate¹⁵ that there are 116 (95% confidence interval 57–174) independent blood pressure variants with effect sizes similar to those

Table 1 | Summary association results for 29 blood pressure SNPs

Locus	Index SNP	Chr	Position	CA/ NCA	CAF	nsSNP	eSNP	SBP			DBP			HTN	
								Beta	P value	Effect in EA/SA/A	Beta	P value	Effect in EA/SA/A	Beta	P value
<i>MOV10</i>	rs2932538	1	113,018,066	G/A	0.75	Y(p)	Y(p)	0.388	1.2×10^{-9}	+/-/+	0.240	9.9×10^{-10}	+/*/+	0.049	2.9×10^{-7}
<i>SLC4A7</i>	rs13082711	3	27,512,913	T/C	0.78	Y(p)	Y(p)	-0.315	1.5×10^{-6}	-/-/+	-0.238	3.8×10^{-9}	-/-/+	-0.035	3.6×10^{-4}
<i>MECOM</i>	rs419076	3	170,583,580	T/C	0.47	-	-	0.409	1.8×10^{-13}	+/*/+	0.241	2.1×10^{-12}	+/*/+	0.031	3.1×10^{-4}
<i>SLC39A8</i>	rs13107325	4	103,407,732	T/C	0.05	Y	Y(+)	-0.981	3.3×10^{-14}	?/+/+	-0.684	2.3×10^{-17}	?/+/+	-0.105	4.9×10^{-7}
<i>GUCY1A3- GUCY1B3</i>	rs13139571	4	156,864,963	C/A	0.76	-	-	0.321	1.2×10^{-6}	+/-/+	0.260	2.2×10^{-10}	+/*/+	0.042	2.5×10^{-5}
<i>NPR3- C5orf23</i>	rs1173771	5	32,850,785	G/A	0.60	-	-	0.504	1.8×10^{-16}	+/*/+	0.261	9.1×10^{-12}	+/*/+	0.062	3.2×10^{-10}
<i>EBF1</i>	rs11953630	5	157,777,980	T/C	0.37	-	-	-0.412	3.0×10^{-11}	+/*/+	-0.281	3.8×10^{-13}	+/*/+	-0.052	1.7×10^{-7}
<i>HFE</i>	rs1799945	6	26,199,158	G/C	0.14	Y	-	0.627	7.7×10^{-12}	+/*/+	0.457	1.5×10^{-15}	+/*/+	0.095	1.8×10^{-10}
<i>BAT2-BAT5</i>	rs805303	6	31,724,345	G/A	0.61	Y(p)	Y(+)	0.376	1.5×10^{-11}	-/-/?	0.228	3.0×10^{-11}	-/-/+	0.054	1.1×10^{-10}
<i>CACNB2(5')</i>	rs4373814	10	18,459,978	G/C	0.55	-	-	-0.373	4.8×10^{-11}	+/*/+	-0.218	4.4×10^{-10}	+/*/+	-0.046	8.5×10^{-8}
<i>PLCE1</i>	rs932764	10	95,885,930	G/A	0.44	-	-	0.484	7.1×10^{-16}	+/*/+	0.185	8.1×10^{-7}	+/*/+	0.055	9.4×10^{-9}
<i>ADM</i>	rs7129220	11	10,307,114	G/A	0.89	-	-	-0.619	3.0×10^{-12}	?/+/+	-0.299	6.4×10^{-8}	?/+/+	-0.044	1.1×10^{-3}
<i>FLJ32810- TMEM133</i>	rs633185	11	100,098,748	G/C	0.28	-	-	-0.565	1.2×10^{-17}	+/*/+	-0.328	2.0×10^{-15}	+/*/+	-0.070	5.4×10^{-11}
<i>FURIN-FES</i>	rs2521501	15	89,238,392	T/A	0.31	-	Y(-)	0.650	5.2×10^{-19}	+/*/+	0.359	1.9×10^{-15}	+/*/+	0.059	7.0×10^{-7}
<i>GOSR2</i>	rs17608766	17	42,368,270	T/C	0.86	-	Y(+)	-0.556	1.1×10^{-10}	+/*/+	-0.129	0.017	+/*/+	-0.025	0.08
<i>JAG1</i>	rs1327235	20	10,917,030	G/A	0.46	-	-	0.340	1.9×10^{-8}	+/*/+	0.302	1.4×10^{-15}	+/*/+	0.034	4.6×10^{-4}
<i>GNAS-EDN3</i>	rs6015450	20	57,184,512	G/A	0.12	Y(p)	-	0.896	3.9×10^{-23}	?/+/+	0.557	5.6×10^{-23}	?/+/+	0.110	4.2×10^{-14}
<i>MTHFR- NPPB</i>	rs17367504	1	11,785,365	G/A	0.15	-	Y(-/r)	-0.903	8.7×10^{-22}	+/*/+	-0.547	3.5×10^{-19}	+/*/+	-0.103	2.3×10^{-10}
<i>ULK4</i>	rs3774372	3	41,852,418	T/C	0.83	Y	Y(r/p)	-0.067	0.39	-/-/+	-0.367	9.0×10^{-14}	+/*/+	-0.017	0.18
<i>FGF5</i>	rs1458038	4	81,383,747	T/C	0.29	-	-	0.706	1.5×10^{-23}	+/*/+	0.457	8.5×10^{-25}	+/*/+	0.072	1.9×10^{-7}
<i>CACNB2(3')</i>	rs1813353	10	18,747,454	T/C	0.68	-	-	0.569	2.6×10^{-12}	+/*/+	0.415	2.3×10^{-15}	+/*/+	0.078	6.2×10^{-10}
<i>C10orf107</i>	rs4590817	10	63,137,559	G/C	0.84	-	Y(r)	0.646	4.0×10^{-12}	-/+/-	0.419	1.3×10^{-12}	-/+/-	0.096	9.8×10^{-9}
<i>CYP17A1- NT5C2</i>	rs11191548	10	104,836,168	T/C	0.91	-	Y(-)	1.095	6.9×10^{-26}	+/*/+	0.464	9.4×10^{-13}	+/*/+	0.097	1.4×10^{-5}
<i>PLEKHA7</i>	rs381815	11	16,858,844	T/C	0.26	-	-	0.575	5.3×10^{-11}	+/*/+	0.348	5.3×10^{-10}	+/*/+	0.062	3.4×10^{-6}
<i>ATP2B1</i>	rs17249754	12	88,584,717	G/A	0.84	-	-	0.928	1.8×10^{-18}	+/*/+	0.522	1.2×10^{-14}	+/*/+	0.126	1.1×10^{-14}
<i>SH2B3</i>	rs3184504	12	110,368,991	T/C	0.47	Y	Y(+)	0.598	3.8×10^{-18}	-/+/-	0.448	3.6×10^{-25}	-/+/-	0.056	2.6×10^{-6}
<i>TBX5-TBX3</i>	rs10850411	12	113,872,179	T/C	0.7	-	-	0.354	5.4×10^{-8}	-/+/-	0.253	5.4×10^{-10}	-/+/-	0.045	5.2×10^{-6}
<i>CYP1A1- ULK3</i>	rs1378942	15	72,864,420	C/A	0.35	-	Y(+)	0.613	5.7×10^{-23}	+/*/+	0.416	2.7×10^{-26}	+/*/+	0.073	1.0×10^{-8}
<i>ZNF652</i>	rs12940887	17	44,757,806	T/C	0.38	-	Y(-)	0.362	1.8×10^{-10}	+/*/+	0.27	2.3×10^{-14}	+/*/+	0.046	1.2×10^{-7}

Summary association statistics, based on combined discovery and follow-up data, for 29 independent SNPs in individuals of European ancestry are shown. New genome-wide significant findings (17 SNPs) are presented in the top half of the table, data on 12 previously published signals are presented in the lower half. Y indicates that the blood pressure index SNP is a non-synonymous (ns)SNP, Y(p) indicates a proxy SNP is a nsSNP. Y(+/-) indicates that the blood pressure index SNP is the strongest known eSNP for a transcript; Y(-) indicates that the blood pressure index SNP is an eSNP but not the strongest known eSNP for any transcript. Y(r) indicates that the blood pressure index SNP is the strongest known eSNP in a targeted real-time PCR experiment. Y(p) indicates that a proxy SNP ($r^2 > 0.8$) to a blood pressure SNP is an eSNP but not the strongest known eSNP. Observed effect directions in East Asian (EA), South Asian (SA) and African (A) ancestry individuals are coded + or - if concordant or discordant with directions in European ancestry results. Effect size estimates (beta) correspond to mm Hg per coded allele for SBP and DBP and ln(odds) per coded allele for hypertension (HTN). CA, coded allele; CAF, coded allele frequency; NCA, non-coded allele. ? denotes missing data. Genomic positions use NCBI Build 36 coordinates.

* Significant, controlling the FDR at 5% over 58 tests per ancestry (Supplementary Tables 5 and 12).

reported here, which collectively can explain ~2.2% of the phenotypic variance for SBP and DBP, compared with 0.9% explained by the 29 associations discovered thus far (Supplementary Fig. 6 and Supplementary Materials section 13).

Most of the 28 blood pressure loci harbour multiple genes (Supplementary Table 15 and Supplementary Fig. 4), and although substantial research is required to identify the specific genes and variants responsible for these associations, several loci contain highly plausible biological candidates. The *NPPA* and *NPPB* genes at the *MTHFR-NPPB* locus encode precursors for atrial- and B-type natriuretic peptides (ANP, BNP), and previous work has identified SNPs—modestly correlated with our index SNP at this locus—which are associated with plasma ANP, BNP and blood pressure¹⁶. We found the index SNP at this locus was associated with opposite effects on blood pressure and on ANP/BNP levels, consistent with a model in which the variants act through increased ANP/BNP production to lower blood pressure¹⁶ (Supplementary Materials section 14).

Two other loci identified in the current study harbour genes involved in natriuretic peptide and related nitric oxide signalling pathways^{17,18}, both of which act to regulate cyclic guanosine monophosphate. The first locus contains *NPR3*, which encodes the natriuretic peptide clearance receptor (NPR-C). *NPR3* knockout mice exhibit reduced clearance of circulating natriuretic peptides and lower blood pressure¹⁹. The second locus includes *GUCY1A3* and *GUCY1B3*, encoding the α and β subunits of soluble guanylate cyclase; knockout of either gene in murine models results in hypertension²⁰.

Another locus contains *ADM*—encoding adrenomedullin—which has natriuretic, vasodilatory and blood-pressure-lowering properties²¹. At the *GNAS-EDN3* locus, *ZNF831* is closest to the index SNP, but *GNAS* and *EDN3* are two nearby compelling biological candidates (Supplementary Fig. 4 and Supplementary Table 15).

We identified two loci with plausible connections to blood pressure via genes implicated in renal physiology or kidney disease. At the first locus, *SLC4A7* is an electro-neutral sodium bicarbonate co-transporter expressed in the nephron and in vascular smooth muscle²². At the second locus, *PLCE1* (phospholipase-C-epsilon-1 isoform) is important for normal podocyte development in the glomerulus; sequence variation in *PLCE1* has been implicated in familial nephrotic syndromes and end-stage kidney disease²³.

Missense variants in two genes involved in metal ion transport were associated with blood pressure in our study. The first encodes a His/Asp change at amino acid 63 (H63D) in *HFE* and is a low-penetrance allele for hereditary hemochromatosis²⁴. The second is an Ala/Thr polymorphism located in exon 7 of *SLC39A8*, which encodes a zinc transporter that also transports cadmium and manganese²⁵. The same allele of *SLC39A8* associated with blood pressure in our study has recently been associated with high-density lipoprotein cholesterol levels²⁶ and BMI²⁷ (Supplementary Table 15).

We have shown that 29 independent genetic variants influence blood pressure in people of European ancestry. The variants reside in 28 loci, 16 of which were novel, and we confirmed association of several of them in individuals of non-European ancestry. A risk score

Table 2 | Genetic risk score and cardiovascular outcome association results

Phenotype	Source	Effect	s.e.	P value	No. SNPs	Contrast top versus bottom		N case/control or total
						Quintiles	Deciles	
Blood pressure phenotypes								
SBP (mm Hg)	WGHS	1.645	0.098	(a) 6.5×10^{-63}	29	4.61	5.77	(a) 23,294
DBP (mm Hg)	WGHS	1.057	0.067	(a) 8.4×10^{-57}	29	2.96	3.71	(a) 23,294
Prevalent hypertension	WGHS	0.211	0.018	(b) 3.1×10^{-33}	29	1.80	2.09	(b) 5,018/18,276
Prevalent hypertension	BRIGHT	0.287	0.031	(b) 7.7×10^{-21}	29	2.23	2.74	(b) 2,406/1,990
Dichotomous endpoints								
Incident heart failure	CHARGE-HF	0.035	0.021	(c) 0.10	29	1.10	1.13	(c) 2,526/18,400
Incident stroke	NEURO-CHARGE	0.103	0.028	(c) 0.0002	28	1.34	1.44	(c) 1,544/18,058
Prevalent stroke	SCG	0.075	0.037	(b) 0.05	29	1.23	1.30	(b) 1,473/1,482
Stroke (combined, incident and prevalent)	CHARGE & SCG	NA	NA	NA 3.3×10^{-5}	NA	NA	NA	NA 3,017/19,540
Prevalent CAD	CARDIoGRAM	0.092	0.010	(b) 1.6×10^{-19}	28	1.29	1.38	(b) 22,233/64,726
Prevalent CAD	C4D ProCARDIS	0.132	0.022	(b) 2.2×10^{-9}	29	1.45	1.59	(b) 5,720/4,381
Prevalent CAD	C4D HPS	0.083	0.027	(b) 0.002	29	1.26	1.34	(b) 2,704/2,804
Prevalent CAD (combined)	CARDIoGRAM & C4D	0.100	0.009	(b) 8.1×10^{-29}	29	1.32	1.42	(b) 30,657/71,911
Prevalent chronic kidney disease	CKDGen	0.014	0.015	(b) 0.35	29	1.04	1.05	(b) 5,807/61,286
Prevalent microalbuminuria	CKDGen	0.008	0.019	(b) 0.68	29	1.02	1.03	(b) 3,698/27,882
Continuous measures of target organ damage								
Left ventricular mass (g)	EchoGen	0.822	0.317	(a) 0.01	29	2.30	2.89	(a) 12,612
Left ventricular wall thickness (cm)	EchoGen	0.009	0.002	(a) 6.0×10^{-6}	29	0.03	0.03	(a) 12,612
Serum creatinine	KidneyGen	-0.001	0.001	(d) 0.24	29	1.00	1.00	(d) 23,812
eGFR (four-parameter MDRD equation)	CKDGen	-0.0001	0.0009	(d) 0.93	29	1.00	1.00	(d) 67,093
Urinary albumin/creatinine ratio	CKDGen	0.005	0.007	(d) 0.43	29	1.01	1.02	(d) 31,580

Association of genetic risk score (using all 29 SNPs at 28 loci, parameterized using the average of SBP and DBP effects (= (SBP effect + DBP effect)/2) from the discovery analysis), tested in results from other GWAS consortia. (a) Units are the unit of phenotypic measurement, either per standard deviation (s.d.) of genetic risk score, or as a difference between top/bottom quintiles or deciles. (b) Units are ln(odds) per s.d. of genetic risk score, or odds ratio between top/bottom quintiles or deciles. (c) Units are ln(hazard) per s.d. of genetic risk score, or hazard ratio between top/bottom quintiles or deciles. (d) Units are ln(phenotype) per s.d. of genetic risk score, or phenotypic ratio between top/bottom quintiles or deciles. s.e., standard error. SCG, UK-US Stroke Collaborative Group; see Supplementary Materials sections 1.79 and 11 for further detail on consortia and studies.

derived from the 29 variants was significantly associated with blood-pressure-related organ damage and clinical cardiovascular disease, but not kidney disease. These loci improve our understanding of the genetic architecture of blood pressure, provide new biological insights into blood pressure control and may identify novel targets for the treatment of hypertension and the prevention of cardiovascular disease.

Note added in proof: Since this manuscript was submitted, Kato *et al.* published a blood pressure GWAS in East Asians that identified a SNP highly correlated to the SNP we report at the *NPR3/C5orf23* locus²⁸.

METHODS SUMMARY

Supplementary Materials provide complete methods and include the following sections: study recruitment and phenotyping, adjustment for antihypertensive medications, genotyping, data quality control, genotype imputation, within-cohort association analyses, meta-analyses of discovery and validation stages, stratified analyses by sex and BMI, identification of eSNPs and non-synonymous SNPs, metabolomic and lipidomic analyses, CNV analyses, pathway analyses, analyses for non-European ancestries, association of a risk score with hypertension and cardiovascular disease, estimation of numbers of undiscovered variants, measurement of natriuretic peptides, and brief literature reviews and GWAS database lookups of all validated blood pressure loci. Full GWAS results for ≈ 2.5 million SNPs are also provided.

Received 16 August 2010; accepted 28 July 2011.

Published online 11 September 2011.

- Levy, D. *et al.* Evidence for a gene influencing blood pressure on chromosome 17. Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham heart study. *Hypertension* **36**, 477–483 (2000).
- Kearney, P. M. *et al.* Global burden of hypertension: analysis of worldwide data. *Lancet* **365**, 217–223 (2005).
- Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360**, 1903–1913 (2002).
- Lifton, R. P., Gharavi, A. G. & Geller, D. S. Molecular mechanisms of human hypertension. *Cell* **104**, 545–556 (2001).
- Newton-Cheh, C. *et al.* Genome-wide association study identifies eight loci associated with blood pressure. *Nature Genet.* **41**, 666–676 (2009).
- Levy, D. *et al.* Genome-wide association study of blood pressure and hypertension. *Nature Genet.* **41**, 677–687 (2009).

- Meyer, T. E. *et al.* *GOSR2* Lys67Arg is associated with hypertension in whites. *Am. J. Hypertens.* **22**, 163–168 (2009).
- Li, N. *et al.* Associations between genetic variations in the *FURIN* gene and hypertension. *BMC Med. Genet.* **11**, 124 (2010).
- Mussig, K. *et al.* 17α -hydroxylase/17,20-lyase deficiency caused by a novel homozygous mutation (Y27Stop) in the cytochrome CYP17 gene. *J. Clin. Endocrinol. Metab.* **90**, 4362–4365 (2005).
- Ridker, P. M. *et al.* Rationale, design, and methodology of the Women's Genome Health Study: a genome-wide association study of more than 25,000 initially healthy american women. *Clin. Chem.* **54**, 249–255 (2008).
- Burt, V. L. *et al.* Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension* **26**, 60–69 (1995).
- Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Br. Med. J.* **336**, 1121–1123 (2008).
- Law, M. R., Morris, J. K. & Wald, N. J. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *Br. Med. J.* **338**, b1665 (2009).
- Lewis, J. B. Blood pressure control in chronic kidney disease: is less really more? *J. Am. Soc. Nephrol.* **21**, 1086–1092 (2010).
- Park, J. H. *et al.* Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. *Nature Genet.* **42**, 570–575 (2010).
- Newton-Cheh, C. *et al.* Association of common variants in *NPPA* and *NPPB* with circulating natriuretic peptides and blood pressure. *Nature Genet.* **41**, 348–353 (2009).
- Schenk, D. B. *et al.* Purification and subunit composition of atrial natriuretic peptide receptor. *Proc. Natl Acad. Sci. USA* **84**, 1521–1525 (1987).
- Schmidt, H. H. & Walter, U. NO at work. *Cell* **78**, 919–925 (1994).
- Matsukawa, N. *et al.* The natriuretic peptide clearance receptor locally modulates the physiological effects of the natriuretic peptide system. *Proc. Natl Acad. Sci. USA* **96**, 7403–7408 (1999).
- Friebe, A., Mergia, E., Dangel, O., Lange, A. & Koesling, D. Fatal gastrointestinal obstruction and hypertension in mice lacking nitric oxide-sensitive guanylyl cyclase. *Proc. Natl Acad. Sci. USA* **104**, 7699–7704 (2007).
- Ishimitsu, T., Ono, H., Minami, J. & Matsuoka, H. Pathophysiologic and therapeutic implications of adrenomedullin in cardiovascular disorders. *Pharmacol. Ther.* **111**, 909–927 (2006).
- Pushkin, A. *et al.* Cloning, tissue distribution, genomic organization, and functional characterization of NBC3, a new member of the sodium bicarbonate cotransporter family. *J. Biol. Chem.* **274**, 16569–16575 (1999).
- Hinkes, B. *et al.* Positional cloning uncovers mutations in *PLCE1* responsible for a nephrotic syndrome variant that may be reversible. *Nature Genet.* **38**, 1397–1405 (2006).

24. Feder, J. N. *et al.* A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genet.* **13**, 399–408 (1996).
25. He, L., Wang, B., Hay, E. B. & Nebert, D. W. Discovery of ZIP transporters that participate in cadmium damage to testis and kidney. *Toxicol. Appl. Pharmacol.* **238**, 250–257 (2009).
26. Teslovich, T. M. *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707–713 (2010).
27. Speliotes, E. K. *et al.* Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nature Genet.* **42**, 937–948 (2010).
28. Kato, N. *et al.* Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. *Nature Genet.* **43**, 531–538 (2011).

Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Acknowledgements A number of the participating studies and authors are members of the CHARGE and Global BPgen consortia. Many funding mechanisms by NIH/NHLBI, European and private funding agencies contributed to this work and a full list is provided in section 21 of the Supplementary Materials.

Author Contributions Full author contributions and roles are listed in Supplementary Materials section 19.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at www.nature.com/nature. Correspondence and requests for materials should be addressed to A.C. (aravinda@jhmi.edu), M.C. (m.j.caulfield@qmul.ac.uk), D.L. (levy@nhlbi.nih.gov), P.B.M. (p.b.munroe@qmul.ac.uk), C.N.-C. (cnewtonch@chgr.mgh.harvard.edu).

George B. Ehret^{1,2,3*}, Patricia B. Munroe^{4*}, Kenneth M. Rice^{5*}, Murielle Bochud^{2*}, Andrew D. Johnson^{6,7*}, Daniel I. Chasman^{8,9*}, Albert V. Smith^{10,11*}, Martin D. Tobin¹², Germaine C. Verwoert^{13,14,15}, Shih-Jen Hwang^{6,7,16}, Vasyli Pihur¹, Peter Vollenweider¹⁷, Paul F. O'Reilly¹⁸, Najaf Amin¹³, Jennifer L. Bragg-Gresham¹⁹, Alexander Teumer²⁰, Nicole L. Glazer²¹, Lenore Launer²², Jing Hua Zhao²³, Yuriy Aulchenko¹³, Simon Heath²⁴, Sirm Söber²⁵, Afshin Parsa²⁶, Jian'an Luan²³, Pankaj Arora²⁷, Abbas Dehghan^{13,14,15}, Feng Zhang²⁸, Gavin Lucas²⁹, Andrew A. Hicks³⁰, Anne U. Jackson³¹, John F. Peden³², Toshiko Tanaka³³, Sarah H. Wild³⁴, Igor Rudan^{35,36}, Wilmar Igl³⁷, Yuri Milanese³⁸, Alex N. Parker³⁸, Cristiano Fava^{39,40}, John C. Chambers^{18,41}, Ervin R. Fox⁴², Meena Kumari⁴³, Min Jin Go⁴⁴, Pim van der Harst⁴⁵, Wen Hong Linda Kao⁴⁶, Marketa Sjögren³⁹, D. G. Vinay⁴⁷, Myriam Alexander⁴⁸, Yasuharu Tabara⁴⁹, Sue Shaw-Hawkins⁵⁰, Peter H. Whincup⁵⁰, Yongmei Liu⁵¹, Gang Shi⁵², Johanna Kuusisto⁵³, Bamidele Tayo⁵⁴, Mark Seielstad^{55,56}, Xuelling Sim⁵⁷, Khanh-Dung Hoang Nguyen¹, Terho Lehtimäki⁵⁸, Giuseppe Matullo^{59,60}, Ying Wu⁶¹, Tom R. Gaunt⁶², N. Charlotte Omland-Moret^{63,64}, Matthew N. Cooper⁶⁵, Carl G. P. Platou⁶⁶, Elin Org²⁵, Rebecca Hardy⁶⁷, Santosh Dahgam⁶⁸, Jutta Palmen⁶⁹, Veronique Vitart⁷⁰, Peter S. Braund^{71,72}, Tatiana Kutznetsova⁷³, Cuno S. P. M. Uiterwaal⁶³, Adebowale Adeyemo⁷⁴, Walter Palmas⁷⁵, Harry Campbell³⁵, Barbara Ludwig⁷⁶, Maciej Tomaszewski^{71,72}, Ioanna Tzoulaki^{77,78}, Nicholette D. Palmer⁷⁹, CARDIOGRAM consortium†, CKDGen Consortium†, KidneyGen Consortium†, EchoGen Consortium†, CHARGE-HF consortium†, Thor Apherlund^{10,11}, Melissa Garcia²², Yen-Pei C. Chang²⁶, Jeffrey R. O'Connell²⁶, Nanette I. Steinle²⁶, Diederick E. Grobbee⁶³, Dan E. Arking⁸⁰, Sharon L. Kardina⁸⁰, Alanna C. Morrison⁸¹, Dena Hernandez⁸², Samer Najjar^{83,84}, Wendy L. McArdle⁸⁵, David Hadley^{50,86}, Morris J. Brown⁸⁷, John M. Connell⁸⁸, Aaron D. Hingorani⁸⁹, Ian N. M. Day⁶², Debbie A. Lawlor⁶², John P. Beilby^{90,91}, Robert W. Lawrence⁶⁵, Robert Clarke⁹², Jemma C. Hopewell⁹², Halit Ongen³², Albert W. Dreisbach⁴², Yali Li⁹³, J. Hunter Young⁹⁴, Joshua C. Bis²¹, Mika Kahönen⁹⁵, Jorma Viikari⁹⁶, Linda S. Adair⁹⁷, Nanette R. Lee⁹⁸, Ming-Huei Chen⁹⁹, Matthias Olden^{100,101}, Cristian Pattaro³⁰, Judith A. Hoffman Bolton¹⁰², Anna Köttgen^{102,103}, Sven Bergmann^{104,105}, Vincent Mosser¹⁰⁶, Nish Chaturvedi¹⁰⁷, Timothy M. Frayling¹⁰⁸, Muhammad Islam¹⁰⁹, Tazeen H. Jafar¹⁰⁹, Jeanette Erdmann¹¹⁰, Smita R. Kulkarni¹¹¹, Stefan R. Bornstein⁷⁶, Jürgen Grässler⁷⁶, Leif Groop^{112,113}, Benjamin F. Voight¹¹⁴, Johannes Kettunen^{115,116}, Philip Howard¹¹⁷, Andrew Taylor⁴³, Simonetta Guarrera⁶⁰, Fulvio Ricceri^{59,60}, Valur Emilsson¹¹⁸, Andrew Plump¹¹⁸, Inês Barroso^{119,120}, Kay-Tee Khaw⁴⁸, Alan B. Weder¹²¹, Steven C. Hunt¹²², Yan V. Sun⁶⁰, Richard N. Bergman¹²³, Francis S. Collins¹²⁴, Lori L. Bonnycastle¹²⁴, Laura J. Scott³¹, Heather M. Stringham³¹, Leena Peltonen^{116,119,125,126}, Markus Perola¹²⁵, Erkki Vartiainen¹²⁵, Stefan-Martin Brand^{127,128}, Jan A. Staessen⁷³, Thomas J. Wang^{6,129}, Paul R. Burton^{12,72}, Maria Soler Artigas¹², Yanbin Dong¹³⁰, Harold Snieder^{130,131}, Xiaoling Wang¹³⁰, Haidong Zhu¹³⁰, Kurt K. Lohman¹³², Megan E. Rudock³¹, Susan R. Heckbert^{133,134}, Nicholas L. Smith^{133,134,135}, Kerri L. Wiggins¹³⁶, Ayo Doughty⁷⁴, Daniel Shrier⁷⁴, Gudrun Veldre^{25,137}, Margus Viigimaa^{138,139}, Sanjay Kinra¹⁴⁰, Dorairaj Prabhakaran¹⁴¹, Vikal Tripathy¹⁴¹, Carl D. Langefeld⁷⁹, Annika Rosengren¹⁴², Dag S. Thelle¹⁴³, Anna Maria Kow¹⁴⁴, Andrew Singleton⁸², Terrence Forrester¹⁴⁵, Gina Hilton¹, Colin A. McKenzie¹⁴⁵, Tunde Salako¹⁴⁶, Naoharu Iwai¹⁴⁷, Yoshikuni Kita¹⁴⁸, Toshio Ogihara¹⁴⁹, Takayoshi Ohkubo^{148,150}, Tomonori Okamura^{147,148}, Hirotsugu Ueshima^{148,151}, Satoshi Umemura¹⁵², Susana Eyheramendy¹⁵³, Thomas Meitinger^{154,155}, H.-Erich Wichmann^{156,157,158}, Yoon Shin Cho⁴⁴, Hyung-Lae Kim⁴⁴, Jong-Young Lee⁴⁴, James Scott¹⁵⁵, Joban S. Sehmi^{41,159}, Weihua Zhang¹⁵⁸, Bo Hedblad³⁹, Peter Nilsson³⁹, George Davey Smith⁶², Andrew Wong⁶⁷, Narisu Narisu¹²⁴, Alena Stančáková⁵³, Leslie J. Raffel¹⁶⁰, Jie Yao¹⁶⁰, Sekar Kathiresan^{27,161}, Christopher J. O'Donnell^{92,77,162}, Stephen M. Schwartz¹³³, M. Arfan Ikram^{13,15}, W. T. Longstreth Jr¹⁶³, Thomas H. Mosley¹⁶⁴, Sudha Seshadri¹⁶⁵, Nick R.G. Shrine¹², Louise V. Wain¹²,

Mario A. Morken¹²⁴, Amy J. Swift¹²⁴, Jaana Laitinen¹⁶⁶, Inga Prokopenko^{51,167}, Paavo Zitting¹⁶⁸, Jackie A. Cooper⁶⁹, Steve E. Humphries⁶⁹, John Danesh⁴⁸, Asif Rasheed¹⁶⁹, Anuj Goel³², Anders Hamsten¹⁷⁰, Hugh Watkins³², Stephan J. L. Bakker¹⁷¹, Wieke H. van Gilst⁴⁵, Charles S. Janipalli⁴⁷, K. Radha Mani⁴⁷, Chittaranjan S. Yajnik¹¹¹, Albert Hofman¹³, Francesco U. S. Mattace-Raso^{13,14}, Ben A. Oostra¹⁷², Aysel Demirkan¹³, Aaron Isaacs¹³, Fernando Rivadeneira^{13,14}, Edward G. Lakatta¹⁷³, Marco Orru^{174,175}, Angelo Scuteri¹⁷³, Mika Ala-Korpela^{176,177,178}, Antti J. Kangas¹⁷⁶, Leo-Pekka Lytykainen¹⁷⁹, Pasi Soininen^{176,177,180}, Taru Tukiainen^{176,179,180}, Peter Würtz^{181,176,179}, Rick Twee-Hee Ong^{56,57,181}, Marcus Dörr¹⁸², Heyo K. Kroemer¹⁸³, Uwe Völker²⁰, Henry Völzke¹⁸⁴, Pilar Galan¹⁸⁵, Serge Hercberg¹⁸⁵, Mark Lathrop²⁴, Diana Zelenika²⁴, Panos Deloukas¹¹⁹, Massimo Mangino²⁸, Tim D. Spector²⁸, Guangju Zhai²⁸, James F. Meschia¹⁸⁶, Michael A. Nalls⁸², Pankaj Sharma¹⁸⁷, Janos Terzic¹⁸⁸, M. V. Kranthi Kumar⁴⁷, Matthew Denniff⁷¹, Ewa Zukowska-Szczeczowska¹⁸⁹, Lynne E. Wagenknecht⁷⁹, F. Gerald R. Fowkes¹⁹⁰, Fadi J. Charchar¹⁹¹, Peter E. H. Schwarz¹⁹², Caroline Hayward⁷⁰, Xiuqing Guo¹⁶⁰, Charles Rotimi⁷⁴, Michiel L. Bots⁶³, Eva Brand¹⁹³, Nilesh J. Samani^{17,72}, Ozren Polasek¹⁹⁴, Philippa J. Talmud⁶², Fredrik Nyberg^{68,195}, Diana Kuh⁶⁷, Maris Luan²⁵, Kristian Hveem⁶⁶, Lyle J. Palmer^{196,197}, Yvonne T. van der Schouw⁶³, Juan P. Casas¹⁹⁸, Karen L. Mohlke⁶¹, Paolo Vineis^{60,199}, Olli Raitakari²⁰⁰, Santhi K. Ganesh²⁰¹, Tien Y. Wong^{202,203}, E Shyong Tai^{57,204,205}, Richard S. Cooper⁵⁴, Markku Laakso⁵³, Dabeeru C. Rao²⁰⁶, Tamara B. Harris²², Richard W. Morris²⁰⁷, Anna F. Dominiczak²⁰⁸, Mika Kivimäki²⁰⁹, Michael G. Marmot²⁰⁹, Tetsuro Miki⁴⁹, Danish Saleheen^{48,169}, Giriraj R. Chandak⁴⁷, Josef Coresh²¹⁰, Gerjan Navis²¹¹, Veikko Salomaa¹²⁵, Bok-Ghee Han⁴⁴, Xiaofeng Zhu⁹³, Jaspal S. Kooner^{41,159}, Olle Melander³⁹, Paul M. Ridker^{8,9,212}, Stefania Bandinelli²¹³, Ulf B. Gyllenstein⁹⁷, Alan F. Wright⁷⁰, James F. Wilson³⁴, Luigi Ferrucci³³, Martin Farrall⁵², Jaakko Tuomilehto^{214,215,216,217}, Peter P. Pramstaller^{30,218}, Roberto Elosua^{29,219}, Nicole Soranzo^{28,119}, Eric J. G. Sijbrands^{13,14}, David Altshuler^{114,220}, Ruth J. F. Loos²³, Alan R. Shuldiner^{26,221}, Christian Gieger¹⁵⁶, Pierre Meneton²²², Andre G. Uitterlinden^{13,14,15}, Nicholas J. Wareham²³, Vilmondur Gudnason^{10,11}, Jerome I. Rotter¹⁶⁰, Rainer Rettig²²³, Manuela Uda¹⁷⁴, David P. Strachan⁵⁰, Jacqueline C. M. Witteman^{13,15}, Anna-Liisa Hartikainen²²⁴, Jacques S. Beckmann^{104,225}, Eric Boerwinkle²²⁶, Ramachandran S. Vasan^{6,227}, Michael Boehnke³¹, Martin G. Larson^{5,228}, Marjo-Riitta Jarvelin^{18,229,230,231,232}, Bruce M. Psaty^{21,134*}, Gonçalo R. Abecasis^{19*}, Aravinda Chakravarti^{1*}, Paul Elliott^{18,232*}, Cornelia M. van Duijn^{13,233*}, Christopher Newton-Cheh^{27,114*}, Daniel Levy^{6,7,16*}, Mark J. Caulfield^{4*} & Toby Johnson^{4*}

¹Center for Complex Disease Genomics, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA. ²Institute of Social and Preventive Medicine (IUMSP), Centre Hospitalier Universitaire Vaudois and University of Lausanne, Bugnon 17, 1005 Lausanne, Switzerland. ³Cardiology, Department of Specialties of Internal Medicine, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland. ⁴Clinical Pharmacology and The Genome Centre, William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK. ⁵Department of Biostatistics, University of Washington, Seattle, Washington 98195, USA. ⁶Framingham Heart Study, Framingham, Massachusetts 01702, USA. ⁷National Heart Lung, and Blood Institute, Bethesda, Maryland 20824, USA. ⁸Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, Massachusetts 02215, USA. ⁹Harvard Medical School, Boston, Massachusetts 02115, USA. ¹⁰Icelandic Heart Association, 201 Kópavogur, Iceland. ¹¹University of Iceland, 101 Reykjavik, Iceland. ¹²Department of Health Sciences, University of Leicester, University Rd, Leicester LE1 7RH, UK. ¹³Department of Epidemiology, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. ¹⁴Department of Internal Medicine, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands. ¹⁵Netherlands Consortium for Healthy Aging (NCHA), Netherland Genome Initiative (NGI), Erasmus 3000 CA Rotterdam, The Netherlands. ¹⁶Center for Population Studies, National Heart Lung, and Blood Institute, Bethesda, Maryland 20824, USA. ¹⁷Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland. ¹⁸Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK. ¹⁹Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan 48103, USA. ²⁰Interfaculty Institute for Genetics and Functional Genomics, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany. ²¹Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, Washington 98101, USA. ²²Laboratory of Epidemiology, Demography, Biometry, National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20892, USA. ²³MRC Epidemiology Unit, Institute of Metabolic Science, Cambridge CB2 0QQ, UK. ²⁴Centre National de Génétique, Commissariat à l'Énergie Atomique, Institut de Génétique, 91057 Evry, France. ²⁵Institute of Molecular and Cell Biology, University of Tartu, Riia 23, Tartu 51010, Estonia. ²⁶University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ²⁷Center for Human Genetic Research, Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. ²⁸Department of Twin Research & Genetic Epidemiology, King's College London, London SE1 7EH, UK. ²⁹Cardiovascular Epidemiology and Genetics, Institut Municipal d'Investigació Mèdica, Barcelona Biomedical Research Park, 88 Doctor Aiguader, 08003 Barcelona, Spain. ³⁰Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso 1, 39100 Bolzano, Italy - Affiliated Institute of the University of Lübeck, Germany. ³¹Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan 48109, USA. ³²Department of Cardiovascular Medicine, The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK. ³³Clinical Research Branch, National Institute on Aging, Baltimore, Maryland 21205, USA. ³⁴Centre for Population Health Sciences, University of Edinburgh, EH8 9AG, UK. ³⁵Centre for Population Health Sciences and Institute of Genetics and Molecular Medicine, College of Medicine and Veterinary Medicine, University of Edinburgh, EH8 9AG, UK. ³⁶Croatian Centre for Global Health,

University of Split, 21000 Split, Croatia.³⁷Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, SE-751 85 Uppsala, Sweden.³⁸Amgen, 1 Kendall Square, Building 100, Cambridge, Massachusetts 02139, USA.³⁹Department of Clinical Sciences, Lund University, 205 02 Malmö, Sweden.⁴⁰Department of Medicine, University of Verona, 37134 Verona, Italy.⁴¹Ealing Hospital, London UB1 3JH, UK.⁴²Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi 39216, USA.⁴³Genetic Epidemiology Group, Epidemiology and Public Health, UCL, London, WC1E 6BT, UK.⁴⁴Center for Genome Science, National Institute of Health, Seoul 122-701, Korea.⁴⁵Department of Cardiology, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands.⁴⁶Departments of Epidemiology and Medicine, Johns Hopkins University, Baltimore, Maryland 21205, USA.⁴⁷Centre for Cellular and Molecular Biology (CCMB), Council of Scientific and Industrial Research (CSIR), Uppal Road, Hyderabad 500 007, India.⁴⁸Department of Public Health and Primary Care, University of Cambridge, CB1 8RN, UK.⁴⁹Department of Basic Medical Research and Education, and Department of Geriatric Medicine, Ehime University Graduate School of Medicine, Toon, 791-0295, Japan.⁵⁰Division of Community Health Sciences, St George's University of London, London SW17 0RE, UK.⁵¹Epidemiology & Prevention, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157, USA.⁵²Division of Biostatistics and Department of Genetics, School of Medicine, Washington University in St. Louis, Saint Louis, Missouri 63110, USA.⁵³Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70210 Kuopio, Finland.⁵⁴Department of Preventive Medicine and Epidemiology, Loyola University Medical School, Maywood, Illinois 60153, USA.⁵⁵Department of Laboratory Medicine & Institute of Human Genetics, University of California San Francisco, 513 Parnassus Ave. San Francisco, California 94143, USA.⁵⁶Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore 138672, Singapore.⁵⁷Centre for Molecular Epidemiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore.⁵⁸Department of Clinical Chemistry, University of Tampere and Tampere University Hospital, Tampere 33521, Finland.⁵⁹Department of Genetics, Biology and Biochemistry, University of Torino, Via Santena 19, 10126 Torino, Italy.⁶⁰Human Genetics Foundation (HUGEF), Via Nizza 52, 10126 Torino, Italy.⁶¹Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA.⁶²MRC Centre for Causal Analyses in Translational Epidemiology, School of Social & Community Medicine, University of Bristol, Bristol BS8 2BN, UK.⁶³Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands.⁶⁴Complex Genetics Section, Department of Medical Genetics - DBG, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands.⁶⁵Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Crawley, Western Australia 6009, Australia.⁶⁶HUNT Research Centre, Department of Public Health and General Practice, Norwegian University of Science and Technology, 7600 Levanger, Norway.⁶⁷MRC Unit for Lifelong Health & Ageing, London WC1B 5JU, UK.⁶⁸Occupational and Environmental Medicine, Department of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 40530 Gothenburg, Sweden.⁶⁹Centre for Cardiovascular Genetics, University College London, London WC1E 6JF, UK.⁷⁰MRC Human Genetics Unit and Institute of Genetics and Molecular Medicine, Edinburgh EH2, UK.⁷¹Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester LE3 9QP, UK.⁷²Leicester NIHR Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK.⁷³Studies Coordinating Centre, Division of Hypertension and Cardiac Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block D, Box 7001, 3000 Leuven, Belgium.⁷⁴Center for Research on Genomics and Global Health, National Human Genome Research Institute, Bethesda, Maryland 20892, USA.⁷⁵Columbia University, New York, New York 10027, USA.⁷⁶Department of Medicine III, Medical Faculty Carl Gustav Carus at the Technical University of Dresden, 01307 Dresden, Germany.⁷⁷Epidemiology and Biostatistics, School of Public Health, Imperial College, London W2 1PG, UK.⁷⁸Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, 45110 Ioannina, Greece.⁷⁹Wake Forest University Health Sciences, Winston-Salem, North Carolina 27157, USA.⁸⁰Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan 48109, USA.⁸¹Division of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas at Houston Health Science Center, 12 Herman Pressler, Suite 453E, Houston, Texas 77030, USA.⁸²Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland 20892, USA.⁸³Laboratory of Cardiovascular Science, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland 21224, USA.⁸⁴Washington Hospital Center, Division of Cardiology, Washington, District of Columbia 20010, USA.⁸⁵ALSPAC Laboratory, University of Bristol, Bristol BS8 2BN, UK.⁸⁶Pediatric Epidemiology Center, University of South Florida, Tampa, Florida 33612, USA.⁸⁷Clinical Pharmacology Unit, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK.⁸⁸University of Dundee, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK.⁸⁹Genetic Epidemiology Group, Department of Epidemiology and Public Health, UCL, London WC1E 6BT, UK.⁹⁰Pathology and Laboratory Medicine, University of Western Australia, Crawley, Western Australia 6009, Australia.⁹¹Molecular Genetics, PathWest Laboratory Medicine, Nedlands, Western Australia 6009, Australia.⁹²Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford OX3 7LF, UK.⁹³Department of Epidemiology and Biostatistics, Case Western Reserve University, 2103 Cornell Road, Cleveland, Ohio 44106, USA.⁹⁴Department of Medicine, Johns Hopkins University, Baltimore 21205, USA.⁹⁵Department of Clinical Physiology, University of Tampere and Tampere University Hospital, Tampere, 33521, Finland.⁹⁶Department of Medicine, University of Turku and Turku University Hospital, Turku 20521, Finland.⁹⁷Department of Nutrition, University of North Carolina, Chapel Hill, North Carolina 27599, USA.⁹⁸Office of Population Studies Foundation, University of San Carlos, Talamban, Cebu City 6000, Philippines.⁹⁹Department of Neurology and Framingham Heart Study, Boston University School of Medicine, Boston, Massachusetts 02118, USA.¹⁰⁰Department of Internal Medicine II, University Medical Center Regensburg, 93053 Regensburg, Germany.¹⁰¹Department of Epidemiology and Preventive Medicine, University Medical Center Regensburg, 93053 Regensburg, Germany.¹⁰²Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland 21205, USA.¹⁰³Renal Division, University Hospital Freiburg, 79095 Freiburg, Germany.¹⁰⁴Département de Génétique Médicale, Université de Lausanne, 1015 Lausanne, Switzerland.¹⁰⁵Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland.¹⁰⁶Division of Genetics, GlaxoSmithKline, Philadelphia, Pennsylvania 19101, USA.¹⁰⁷International Centre for Circulatory Health, National Heart & Lung Institute, Imperial College, London SW7 2AZ, UK.¹⁰⁸Genetics of Complex Traits, Peninsula Medical School, University of Exeter, Exeter EX4 4QJ, UK.¹⁰⁹Department of Community Health Sciences & Department of Medicine, Aga Khan University, Karachi 74800, Pakistan.¹¹⁰Medizinische Klinik II, Universität zu Lübeck, 23538 Lübeck, Germany.¹¹¹Diabetes Unit, KEM Hospital and Research Centre, Rasta Peth, Pune-411011, Maharashtra, India.¹¹²Department of Clinical Sciences, Diabetes and Endocrinology Research Unit, University Hospital, 205 02 Malmö, Sweden.¹¹³Lund University, Malmö 20502, Sweden.¹¹⁴Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02139, USA.¹¹⁵Department of Chronic Disease Prevention, National Institute for Health and Welfare, 00251 Helsinki, Finland.¹¹⁶FIMM, Institute for Molecular Medicine, Finland, Biomedicum, P.O. Box 104, 00251 Helsinki, Finland.¹¹⁷William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK.¹¹⁸Merck Research Laboratory, 126 East Lincoln Avenue, Rahway, New Jersey 07065, USA.¹¹⁹Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, UK.¹²⁰University of Cambridge Metabolic Research Labs, Institute of Metabolic Science Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.¹²¹Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.¹²²Cardiovascular Genetics, University of Utah School of Medicine, Salt Lake City, Utah 84132, USA.¹²³Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, USA.¹²⁴National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.¹²⁵National Institute for Health and Welfare, 00271 Helsinki, Finland.¹²⁶Broad Institute, Cambridge, Massachusetts 02142, USA.¹²⁷Leibniz-Institute for Arteriosclerosis Research, Department of Molecular Genetics of Cardiovascular Disease, University of Münster, 48149 Münster, Germany.¹²⁸Medical Faculty of the Westfalian Wilhelms University Muenster, Department of Molecular Genetics of Cardiovascular Disease, University of Münster, 48149 Münster, Germany.¹²⁹Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.¹³⁰Georgia Prevention Institute, Department of Pediatrics, Medical College of Georgia, Augusta, Georgia 30912, USA.¹³¹Unit of Genetic Epidemiology and Bioinformatics, Department of Epidemiology, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands.¹³²Department of Biostatistical Sciences, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157, USA.¹³³Department of Epidemiology, University of Washington, Seattle, Washington 98195, USA.¹³⁴Group Health Research Institute, Group Health Cooperative, Seattle, Washington 98124, USA.¹³⁵Seattle Epidemiologic Research and Information Center, Veterans Health Administration Office of Research & Development, Seattle, Washington 98108, USA.¹³⁶Department of Medicine, University of Washington, Seattle, Washington 98195, USA.¹³⁷Department of Cardiology, University of Tartu, L. Puusepa 8, 51014 Tartu, Estonia.¹³⁸Tallinn University of Technology, Institute of Biomedical Engineering, Ehitajate tee 5, 19086 Tallinn, Estonia.¹³⁹Centre of Cardiology, North Estonia Medical Centre, Sütiste tee 19, 13419 Tallinn, Estonia.¹⁴⁰Department of Non-communicable disease Epidemiology, The London School of Hygiene and Tropical Medicine London, Keppel Street, London WC1E 7HT, UK.¹⁴¹South Asia Network for Chronic Disease, Public Health Foundation of India, C-1/52, SDA, New Delhi 100016, India.¹⁴²Department of Emergency and Cardiovascular Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 41685 Gothenburg, Sweden.¹⁴³Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, 0317 Oslo, Norway.¹⁴⁴Tuscany Regional Health Agency, 50129 Florence, Italy.¹⁴⁵Tropical Medicine Research Institute, University of the West Indies, Mona, Kingston, Jamaica.¹⁴⁶University of Ibadan, 200284 Ibadan, Nigeria.¹⁴⁷Department of Genomic Medicine, and Department of Preventive Cardiology, National Cerebral and Cardiovascular Research Center, Suita, 565-8565, Japan.¹⁴⁸Department of Health Science, Shiga University of Medical Science, Otsu, 520-2192, Japan.¹⁴⁹Department of Geriatric Medicine, Osaka University Graduate School of Medicine, Suita, 565-0871, Japan.¹⁵⁰Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Sendai, 980-8578, Japan.¹⁵¹Lifestyle-related Disease Prevention Center, Shiga University of Medical Science, Otsu, 520-2192, Japan.¹⁵²Department of Medical Science and Cardiorenal Medicine, Yokohama City University School of Medicine, Yokohama, 236-0004, Japan.¹⁵³Department of Statistics, Pontificia Universidad Católica de Chile, Vicuña Mackenna 4860, Santiago, Chile.¹⁵⁴Institute of Human Genetics, Helmholtz Zentrum Munich, German Research Centre for Environmental Health, 85764 Neuherberg, Germany.¹⁵⁵Institute of Human Genetics, Klinikum rechts der Isar, Technical University of Munich, 81675 Munich, Germany.¹⁵⁶Institute of Epidemiology, Helmholtz Zentrum Munich, German Research Centre for Environmental Health, 85764 Neuherberg, Germany.¹⁵⁷Chair of Epidemiology, Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, 81377 Munich, Germany.¹⁵⁸Klinikum Grosshadern, 81377 Munich, Germany.¹⁵⁹National Heart and Lung Institute, Imperial College London, London W12 0HS, UK.¹⁶⁰Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA.¹⁶¹Medical Population Genetics, Broad Institute of Harvard and MIT, 5 Cambridge Center, Cambridge, Massachusetts 02142, USA.¹⁶²National Heart, Lung and Blood Institute and its Framingham Heart Study, 73 Mount Wayte Ave., Suite #2, Framingham, Massachusetts 01702, USA.¹⁶³Department of Neurology and Medicine, University of Washington, Seattle, Washington 98195, USA.¹⁶⁴Department of Medicine (Geriatrics), University of Mississippi Medical Center, Jackson, Mississippi 39216, USA.¹⁶⁵Department of Neurology, Boston University School of Medicine, Massachusetts 02118, USA.¹⁶⁶Finnish Institute of Occupational Health, Aapistie 1, 90220 Oulu, Finland.¹⁶⁷Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK.¹⁶⁸Lapland Central Hospital, Department of Psychiatry, Box 8041, 96101 Rovaniemi, Finland.¹⁶⁹Center for

Non-Communicable Diseases Karachi 74800, Pakistan.¹⁷⁰Atherosclerosis Research Unit, Department of Medicine, Karolinska Institute, 171 77 Stockholm, Sweden.¹⁷¹Department of Internal Medicine, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands.¹⁷²Department of Clinical Genetics, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands.¹⁷³Gerontology Research Center, National Institute on Aging, Baltimore, Maryland 21224, USA.¹⁷⁴Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Cittadella Universitaria di Monserrato, 09042 Monserrato, Cagliari, Italy.¹⁷⁵Unita Operativa Semplice Cardiologia, Divisione di Medicina, Presidio Ospedaliero Santa Barbara, 09016 Iglesias, Italy.¹⁷⁶Computational Medicine Research Group, Institute of Clinical Medicine, University of Oulu and Biocenter Oulu, 90014 University of Oulu, Oulu, Finland.¹⁷⁷NMR Metabonomics Laboratory, Department of Biosciences, University of Eastern Finland, 70211 Kuopio, Finland.¹⁷⁸Department of Internal Medicine and Biocenter Oulu, Clinical Research Center, 90014 University of Oulu, Oulu, Finland.¹⁷⁹Institute for Molecular Medicine Finland FIMM, 00014 University of Helsinki, Helsinki, Finland.¹⁸⁰Department of Biomedical Engineering and Computational Science, School of Science and Technology, Aalto University, 00076 Aalto, Espoo, Finland.¹⁸¹NUS Graduate School for Integrative Sciences & Engineering (NGS) Centre for Life Sciences (CeLS), Singapore 117456, Singapore.¹⁸²Department of Internal Medicine B, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany.¹⁸³Institute of Pharmacology, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany.¹⁸⁴Institute for Community Medicine, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany.¹⁸⁵U557 Institut National de la Santé et de la Recherche Médicale, U1125 Institut National de la Recherche Agronomique, Université Paris 13, 93017 Bobigny, France.¹⁸⁶Department of Neurology, Mayo Clinic, Jacksonville, Florida 32224, USA.¹⁸⁷Imperial College Cerebrovascular Unit (CCRU), Imperial College, London W6 8RF, UK.¹⁸⁸Faculty of Medicine, University of Split, 21000 Split, Croatia.¹⁸⁹Department of Internal Medicine, Diabetology, and Nephrology, Medical University of Silesia, 41-800, Zabrze, Poland.¹⁹⁰Public Health Sciences section, Division of Community Health Sciences, University of Edinburgh, Medical School, Teviot Place, Edinburgh, EH8 9AG, UK.¹⁹¹School of Science and Engineering, University of Ballarat, 3353 Ballarat, Australia.¹⁹²Prevention and Care of Diabetes, Department of Medicine III, Medical Faculty Carl Gustav Carus at the Technical University of Dresden, 01307 Dresden, Germany.¹⁹³University Hospital Münster, Internal Medicine D, 48149 Münster, Germany.¹⁹⁴Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Stampar School of Public Health, University of Zagreb, 10000 Zagreb, Croatia.¹⁹⁵AstraZeneca R&D, 431 83 Mölndal, Sweden.¹⁹⁶Genetic Epidemiology & Biostatistics Platform, Ontario Institute for Cancer Research, Toronto, Ontario M5G 1L7, Canada.¹⁹⁷Samuel Lunenfeld Institute for Medical Research, University of Toronto, Toronto, Ontario M5S 1A1, Canada.¹⁹⁸Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK.¹⁹⁹Department of Epidemiology and Public Health, Imperial College, Norfolk Place, London W2 1PG, UK.²⁰⁰Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and the Department of Clinical Physiology, Turku University Hospital, Turku, 20521, Finland.²⁰¹Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical Center, Ann Arbor, Michigan 48109, USA.²⁰²Singapore Eye Research Institute, Singapore 168751, Singapore.²⁰³Department of Ophthalmology, National University of Singapore, Singapore 119074, Singapore.²⁰⁴Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 119074, Singapore.²⁰⁵Duke-National University of Singapore Graduate Medical School, Singapore 169857, Singapore.²⁰⁶Division of Biostatistics, Washington University School of Medicine, Saint Louis, Missouri 63110, USA.²⁰⁷Department of Primary Care & Population Health, UCL, London NW3 2PF, UK.²⁰⁸BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK.²⁰⁹Epidemiology Public Health, UCL, London WC1E 6BT, UK.²¹⁰Departments of Epidemiology, Biostatistics, and Medicine, Johns Hopkins University, Baltimore, Maryland 21205, USA.²¹¹Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands.²¹²Division of Cardiology, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, Massachusetts 02215, USA.²¹³Geriatric Rehabilitation Unit, Azienda Sanitaria Firenze (ASF), 50100 Florence, Italy.²¹⁴National Institute for Health and Welfare, Diabetes Prevention Unit, 00271 Helsinki, Finland.²¹⁵Hjelt Institute, Department of Public Health, University of Helsinki, 00014 Helsinki, Finland.²¹⁶South Ostrobothnia Central Hospital, 60220 Seinäjoki, Finland.²¹⁷Red RECAVA Grupo RD06/0014/0015, Hospital Universitario La Paz, 28046 Madrid, Spain.²¹⁸Department of Neurology, General Central Hospital, 39100 Bolzano, Italy.²¹⁹CIBER Epidemiología y Salud Pública, 08003 Barcelona, Spain.²²⁰Department of Medicine and Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA.²²¹Geriatric Research and Education Clinical Center, Veterans Administration Medical Center, Baltimore, Maryland 21201, USA.²²²U872 Institut National de la Santé et de la Recherche Médicale, Centre de Recherche des Cordeliers, 75006 Paris, France.²²³Institute of Physiology, Ernst-Moritz-Arndt-University Greifswald, 17487 Greifswald, Germany.²²⁴Institute of Clinical Medicine/Obstetrics and Gynecology, University of Oulu, 90014 Oulu, Finland.²²⁵Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.²²⁶Human Genetics Center, 1200 Hermann Pressler, Suite E447 Houston, Texas 77030, USA.²²⁷Division of Epidemiology and Prevention, Boston University School of Medicine, Boston, Massachusetts 02215, USA.²²⁸Department of Mathematics, Boston University, Boston, Massachusetts 02215, USA.²²⁹Institute of Health Sciences, University of Oulu, BOX 5000, 90014 University of Oulu, Finland.²³⁰Biocenter Oulu, University of Oulu, BOX 5000, 90014 University of Oulu, Finland.²³¹National Institute for Health and Welfare, Box 310, 90101 Oulu, Finland.²³²MRC-HPA Centre for Environment and Health, School of Public Health, Imperial College London, Norfolk Place, London W2 1PG, UK.²³³Centre of Medical Systems Biology (CMSB 1-2), NGL Erasmus Medical Center, Rotterdam, The Netherlands.

*These authors contributed equally to this work.

†A full list of authors and affiliations appears in Supplementary Information.

‡Deceased.