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Genome-wide association study identifies six new loci influencing pulse pressure and mean arterial pressure

Numerous genetic loci have been associated with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in Europeans^{1–3}. We now report genome-wide association studies of pulse pressure (PP) and mean arterial pressure (MAP).

In discovery ($N = 74,064$) and follow-up studies ($N = 48,607$), we identified at genome-wide significance ($P = 2.7 \times 10^{-8}$ to $P = 2.3 \times 10^{-13}$) four new PP loci (at 4q12 near *CHIC2*, 7q22.3 near *PIK3CG*, 8q24.12 in *NOV* and 11q24.3 near *ADAMTS8*), two new MAP loci (3p21.31 in *MAP4* and 10q25.3 near *ADRB1*) and one locus associated with both of these traits (2q24.3 near *FIGN*) that has also recently been associated with SBP in east Asians. For three of the new PP loci, the estimated effect for SBP was opposite of that for DBP, in contrast to the majority of common SBP- and DBP-associated variants, which show concordant effects on both traits. These findings suggest new genetic pathways underlying blood pressure variation, some of which may differentially influence SBP and DBP.

High blood pressure is a major risk factor for coronary heart disease and stroke⁴. Large genome-wide association studies in Europeans have reported 29 new loci for SBP and DBP, in which alleles have effect sizes of up to 0.5–1.0 mm Hg^{1–3}. Even small increments in blood pressure levels have important effects on cardiovascular morbidity and mortality at the population level⁵. We undertook a genome-wide association study of two further blood pressure phenotypes, PP (the difference between SBP and DBP), a measure of stiffness of the main arteries and MAP, a weighted average of SBP and DBP. Both PP and MAP are predictive of hypertension⁶ and cardiovascular disease^{7–9}.

This study was undertaken by the International Consortium of Blood Pressure Genome-Wide Association Studies (ICBP-GWAS), which aims to further the understanding of the genetic architecture underlying blood pressure. A concurrent publication by this consortium¹ studied SBP and DBP with discovery GWAS among 69,395 people and a combined sample of ~200,000 Europeans. All but one study that was included in the discovery GWAS of SBP and DBP were included in the discovery GWAS stage of this study. In addition, we included here a further six studies added subsequent to the analyses of SBP and DBP¹, bringing our discovery GWAS sample size to 74,064.

We first conducted a genome-wide association meta-analysis of PP and MAP in these 74,064 individuals of European ancestry from 35 studies (Supplementary Table 1a). We imputed the genotypes using HapMap. To account for effects of anti-hypertensive treatments,

we imputed underlying SBP and DBP by adding a constant to each^{2,3}. We adjusted the associations for age, age², sex and body mass index. We combined the results across studies using an inverse-variance-weighted meta-analysis and, to correct for residual test statistic inflation, applied genomic control (GC) both to study-level association statistics and to the meta-analysis (genomic control inflation factor, $\lambda_{GC} = 1.08$ for PP and $\lambda_{GC} = 1.12$ for MAP)¹⁰. The quantile-quantile plots show an excess of extreme values largely accounted for by a modest number of genomic regions (Supplementary Fig. 1a,b). We performed independent follow-up analyses in 48,607 individuals of European ancestry (Online Methods and Supplementary Note).

SNPs in 12 regions showed genome-wide significant association ($P < 5 \times 10^{-8}$) with either PP or MAP in our discovery data (stage 1) (Supplementary Fig. 1c,d), including two previously unidentified regions for PP (7q22.3 near *PIK3CG*, $P = 1.2 \times 10^{-10}$ and 11q24.3 near *ADAMTS8*, $P = 8.5 \times 10^{-11}$; Table 1) and 10 regions previously associated with SBP and DBP (see Supplementary Table 2a for PP and Supplementary Table 2b for MAP)^{1–3}. For follow-up in a series of independent cohorts, we selected 99 SNPs comprising those with $P < 1 \times 10^{-5}$ for either PP or MAP and SNPs reported in recent large genome-wide association studies of SBP and DBP^{1–3} to evaluate their effects on PP and MAP (stage 2; Online Methods and Supplementary Note).

After the meta-analysis of the stage 1 and 2 data together (Supplementary Table 2c), the two new regions showing genome-wide association with PP after stage 1 (near *PIK3CG* and near *ADAMTS8*) remained genome-wide significant. In addition, we found genome-wide significant associations for SNPs at two further new loci for PP (at 4q12 near *CHIC2* and 8q24.12 in *NOV*), two new loci for MAP (3p21.31 in *MAP4* and 10q25.3 near *ADRB1*) and one locus for both traits (2q24.3 near *FIGN*) (Table 1 and Fig. 1), a locus which has not previously shown an association with SBP or DBP in Europeans but which has recently been associated with SBP in east Asians (Supplementary Note)¹¹. Forest plots of the stage 1 effect sizes and standard errors are shown in Supplementary Figure 2. The new signals for MAP were strongly associated with both SBP and DBP ($P = 7.7 \times 10^{-7}$ to $P = 1.8 \times 10^{-12}$), reflecting the high inter-correlations among these three blood pressure traits^{12,13}. For the sentinel SNPs in three of the new PP loci, the estimated effects on SBP were in the opposite direction to the effects on DBP (Table 1, Fig. 2 and Supplementary Table 2d,e). Our findings show that analyses of PP and MAP identify loci influencing blood pressure phenotypes that may not be detectable by studying SBP and DBP separately.

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Table 1 Top genome-wide association results for pulse pressure and mean arterial pressure

Locus	Coded allele (frequency)	Stage 1			Stage 2			Stages 1+2			SBP stages 1+2		DBP stages 1+2	
		N_{eff}	β (s.e.m.)	P	N_{eff}	β (s.e.m.)	P	N_{eff}	β (s.e.m.)	P	β (s.e.m.)	P	β (s.e.m.)	P
Pulse pressure														
rs13002573 near <i>FIGN</i> , chr2:164,623,454	G (0.203)	73,043	-0.320 (0.07)	5.43×10^{-6}	43,955	-0.296 (0.089)	8.58×10^{-4}	116,998	-0.310 (0.055)	1.76×10^{-8}	-0.416 (0.081)	3.25×10^{-7}	-0.107 (0.052)	4.02×10^{-2}
rs871606 near <i>CHIC2</i> , chr4:54,494,002	T (0.85)	71,444	0.428 (0.096)	9.28×10^{-6}	44,082	0.431 (0.121)	3.75×10^{-4}	115,525	0.429 (0.075)	1.32×10^{-8}	0.403 (0.112)	3.04×10^{-4}	-0.010 (0.072)	8.85×10^{-1}
rs17477177 near <i>PIK3CG</i> , chr7:106,199,094	T (0.717)	72,997	-0.460 (0.071)	1.19×10^{-10}	39,999	-0.344 (0.094)	2.72×10^{-4}	112,996	-0.418 (0.057)	2.27×10^{-13}	-0.552 (0.084)	5.67×10^{-11}	-0.081 (0.055)	1.40×10^{-1}
rs2071518 <i>NOV</i> (3' UTR), chr8:120,504,993	T (0.167)	73,252	0.304 (0.067)	5.72×10^{-6}	45,804	0.323 (0.086)	1.60×10^{-4}	119,056	0.312 (0.053)	3.66×10^{-9}	0.181 (0.078)	2.08×10^{-2}	-0.145 (0.050)	3.89×10^{-3}
rs11222084 near <i>ADAMTS8</i> , chr11:129,778,440	T (0.375)	67,704	0.415 (0.064)	8.45×10^{-11}	40,391	0.211 (0.081)	9.17×10^{-3}	108,095	0.337 (0.05)	1.90×10^{-11}	0.263 (0.074)	4.00×10^{-4}	-0.101 (0.048)	3.44×10^{-2}
Mean arterial pressure														
rs1446468 near <i>FIGN</i> , chr2:164,671,732	T (0.534)	69,264	-0.291 (0.061)	1.68×10^{-6}	39,650	-0.418 (0.082)	3.80×10^{-7}	108,914	-0.336 (0.049)	6.46×10^{-12}	-0.499 (0.071)	1.82×10^{-12}	-0.265 (0.046)	6.88×10^{-9}
rs319690 <i>MAP4</i> (intron), chr3:47,902,488	T (0.51)	59,137	0.306 (0.066)	3.88×10^{-6}	34,359	0.280 (0.09)	1.89×10^{-3}	93,496	0.297 (0.053)	2.69×10^{-8}	0.423 (0.077)	4.74×10^{-8}	0.282 (0.05)	1.84×10^{-8}
rs2782980 near <i>ADRB1</i> , chr10:115,771,517	T (0.198)	61,284	-0.345 (0.071)	1.14×10^{-6}	37,788	-0.326 (0.094)	5.55×10^{-4}	99,072	-0.338 (0.057)	2.46×10^{-9}	-0.406 (0.082)	7.66×10^{-7}	-0.283 (0.053)	9.60×10^{-8}

Pulse pressure (PP) and mean arterial pressure (MAP) association results from stages 1 and 2, and stages 1 and 2 combined, for all SNPs that showed genome-wide significant ($P < 5 \times 10^{-5}$) association with PP and/or MAP in the combined analysis and which had not previously been reported for systolic (SBP) or diastolic blood pressure (DBP). Also shown are the SBP and DBP combined stages 1 and 2 association results based on the same sample set as for PP and MAP (the full SBP and DBP results are listed in **Supplementary Table 2d,e**). Genome-wide significant associations ($P < 5 \times 10^{-5}$) are shown in bold. N_{eff} , N effective; UTR, untranslated region.

Identification of new genetic associations could help inform understanding about possible distinct mechanisms underlying relationships of PP with vascular risk^{14,15}.

Five additional loci for PP and 19 loci for MAP reaching genome-wide significance ($P < 5 \times 10^{-8}$ for stage 1 and 2 combined) were recently shown to be associated with SBP and/or DBP¹⁻³ (**Supplementary Table 2a,b**). We used sentinel SNPs from both the new and known regions showing genome-wide significant associations with PP or MAP in the combined stage 1 and 2 data to create weighted risk scores for PP (10 independent SNPs) and MAP (22 SNPs) (**Supplementary Table 2f**). We studied the associations of both risk scores with hypertension and blood pressure-related outcomes including coronary heart disease, heart failure, stroke, echocardiographic measures of left ventricular structure, pulse wave velocity, renal function and renal failure. Adjusting for multiple testing for the 12 traits evaluated ($P = 0.05/12 = 4.1 \times 10^{-3}$), the PP SNP risk score was associated with prevalent hypertension ($P = 7.9 \times 10^{-6}$), incident stroke ($P = 4.9 \times 10^{-4}$) and coronary heart disease ($P = 4.3 \times 10^{-4}$), and the MAP SNP risk score was associated with hypertension ($P = 5.1 \times 10^{-16}$), coronary heart disease ($P = 4.0 \times 10^{-20}$), stroke ($P = 0.0019$) and left ventricular wall thickness ($P = 2.1 \times 10^{-4}$) (**Supplementary Table 3a**), confirming the clinical relevance of these measures of blood pressure phenotype^{8,9}. For a range of blood pressure-related outcomes (**Supplementary Note**), we compared P values for the PP risk score and a series of 1,000 permutations of SBP risk scores, each based on 10 of the 26 blood pressure SNPs associated with SBP but not with PP, and constraining the selection of SNPs to have similar sized effects for SBP as the 10 SNPs for PP. The PP risk score had a significantly ($P < 0.05$) greater association with risk of ischemic stroke than the SBP risk score (**Supplementary Note** and **Supplementary Table 3b**).

None of the genes in the identified newly associated regions is a strong candidate for blood pressure regulation, although several of them are implicated in mechanisms that may influence blood pressure. The most significant association with PP is within a putative

mRNA clone (AF086203) spanning ~13.7 kb at 7q22.3, 94 kb upstream of *PIK3CG* (rs17477177, $P = 2.3 \times 10^{-13}$; **Table 1** and **Fig. 1a**). *PIK3CG* encodes the phosphoinositide-3-kinase, catalytic, γ polypeptide protein (PI3K γ), which phosphorylates phosphoinositides and modulates extracellular signals. This region was earlier associated with mean platelet volume, platelet count and platelet aggregation¹⁶⁻¹⁸, but the sentinel SNPs reported in those previous studies are independent of the SNP reported here, rs17477177 ($r^2 < 0.01$). Mice lacking the catalytic subunit of PI3K γ have shown resistance to the SBP-lowering effects of β -adrenergic receptor agonists¹⁹; PI3K γ activity is increased in the failing human heart and is associated with downregulation of β -adrenergic receptors in the plasma membrane²⁰. The second locus for PP, located at 11q24.3, spans 35.5 kb, with the top-ranking SNP (rs11222084, $P = 1.9 \times 10^{-11}$; **Fig. 1b**) lying 1.6 kb downstream of *ADAMTS8*. This gene is highly expressed in macrophage-rich areas of human atherosclerotic plaques and may affect extracellular matrix remodeling²¹. The third locus for PP spans 28.5 kb at 8q24.12, with the sentinel SNP (rs2071518, $P = 3.7 \times 10^{-9}$; **Fig. 1c**) located in the 3' untranslated region of *NOV*, encoding the nephroblastoma over-expressed (CCN3) protein, which is associated with angiogenesis, proliferation and inhibition of vascular smooth muscle cell growth and migration²² and with reduced neointimal thickening in mice null for CCN3²³. Mice with mutations in *Nov* that truncate the NOV protein show abnormal cardiac development²⁴. Of the genes evaluated for expression in human aortic samples at the new PP loci, *NOV* showed by far the highest expression levels (**Supplementary Note** and **Supplementary Fig. 3**). The fourth locus for PP is 4q12, with the top-ranking SNP (rs871606, $P = 1.3 \times 10^{-8}$; **Fig. 1d**) located 76.7 kb downstream of *CHIC2*, encoding a cysteine-rich hydrophobic domain-containing protein that is associated with acute myeloid leukemia²⁵. This SNP is located 296 kb upstream of *PDGFRA*, which encodes platelet-derived growth factor receptor α , a cell surface receptor for members of the platelet-derived growth factor family involved in kidney development. Variants in *PDGFRA* have

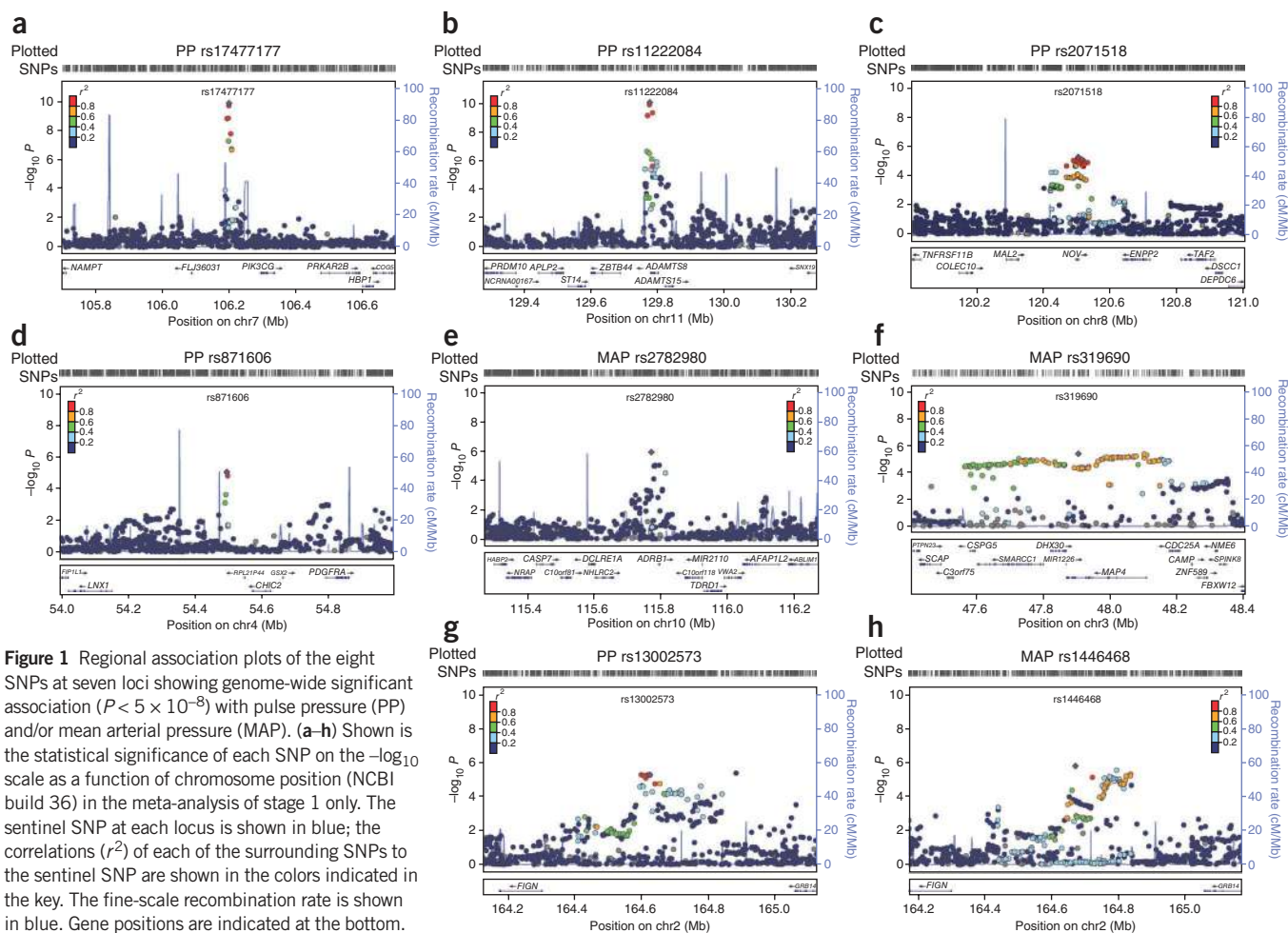


Figure 1 Regional association plots of the eight SNPs at seven loci showing genome-wide significant association ($P < 5 \times 10^{-8}$) with pulse pressure (PP) and/or mean arterial pressure (MAP). (**a–h**) Shown is the statistical significance of each SNP on the $-\log_{10} P$ scale as a function of chromosome position (NCBI build 36) in the meta-analysis of stage 1 only. The sentinel SNP at each locus is shown in blue; the correlations (r^2) of each of the surrounding SNPs to the sentinel SNP are shown in the colors indicated in the key. The fine-scale recombination rate is shown in blue. Gene positions are indicated at the bottom.

been associated with red blood cell count and other haematological indices²⁶ but are independent ($r^2 < 0.3$) of rs871606.

For MAP, we identified two newly associated loci. The first locus for MAP is at 10q25.3, 22.3 kb upstream of *ADRB1* (rs2782980, $P = 2.5 \times 10^{-9}$; **Fig. 1e**). *ADRB1* encodes the β -1-adrenergic receptor, which mediates the effects of the stimulatory G protein and cAMP/protein kinase A pathway to increase heart rate and myocardial contraction. Polymorphisms in this gene have been associated with resting heart rate, response to beta blockers²⁷ and hypertension²⁸. *Adrb1* knockout

mice have no difference in heart rate or blood pressure compared with wild type but do have a significant reduction in the response of both phenotypes to catecholamines²⁹. rs2782980 is associated with expression of an *ADRB1* transcript in brain tissue (**Supplementary Note** and **Supplementary Fig. 4a**). The second locus for MAP spans over 300 kb at 3p21.31, with the top-ranking SNP (rs319690, $P = 2.7 \times 10^{-8}$; **Fig. 1f**) lying within an intron of *MAP4*, encoding microtubule-associated protein 4. Coating of microtubules by MAP4 may inhibit β -adrenergic-receptor recycling and number, as seen in cardiac hypertrophy and failure³⁰. *MAP4* was detectably expressed in human aortic samples (**Supplementary Note** and **Supplementary Fig. 3**).

The locus associated both with PP (rs13002573, $P = 1.8 \times 10^{-8}$; **Fig. 1g**) and MAP (rs1446468, $P = 6.5 \times 10^{-12}$; **Fig. 1h**) is in an intergenic region spanning ~ 280 kb at 2q24.3. Although the two signals are

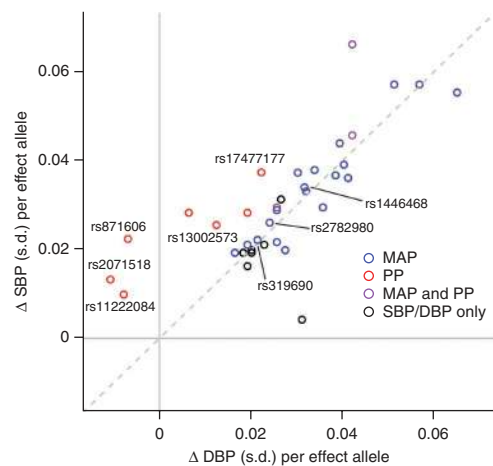


Figure 2 Systolic blood pressure (SBP) and diastolic blood pressure (DBP) effect sizes (β coefficients) for all blood pressure SNPs identified in the present study and a concurrent study¹ obtained from follow-up samples only. β coefficients are shown as standard deviation (s.d.) differences so that SBP and DBP are measured on comparable scales. Points are color coded according to whether they are genome-wide significant ($P < 5 \times 10^{-8}$) for pulse pressure (PP) (red), mean arterial pressure (MAP) (blue) or both MAP and PP (purple) in stages 1 and 2 of the present study, whereas those that are significant only for SBP and/or DBP from the concurrent study¹ are shown in black. The new SNPs found in the present study are labeled with their rs numbers. For illustration purposes, the effect allele for each SNP is defined such that the direction of the SBP effect is always positive.

~50 kb apart and are statistically independent ($r^2 = 0.075$), rs13002573 is highly correlated with rs16849225 ($r^2 = 1$ in the HapMap CEU population and $r^2 = 0.87$ in the HapMap JPT+CHB population), which has recently been reported as showing association with SBP in a GWAS of 19,608 subjects of east Asian origin with follow up in a further 30,765 individuals (combined $P = 3.5 \times 10^{-11}$) (ref. 11 and **Supplementary Note**). In our combined dataset of 116,998 Europeans, the association P value for rs13002573 with SBP was $P = 3.25 \times 10^{-7}$. The top PP SNP lies ~320 kb upstream of *FIGN* and ~430 kb downstream of *GRB14* (encoding growth factor receptor-bound protein 14). Relatively little is known regarding *FIGN* (encoding fidgetin).

We report six new loci associated with PP and MAP based on genome-wide discovery and follow-up in over ~120,000 individuals and a further locus (near *FIGN*) not previously reported in Europeans. Our results expand the knowledge of the genetic architecture of blood pressure and PP regulation and may give clues as to possible targets for blood pressure therapies.

METHODS

Methods and any associated references are available in the online version of the paper at <http://www.nature.com/naturegenetics/>.

Note: Supplementary information is available on the Nature Genetics website.

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ONLINE METHODS

Phenotypes. PP was defined as systolic minus diastolic pressure, and MAP was defined as 2/3 diastolic plus 1/3 systolic pressure. A two-staged analysis was used to discover genes associated with PP and MAP.

Stage 1 samples and analyses. Stage 1 was a meta-analysis of directly genotyped and imputed SNPs from population-based or control samples from case-control studies in the International Consortium of Blood Pressure Genome-wide Association Studies (ICBP-GWAS). The characteristics of the 35 studies, including demographics, genotyping arrays, quality control filters and statistical analysis methods used, are listed in **Supplementary Table 1a,b**. Imputation of the allele dosage of ungenotyped SNPs in HapMap CEU v21a or v22 was carried out by each of the studies using MACH³¹, IMPUTE³² or BIMBAM³³ with parameters and pre-imputation filters as specified in **Supplementary Table 1b**. SNPs were excluded from analysis if the study-specific imputation quality ($r2.hat$ in MACH or $.info$ in IMPUTE) was <0.3 . In total, up to 2,652,054 genotyped or imputed autosomal SNPs were analyzed. Full details of the models, methods and corrections for antihypertensive treatment are provided in the **Supplementary Note**. All analyses assumed an additive genetic model and were adjusted for sex, age, age², body mass index and ancestry principal components. In related individuals, regression methods that account for relatedness were applied. All study-specific effect estimates and coded alleles were oriented to the forward strand of the HapMap release 22, with the alphabetically higher allele as the coded allele. To capture loss of power caused by imperfect imputation, we estimated 'N effective' as the sum of the study-specific products of the imputation quality metric and the sample size. No filtering on minor allele frequency was done. Genomic control was carried out on study-level data, and inverse-variance weighting was used for the meta-analysis of stage 1. The meta-analysis results were subject to genomic control. Genomic control inflation factor, λ_{GC} , estimates are given in **Supplementary Table 1a**.

Selection of SNPs for stage 2. We aimed in stage 2 to follow up SNPs which had evidence of association with PP or MAP and, for completeness, to evaluate the effects on PP and MAP of SNPs reported in recent large genome-wide association studies of SBP and DBP¹⁻³. All SNPs with $P < 1 \times 10^{-5}$ for association with either PP or MAP (or both) were divided into independent regions based on linkage disequilibrium, and the most significant SNP was selected from each region. Within the *FIGN* region, different SNPs were associated with PP and with MAP, and both of these SNPs were followed up in stage 2. For SNPs with an *N* effective of $<75\%$ of the total *N*, a proxy was also included if it had $P < 1 \times 10^{-5}$ and $r^2 > 0.6$ with the top SNP (this occurred for one SNP). For all regions that had previously shown association with SBP or DBP¹⁻³, the sentinel SNP for PP

and MAP and the previously reported SNP for SBP and DBP were followed up. In all, 99 SNPs were followed up in stage 2 (**Supplementary Note**) comprising: 44 SNPs from 22 loci with PP or MAP associations ($P < 1 \times 10^{-5}$) in stage 1 data and with previously reported SBP or DBP associations; 47 SNPs from 45 loci with PP or MAP associations ($P < 1 \times 10^{-5}$) in stage 1 data only and; 8 SNPs from 7 loci with previously reported SBP or DBP associations and no association ($P < 1 \times 10^{-5}$) with PP or MAP in the stage 1 data.

Stage 2. The characteristics of the stage 2 studies, including the genotyping and imputation approaches, are described in **Supplementary Table 1a,b**, and the details of the corrections for treatment are described in the **Supplementary Note**. For the 99 SNPs selected for follow-up, the stage 2 studies followed the analysis approach adopted in the stage 1 analyses. The meta-analysis was done using the inverse-variance weights method.

Pooled analysis of first- and second-stage samples. The meta-analysis from stages 1 and 2 was conducted using inverse-variance weighting, and genomic control was applied. A threshold of $P = 5 \times 10^{-8}$ was taken for genome-wide significance.

Calculation of risk scores. We calculated risk scores based on the most significantly associated SNP from all regions that were genome-wide significant after the meta-analysis of stages 1 and 2 for PP (10 SNPs) and MAP (22 SNPs) (**Supplementary Table 2f**). Each risk score was constructed using an approach described in the **Supplementary Note** and was tested for association with hypertension, coronary artery disease, stroke, hypertension, chronic kidney disease, heart failure and microalbuminuria and with the continuous traits of left ventricular mass, left ventricular wall thickness, pulse wave velocity, serum creatinine, eGFR and urinary albumin:creatinine ratio (**Supplementary Table 3**).

Additional analyses. Identification of potentially functional SNPs in linkage disequilibrium with the reported sentinel SNPs, expression quantitative trait loci analyses and expression analyses in human aortic samples were also carried out as discussed in the **Supplementary Note** and **Supplementary Figures 3 and 4**.

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