GENETIC AETIOLOGY OF BLOOD PRESSURE RELATES TO AORTIC STIFFNESS WITH BI-DIRECTIONAL CAUSALITY

Evidence from heritability, blood pressure polymorphisms and Mendelian randomisation

Short title: Blood pressure genes and hemodynamics

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ABSTRACT

Introduction: Hemodynamic determinants of blood pressure (BP) include cardiac output (CO), systemic vascular resistance (SVR) and arterial stiffness. We investigated the heritability of these phenotypes, their association with BP-related single nucleotide polymorphisms (SNPs), and the causal association between BP and arterial stiffness.

Methods and Results: We assessed BP, central BP components and hemodynamic properties (during a single visit) including CO, SVR and pulse wave velocity (PWV, measure of arterial stiffness) in 3,531 (1934 monozygotic, 1586 dizygotic) female TwinsUK participants. Heritability was estimated using structural equation modelling. Association with 984 BP-associated SNP was examined using least absolute shrinkage and selection operator (LASSO) and generalised estimating equation (GEE) regression. One and two-sample Mendelian randomisation (MR) was used to estimate the causal direction between BP and arterial stiffness including data on 436,419 Biobank participants. We found high heritability for systolic and pulsatile components of BP (>50%) and PWV (65%) with overlapping genes accounting for >50% of their observed correlation. Environmental factors explained most of the variability of CO and SVR(>80%). Regression identified SNPs (n=5) known to associated with BP to be associated with PWV. One-sample MR showed evidence of bi-directional causal association between BP and PWV in TwinsUK participants. Two-sample MR, confirmed a bi-directional causal effect of PWV on BP (inverse variance weighted (IVW) beta=0.11,P<0.02) and BP on arterial stiffness (IVW beta=0.004,P<0.0001)

Conclusion: The genetic basis of BP is mediated by genes regulating BP but also by genes that influence arterial stiffness. MR indicates a bi-directional causal association between BP and arterial stiffness.

Key words: Blood pressure, genes, hemodynamics, arterial stiffness, mendelian randomisation

INTRODUCTION

Hypertension is one of the most important risk factors for cardiac, cerebrovascular and renal associated morbidity and mortality and the largest contributor to the global burden of disease [1]. Twin and family studies have identified a substantial (49-54%) heritable component to blood pressure (BP) [2] and genetic association studies have now identified a large number of individual single nucleotide polymorphisms that associate with BP [3]. Hemodynamic determinants of BP include cardiac output (CO), systemic vascular resistance (SVR, determined by the microvasculature), and stiffness of large arteries (Table 1). CO and SVR determine steady state or mean arterial pressure (MAP). Stroke volume (SV), large artery stiffness (and other properties) determine the pulse pressure (PP). We investigated the heritability and shared heritability of these underlying hemodynamic properties with those of conventional peripheral BP and components of central aortic BP (Figure 1) in the Twins UK cohort. To understand the mechanism by which genetic polymorphisms influence BP, we examined the association of BP phenotypes and cardiovascular properties with genetic variants previously associated with BP and examined the direction of causality between BP and heritable hemodynamic properties using Mendelian randomization. This was performed in the Twins UK and UK Biobank cohorts as these two cohorts have complimentary properties. Arterial stiffness (measured using the "gold standard" carotid-femoral pulse wave velocity) and BP were available within Twins UK. In the much larger UK Biobank cohort BP was available and arterial stiffness was estimated from a pulse wave-derived index.

METHODS

Participants

Study participants were 3,531 monozygotic (MZ) and dizygotic (DZ) female twins (2,442 with genotyping) enrolled in the Twins UK national registry of adult twins without regard to phenotype status [4]. Twins UK began in 1992 and initially only recruited middle-aged women to investigate osteoarthritis and osteoporosis in women. As a result, the cohort is predominantly female and only women were included in the present study [4]. Peripheral BP, central BP (including height of the first systolic shoulder, P1 and augmentation pressure, AP, Figure 1) and carotid-femoral pulse wave velocity (PWV) were measured in all participants. In addition, 1,625 participants underwent echocardiography to measure left ventricular outflow track (LVOT) diameter, stroke volume (SV) and cardiac output (CO). Systemic vascular resistance (SVR) was calculated from mean arterial pressure (MAP) and CO. The study was approved by St Thomas' Hospital research Ethics Committee and written informed consent was obtained from all participants. Details of the genotyping, BP and cardiovascular measurements are provided in supplementary material online.

Heritability

Influence of genetic factors (A) and environmental factors were modelled in twins using the ACE twin model. Environmental influences were partitioned into those that are shared between twins (C) and therefore make them more similar (e.g. raised in same household); and those that are unique to individuals (E) and result in differences between twins (and which includes measurement error). Shared environment was assumed to correlate perfectly for both monozygotic and dizygotic twins while unique environment was assumed to be uncorrelated in twins. Environmental factors represent the totality of all such factors whether measured or

unmeasured. Details of the heritability modelling are provided in the supplementary material online.

Blood Pressure Associated Gene Variants

To determine to what extent genes that influence BP associate with specific hemodynamic determinants of BP we selected 984 single nucleotide polymorphisms (SNPs) shown to be robustly associated with BP in the most recent genome wide association studies (GWAS) [3]. Of these, data for 896 SNPs were available from genotyping in the Twins UK. It was not expected that all known SNPs would contribute to blood pressure in our cohort. Therefore, in order to identify the most informative SNPs associated with BP and to protect against weak instrument bias[5] in Mendelian randomisation we performed least absolute shrinkage and selection operator (LASSO) regression using Stata version 14 and the *cvlasso* function on 799 SNPs (number of variables is limited to 800 in the *cvlasso* function, so we selected polymorphisms with an allele frequency >0.10). LASSO regression performs variable selection and shrinkage at the same time by penalising parameters that contribute little to the fit of the model. This analysis is based on a type of machine learning where data is split into training (30%) and validation datasets (70%) and results are based on 10-fold cross-validation analysis [6]. Selecting SNPs that associated with BP in LASSO regression, we then examined the association of those SNPs to BP components and heritable hemodynamic properties using generalized estimating equations (GEE) which account for the relationship structure of twins. All SNPs were included in the model at the same time. In addition, we repeated the analysis using LASSO regression. Results are shown for SNPs with both a P-value <0.05 in GEE and that were selected in LASSO regression. Augmentation pressure was transformed (square root) for the analysis.

Mendelian Randomisation-Twins UK

To determine the direction of causality between BP and arterial stiffness we first performed one-sample bi-directional Mendelian randomisation (MR) using a 2-stage least squares regression analysis with STATA software and the command *ivregress* using a multiple instruments model[7] in TwinsUK. For this analysis, the exposure is estimated by the genotypes (instrumental variables, IV) by calculating predictive values from the regression of the exposure on the genotypes and then regressing the outcome variable (pulse wave velocity, PWV) on the predicted exposure to obtain a causal effect estimate [8]. The IV was all SNPs identified from LASSO regression analysis to associate with BP in the TwinsUK cohort (n=56). Genotypes were coded 0, 1 and 2 and an additive genetic model was assumed (we also performed the analysis with all SNPs irrespective of whether they were selected by LASSO). Secondly, the causal effect of PWV on blood pressure was investigated. In this case, the IVs were two SNPs previously identified to robustly associate with PWV from GWAS ($P<5\times10^{-8}$)[9], the exposure was PWV and the outcome was BP. Sensitivity analysis was performed including only one twin in the analysis to ensure the twin family structure did not influence the results.

Mendelian Randomisation-Biobank UK

Since one-sample MR may provide biased estimates of effect size[10], a 2-sample MR was also performed using summary-level GWAS data available from Biobank UK and the MR-Base platform (http://www.mrbase.org). UK Biobank comprises 502,000 genotyped adults aged between 40 and 69 years of age of whom 436,419 have BP data. To determine whether PWV associated SNPs are associated with BP, the IV were built considering GWAS significant SNPs ($P<5\times10^{-8}$) and suggestive SNPs ($P<1\times10^{-5}$) from separate loci defined by linkage

disequilibrium (LD) structure (r^2<0.80). The more liberal P-value threshold of $P<1\times10^{-5}$ was adopted because only one SNP was available for the more conservative P value analysis. Statistical associations between individual SNPs and PWV were taken from Mitchel et al[9]. If a SNP was absent in the summary GWAS statistics, a proxy SNP in high LD with $r^2 \geq 0.80$ was used where available. However, if this was not successful, the SNP was excluded and thus not all 18 SNPs were included in the final analysis. The association between IV and outcome was assessed using inverse-variance weighted (IVW) regression models. We also assessed the association using the weighted median method which is less sensitive to outliers[11]. We performed an MR-Egger test to look for directional pleiotropy [12]. Leave-one-out sensitivity was performed to exclude the possibility of one SNP having a large effect on the overall results. To determine whether BP associated SNPs were associated with arterial stiffness, IV were built considering the 984 SNPs previously identified from GWAS. In this case, the outcome was arterial stiffness index (SI), an estimate of arterial stiffness obtained using the PulseTrace (PCA2, CareFusion, USA) device, which is correlated to carotid-femoral PWV [13].

RESULTS

Participant characteristics (n=3,531, 1934 MZ and 1586 DZ) in the Twins UK cohort by zygosity are shown in Table 2. Mean (± SD) age for women was 57.7±12.9 years, with average peripheral systolic and diastolic BP of 126±17 and 74±9 mm Hg, respectively. Twenty two percent were on antihypertensive treatment and 14% were on lipid lowering therapy. Three per cent were treated for diabetes mellitus and 9% were current smokers. Compared to MZ twins, DZ twins were older, had higher systolic and diastolic BP, and a higher percentage were current smokers and on treatment for hypertension and hypercholesterolemia.

Heritability of Blood Pressure and Hemodynamic Parameters

Unadjusted intra-class correlation coefficients for all BP components were higher for MZ compared to DZ twin pairs suggesting a genetic influence on these measures (Supplementary material online, Table S1). Compared with BP, differences in intra-class correlations between MZ and DZ twins for SV, CO, LVOT diameter and SVR were smaller suggesting a comparatively smaller genetic influence on these measures. After adjusting for age, univariable model fitting confirmed a substantial additive genetic component for peripheral systolic and diastolic BP (63% and 58%, respectively) and for other BP components including pulse pressure, AP and P1: the additive genetic component was >55% for these components in the ACE model (Figure 2). Out of all the cardiovascular determinants of BP, a substantial additive genetic component was observed only for PWV (67%) after age adjustment. Estimates of shared environment were close to zero and the most parsimonious model for BP components and PWV was the AE model (Supplementary material online, Table S2).

Heritability estimates for SV (8%), CO (15%), LVOT diameter (17%), and SVR (5%) were much lower compared to those for BP components and PWV in the ACE model (Figure 2). Further adjusting the model for height or BMI did not appreciably change the estimates. For these phenotypes, the CE model was the most parsimonious model suggesting a non-significant genetic effect (Supplementary material online, Table S2). Shared environment accounted for 28%, 29%, 52% and 32% of the variability for SV, CO, LVOT diameter and SVR in the CE model, respectively. Sensitivity analysis excluding individuals on antihypertensive therapy produced comparable results for all phenotypes (Supplementary material online, Table S3).

Phenotypic Correlation and Shared Genetic Heritability between Blood Pressure Components and Pulse Wave Velocity

We next performed bivariate heritability analysis to determine to what extent the correlation between BP components and PWV (which were highly heritable) can be explained by overlapping genetic factors (Supplementary material online, Table S4). The phenotypic correlation between systolic BP (SBP) and other BP components (PP, AP, P1), apart from diastolic BP (DBP) was moderately high ($r \geq 0.49$). Similarly, the phenotypic correlation between BP components, apart from DBP and AP, with PWV was moderately high ($r \geq 0.55$). Bivariate heritability analysis of the association between BP components and PWV suggested a large genetic overlap (>50% of the co-variance explained by additive genetic factors, Supplement Table 4). Common genetic factors explained a large percentage of the correlation between P1 and PWV (49%) but only a modest proportion between AP and PWV (20%).

Association between Blood Pressure Associated SNPs with Components of Blood Pressure and Hemodynamic Parameters

LASSO regression identified 56 SNPs associated with SBP, DBP or PP in the current cohort (Supplementary material online, Table S5). We next tested the association between these 56 SNPs with blood pressure components and PWV (Table 3). From LASSO regression analysis, we observed an association between 6 SNPs (rs10923038, rs3184504, rs3745318, rs10842991, rs3742182 and rs1055144) and AP (Table 3). Five SNPs (rs2390258, rs9888615, rs9860290, rs4810332 and rs11909120) associated with P1. Five SNPs (rs9888615, rs2390258, rs4553000 and rs4980515) associated with PWV. There was little overlap between association of SNPs with different BP components and PWV except for P1 and PWV for which two SNPs associated with both P1 and PWV (rs2390258 and rs9888615, Table 3).

One-sample Mendelian Randomisation between Blood Pressure and Arterial Stiffness

Using all SNPs associated with SBP in LASSO regression as an IV, a one SD increase in IV-predicted SBP associated with 0.08 m/sec increase in PWV ($P<0.0001$, Table 4). This was similar to the association estimated from the observational data (Table 4). Using SNPs associated with DBP as an IV, a one-SD increase in predicted DBP was associated with a 0.07 m/sec increase in PWV ($P<0.0001$), and a one-SD increase in PP predicted by PP associated alleles was associated with a 0.12 m/sec increase in PWV ($P<0.0001$). When using all SNPs as IV rather than the sub-sample identified by LASSO, point estimates of the beta coefficients did not differ appreciably (data not shown). Previous GWAS have identified SNPs associated with PWV which are independent of those associated with blood pressure and vice-versa. Using alleles previously associated with PWV (rs3742207 of gene COL4A1 and rs7152623of gene 3'-BCL11B) as instruments, a one-SD increase in predicted PWV associated with a 4.84

mmHg increase in SBP (P=0.011) and a 3.34 mmHg increase in PP (P<0.01) but not with DBP or MAP (Table 4). Sensitivity analysis including only one twin produced comparable beta coefficients for all phenotypes (data not shown).

Two-Sample Mendelian Randomisation in Biobank Cohort using MR-Base

Of the 18 alleles included in the 2-sample MR analysis with PWV as the exposure, 6 were available in summary-level outcome data. The main MR results are shown in Figure 3. Based on MR analysis with an inverse weighted method, we found evidence for a causal effect of PWV on SBP (Figure 3A, inverse-variance weighted analysis beta=0.11, P<0.02) and DBP (Figure 3B, beta=0.09, P<0.0001) suggesting a causal effect of PWV on both systolic and diastolic BP. The weighted median regression estimates were consistent with these findings. Positive effects of similar magnitude and significance were found for leave-one-out sensitivity analysis. The MR-Egger regression intercept did not suggest any evidence of horizontal pleiotropy (beta=-0.017, P=0.291 for SBP and beta=-0.006, P=0.489 for DBP).

Of the 984 alleles included in the 2-sample MR analysis with BP as the exposure, 575 were available in summary-level outcome data. The main MR results are shown in Figure 4. Based on MR with inverse weighted method, we found evidence for a causal effect of BP on arterial stiffness (Figure 4, inverse-variance weighted analysis beta=0.004, P<0.0001). The weighted median regression estimates were consistent with these findings. The MR-Egger regression intercept did not suggest any evidence of horizontal pleiotropy (beta=0.00, P=0.871). A sensitivity analysis as recommended by Burgess et al [14] using fewer but stronger genetic variants to investigate bias resulting from an overlap in participants in the discover sets for the

BP associated SNPs and participants in the MR analysis did not influence our conclusions (data not shown).

DISCUSSION

Understanding the mechanism by which genetic polymorphisms influence BP is key to identifying novel pathways underlying hypertension. To date, GWAS investigating the genetic cause of hypertension have mostly focused on systolic and diastolic blood pressure. However, these values provide limited information on the BP phenotype. Mean and diastolic BP are determined mainly by CO and SVR whereas SBP and pulsatile components of BP are more closely related to SV and arterial stiffness.

To our knowledge this is the first study to examine the heritability and shared heritability of BP components and their hemodynamic determinants. The main finding is that, of the cardiovascular properties that determine BP, arterial stiffness is the one with the highest heritability and that shared genes account for a large proportion of the correlation between systolic BP and arterial stiffness. When examining gene variants known to relate to BP, to determine to which BP components and hemodynamic determinants of BP they relate most strongly, our finding of a number being related to PWV is consistent with high shared heritability of BP with PWV. Such genes could influence PWV through BP or through a direct influence on the arterial wall. In this regard it is notable that we identified a SNP that is likely to act through a direct effect on the arterial wall. rs9888615 is located on chromosome 14 within gene FERMT2 which has been implicated in cell-extracellular matrix interactions [15] that could affect arterial stiffness. Of the components of central SBP, it is notable that AP shows high heritability. AP refers to the portion of central systolic pulse pressure arising after myocardial wall stress has peaked early in systole but left ventricular pressure and central BP continues to rise. It is thought to depend less on aortic stiffness than the other components of pulse pressure and more on cardiac dynamics and wave reflection. That shared genes account for only a small

proportion of the phenotypic correlation between AP and PWV is consistent with AP being only weakly linked to PWV and relating more closely to other aspects of ventricular-vascular coupling [16]. Relatively high heritability of DBP but low heritability of CO and SVR, the main determinants of DBP (which is close to MAP), would appear a paradox at first sight but might be explained by a genetic regulation of BP itself rather than genetic regulation of CO and SVR; CO and SVR, despite being influenced by environmental factors, may be balanced through feedback mechanisms to achieve a genetically regulated "set point" of MAP or DBP. Such a set-point could occur through renal (pressure-natriuretic) [17] or neural (long term effects of baroreceptor setting or other neural set point) mechanisms [18]. The finding of no statistically significant effect of shared environment on BP is consistent with a recent family study [19] that found a greater effect of genetic and unique environmental factors compared to shared environmental factors on BP.

Shared heritability of BP and PWV could be due to a bi-directional relationship between BP and PWV. Although PWV is a hemodynamic determinant of the pulsatile components of BP, it is influenced by BP via the non-linear elastic properties of wall of the artery which result in a functional stiffening of the artery when distended by a higher BP. Long-term effect of steady state or pulsatile BP components may also lead to stiffening of the arterial wall through growth or remodelling processes. Thus, whether arterial stiffening is the cause or consequence of hypertension has been debated, with previous epidemiological studies differing in their conclusions [20]. The Framingham Heart study found that higher aortic stiffness was associated with a higher incidence of hypertension but not vice versa for progression of PWV [21]. However, in a younger cohort Chen et al [22] used cross-lagged path coefficients to investigate the temporal association between BP and PWV in 584 adults aged between 32-51 years in the Bogalusa Heart study. Over a 7-year follow-up they concluded that a BP rise preceded large artery

stiffening. Our finding of shared heritability of BP and PWV and of an association between BP-associated SNPs and PWV suggests a causal relationship between BP and PWV but does not identify the direction of causality. Using Mendelian randomisation, which may be less susceptible to bias from confounding than studies using phenotypic correlations and which provides evidence of longer term influences of potential determinants of outcomes, we found evidence of a causal role of BP in increasing aortic stiffness using 56 BP-associated SNPs as instrumental variables but also a causal role of PWV to increase SBP and PP but not MAP or DBP. Two-sample MR in the Biobank cohort confirmed the causal role of BP to increase arterial stiffness, as measured by arterial stiffness index, using 575 GWAS significant BP SNPs. The analysis in Biobank also identified a role of PWV to increase BP when using GWAS significant PWV SNPs ($P<5\times10^{-8}$) and suggestive PWV SNPs ($P<1\times10^{-5}$) as instruments. These results were supported by several sensitivity analyses including leave one out analysis, MR Egger and weighted median MR. An important assumption of MR is that genotype is related to the outcome only via its association with its risk factors (exclusion restriction assumption) i.e. that gene variants influence BP or PWV via specific mechanisms on one or other of these properties. For the majority of gene variants used in the present analysis the mechanism underlying their association with BP or PWV is unknown and could potentially be linked to one or both of these properties (i.e. exhibit horizontal pleiotropy). However, a lack of horizontal pleiotropy is supported by the low P-value in MR Egger analysis. Furthermore, use of multiple genetic variants as instrumental variables that are located on separate chromosomes and with independent effects on the risk factor is likely to minimise the effect of pleiotropy and strengthens the evidence for a bi-directional causal association between aortic stiffness and BP [7]. Gottsäter et al [23], investigated the causal association between SBP and PWV using systolic blood pressure associated SNPs as instrumental variables and found no causal association. However, this study used 29 SBP associated SNPs as instrumental variables which is likely to

have accounted for a smaller percentage of BP variance and thus be more susceptible to weak instrument bias which in MR biases the results towards the null [24]. High shared heritability of PWV and BP together with a bidirectional causal relationship between these two phenotypes suggest that PWV GWAS with similar power to that recently achieved for BP is an important objective for future studies to identify genetic determinants of BP regulation that are mediated through arterial stiffness.

Strengths and Limitations

The present study has several strengths. We used detailed cardiovascular phenotyping in a relatively large Twin cohort to determine the heritability of hemodynamic properties that determine BP and to explore hemodynamic mechanisms through which BP-associated polymorphisms may influence BP. While we are not able to infer the contribution from individual environmental factors, a major advantage of the twin design is that we can quantify the contribution of the totality of environmental factors on phenotypes, since by definition the environmental factors incorporate all those that are not inherited**.** MR techniques have the advantage of overcoming confounding by unmeasured/unknown factors due to the independent assortment of the instrumental variable risk alleles with confounding factors. Using both one- and two-sample MR design allowed us to use a large sample size maximising our statistical power and providing evidence of causality. In addition, we used multiple SNPs as instrumental variables instead of creating a weighted allele score. This has higher statistical power[7] and protects against bias arising from horizontal pleiotropy[12].

The study also has several limitations. We cannot rule out that our measures of heritability include effects on DNA methylation which may play a role in regulating BP independently of known genetic variants. Most of our analysis is limited to female twins and cannot be generalised to men. However, this cohort has been shown to be comparable to the general female population in the UK[25]. Although there were some significant differences between MZ and DZ twins (blood pressure, medication use and hemodynamic properties), most of these differences were explained by DZ twins being older compared to MZ. We accounted for this by adjusting for age in the heritability analysis. Our study did not identify pathways lying upstream of the intermediate phenotypes (BP and stiffness). Replication studies are required to confirm the link between gene variants associated with BP and PWV that we identified together with functional studies to determine the specific biological pathways through which these may act. Many pathways are likely to be involved and may including those related to telomere length, glucose and inflammation [26-28].

Limitations of Mendelian randomisation have been reviewed elsewhere [29] and include failure to establish associations between genotype and intermediate phenotype, confounding of these associations, pleiotropy and canalization and developmental compensation. In the present study these were mitigated by selection of gene variants that were robustly associated with phenotypes, the use of multiple gene variants located on different chromosomes and consistency of results in two populations. It should, however be noted that, in the Biobank MR analysis, arterial stiffness was estimated using arterial stiffness index which is an indirect measure of arterial stiffness that may be influenced by other hemodynamic properties [30]. IV for arterial stiffness in the Biobank analysis were also less robust than for BP. There was an overlap in participants for the discovery sets that led to identification of the 984 BP SNPs and the participants included in MR analysis (but a sensitivity analysis to guard against bias introduced

by this,[14] did not influence our main conclusions). Further work in other cohorts and/or direct measurement of arterial stiffness in Biobank would therefore be valuable.

We used MR to examine the association between intermediate phenotypes (BP and stiffness) but there are other important categories of inference that can be derived from mendelian randomisation such as propensity to exposure to a risk factor, the category of exposure of importance, characterising "difficult to measure" environmental exposures and modifiers of environmental exposure. Future work using Mendelian randomisation to explore the specific environmental determinants of BP phenotypes, particularly those with a large environmental component, is likely to be productive.

Conclusion

We provide evidence of significant heritability of BP components and of large artery stiffness but not CO or SVR, which appear to be influenced more by environmental rather than genetic factors. Bivariate heritability analysis identified a high proportion of shared genes underlying the association of pulsatile components of BP other than AP with arterial stiffness and several of the gene variants known to be associated with BP are associated with arterial stiffness. MR suggests a bi-directional causal relationship between BP and arterial stiffness. The genetic basis of BP may be mediated at a hemodynamic level by genes that influence arterial stiffness and in part by genes that act directly to regulate BP. The finding of a bidirectional relationship between BP and PWV is key to tackling the epidemic of predominantly systolic hypertension in our ageing societies characterised by elevated PWV. It suggests that the most effective

treatments will be a combination of conventional antihypertensive agents to lower BP and specific agents to lower PWV.

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CONFLICT OF INTEREST

None

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Table 1. Glossary of key definitions relating to heritability and cardiovascular measures.

Heritability Definitions	
ACE Model	This model assumes that the source of phenotype variance can be attributed to genetic influences (A), shared environmental factors (C) and unique environmental factors (E). Environmental factors are all those that are not inherited irrespective of whether they are explicitly measured.
CE Model	Assumes that the source of phenotype variance can be attributed to shared environmental factors (C) and unique environmental factors (E)
Heritability	Proportion of population variance of a phenotype attributed to genetic factors at a particular time-point.
Cardiovascular Definitions	
Augmentation Pressure	Augmentation pressure (AP) is the difference between central systolic blood pressure and P1. See Figure 1.
Cardiac Output	Volume of blood ejected by the left ventricle per minute.
Pressure at P1	Pressure at the first systolic shoulder of the central pressure waveform. P1 represents the pressure at the first systolic shoulder or peak and corresponds to the time of peak myocardial wall stress. See Figure 1.
Pulse Pressure	Pulse pressure is the pressure difference between systolic and diastolic pressure.
Pulse Wave Velocity	Pulse wave velocity is the velocity at which the pressure pulse propagates along the arterial tree and is regarded as the gold-standard measure of arterial stiffness.
Stiffness Index	An index of arterial stiffness derived from the finger photoplethysmography that both theoretically and empirically relates to PWV.
Systemic Vascular Resistance	Resistance to blood flow offered by the systemic vasculature.

Table 1. Table of Participant Characteristics for the Twins UK Cohort and by zygosity.

Variable	N	Twins UK Cohort	MZ twins (N=1934)	DZ Twins (N=1586)	P value
Age (years)	3531	56.7±12.9	55.2±13.8	58.6±11.1	<0.001
SBP (mm Hg)	3416	125.6±17.3	124.5±17.3	127.0±12.4	<0.001
DBP (mm Hg)	3416	73.7±8.9	73.2±8.8	74.2±9.0	<0.001
PP (mm Hg)	3416	52.0±12.7	51.3±12.9	52.8±12.3	<0.001
Antihypertensive treatment, %	3502	21.5	20.3	23.2	=0.040
Lipid-lowering treatment, %	3503	14.2	12.7	16.1	=0.004
Diabetes mellitus treatment, %	3531	2.5	2.1	3	=0.070
Current smoker, %	3528	9.4	8.0	11.0	=0.002
AP (mm Hg)	3371	13.8±8.0	13.2±8.1	14.6±7.6	<0.001
P1 (mm Hg)	3371	28.7±6.8	28.4±6.9	29.1±6.6	=0.001
PWV (m/sec)	3309	9.2±2.1	9.1±2.1	9.4±2.1	<0.001
LVOT diameter (mm)	1625	20.0±1.9	19.9±1.9	20.1±1.8	=0.008
Cardiac Output (l/min)	1582	4.49±1.2	4.46±1.2	4.52±1.3	=0.290
SVR (dyn□s□cm^{-5})	1540	1761±563	1747±543	1779±588	=0.280

Subject characteristics are summarised as means and standard deviation unless otherwise stated. Comparison between groups were made using Students' t-test and Chi-squared test. MZ=monozygotic; DZ=dizygotic; SBP = systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure; PP=pulse pressure; AP=augmentation pressure; PWV=pulse wave velocity; LVOT=left ventricular outflow tract; SVR=systemic vascular resistance.

Table 3. Association between Blood Pressure Single Nucleotide Polymorphisms with Components of Blood Pressure Components and Pulse Wave Velocity

			Augmentation Pressure			Blood pressure at P1			Pulse wave Velocity		
SBP ID	**Gene**	**BP trait**	**beta**	**P**	**OLS**	**beta**	**P**	**OLS**	**beta**	**P**	**OLS**
rs10923038		DBP	-0.09	<0.01	-0.09	-	-	-	-	-	-
rs3742182		DBP	0.11	<0.01	0.09	-	-	-	-	-	-
rs3184504	**SHB3**	DBP/SBP/PP	0.08	<0.05	0.06	-	-	-	-	-	-
rs3745318	**KLF2**	DBP	0.07	<0.05	0.07	-	-	-	-	-	-
rs10842991		DBP	0.09	<0.05	0.08	-	-	-	-	-	-
rs1055144	**LOC100506236**	SBP	-0.1	<0.05	-0.11	-	-	-	-	-	-
rs11909120	**N6AMT1**	DBP	-	-	-	-0.6	<0.05	-0.67	-	-	-
rs4810332		SBP	-	-	-	0.55	<0.05	0.55	-	-	-
rs9860290	**CMSS1**	PP	-	-	-	-0.52	0.05	-0.58	-	-	-
rs9888615	**FERMT2**	SBP	-	-	-	-0.59	<0.05	-0.54	-0.17	<0.05	-0.16
rs2390258		DBP/SBPPP	-	-	-	0.45	0.05	0.47	0.23	0.001	0.26
rs4553000	**UBAP1**	DBP/SBP/PP	-	-	-	-	-	-	-0.22	0.001	-0.19
rs4980515		DBP	-	-	-	-	-	-	-0.21	0.001	-0.23

P1 = pressure at the first systolic shoulder; DBP = diastolic blood pressure; SBP = systolic blood pressure; PP= pulse pressure; OLS = ordinary least squares

Table 4. One-sample bi-directional Mendelian Randomisation between Blood Pressure Components and Pulse Wave Velocity in the Twins UK cohort.

Exposure Variable	Outcome Variable	N	Association exposure-outcome		MR (IV-exposure-PWV)	
			beta	P	beta	P
SBP	PWV	2,088	0.07	<0.0001	0.08	<0.0001
DBP	PWV	2,088	0.09	<0.0001	0.07	<0.0001
PP	PWV	2,088	0.10	<0.0001	0.12	<0.0001
PWV	SBP	1,758	4.84	<0.0001	7.42	0.011
PWV	DBP	1,758	1.5	<0.0001	0.83	0.613
PWV	PP	1,758	3.34	<0.0001	6.59	0.006
PWV	MAP	1,758	2.87	<0.0001	3.17	0.207

MR = Mendelian randomisation; SBP=systolic blood pressure; DBP=diastolic blood pressure, PP=pulse pressure; PWV=pulse wave velocity; MAP=mean arterial pressure.

Figure 1. Example of a central blood pressure waveform separated into its components P1 (pressure at the first systolic shoulder) and augmentation pressure (AP), systolic blood pressure (SBP) and diastolic blood pressure (DBP).

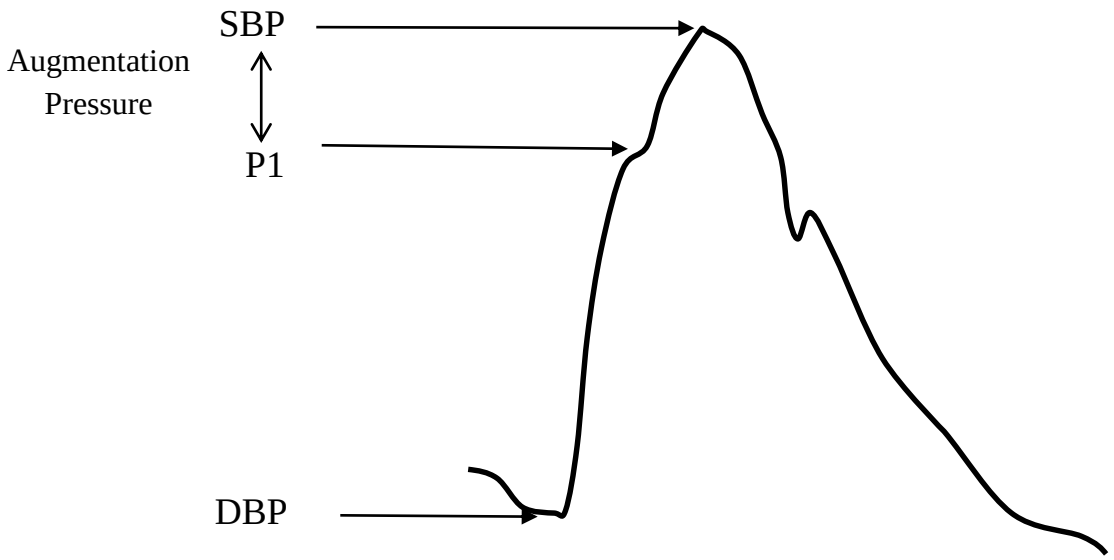
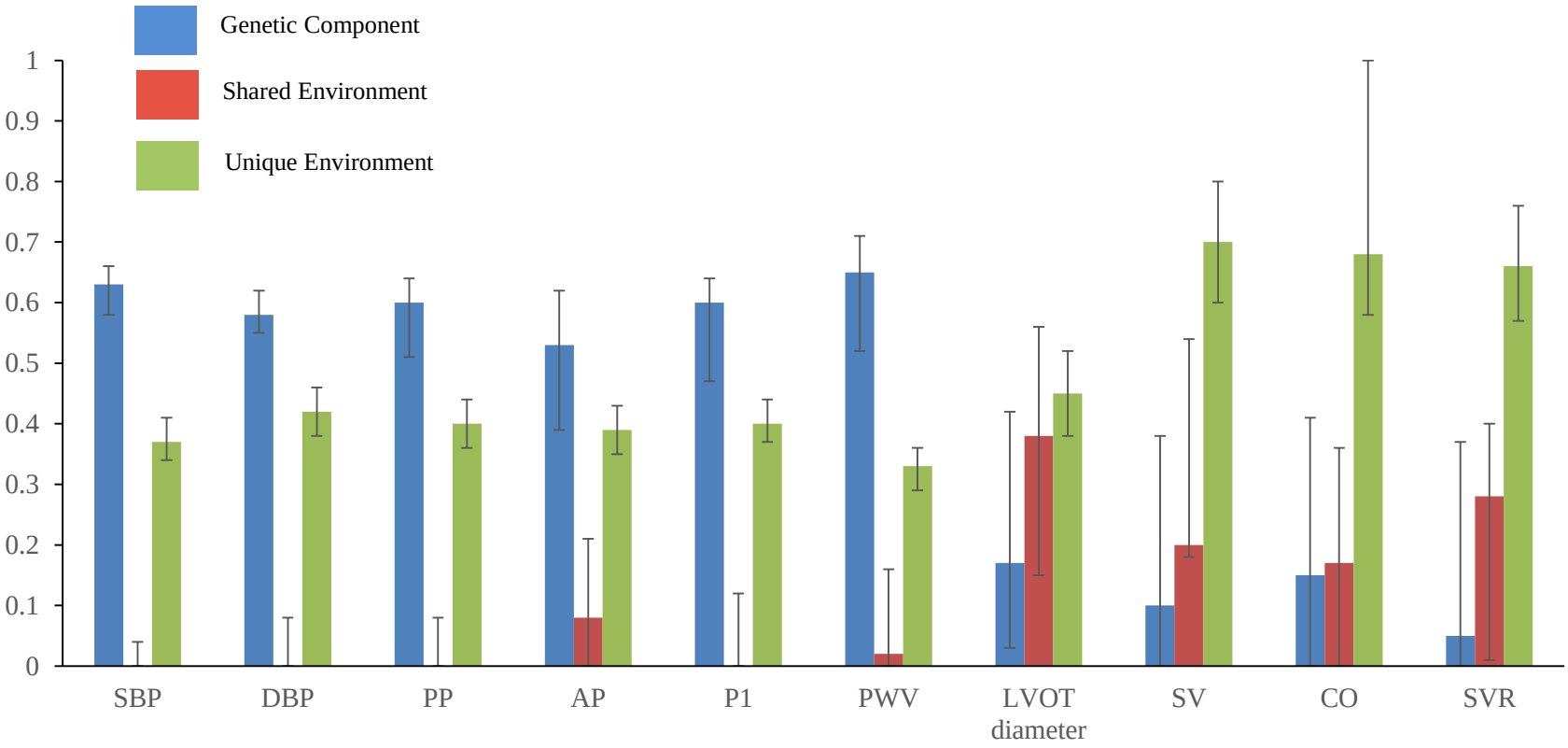
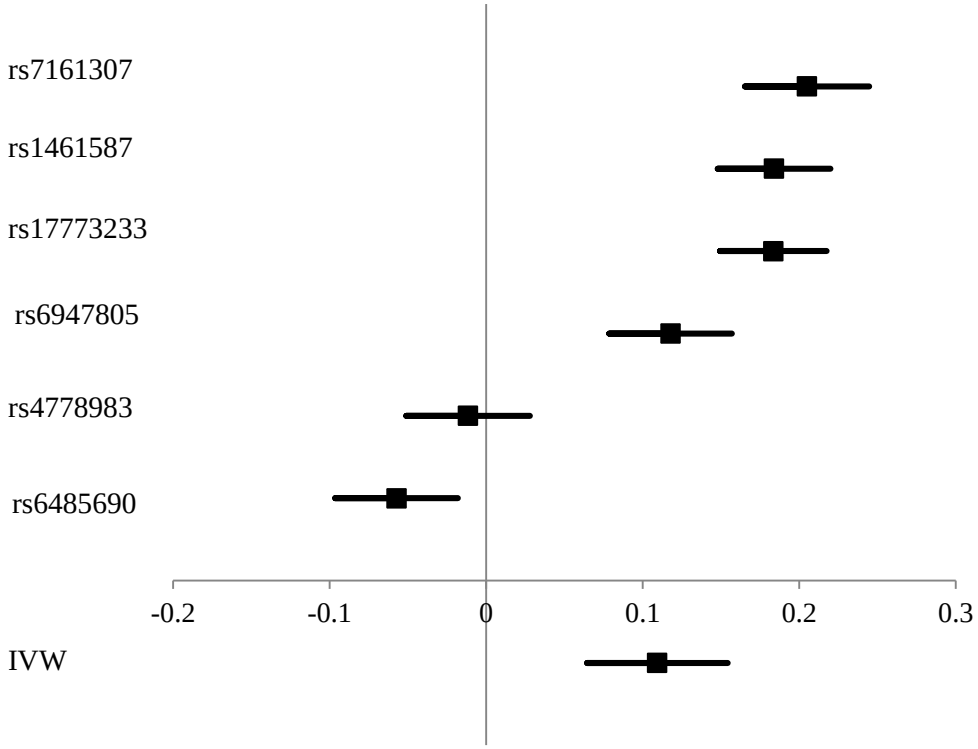


Figure 2. Bar graph of ACE modelling estimates.



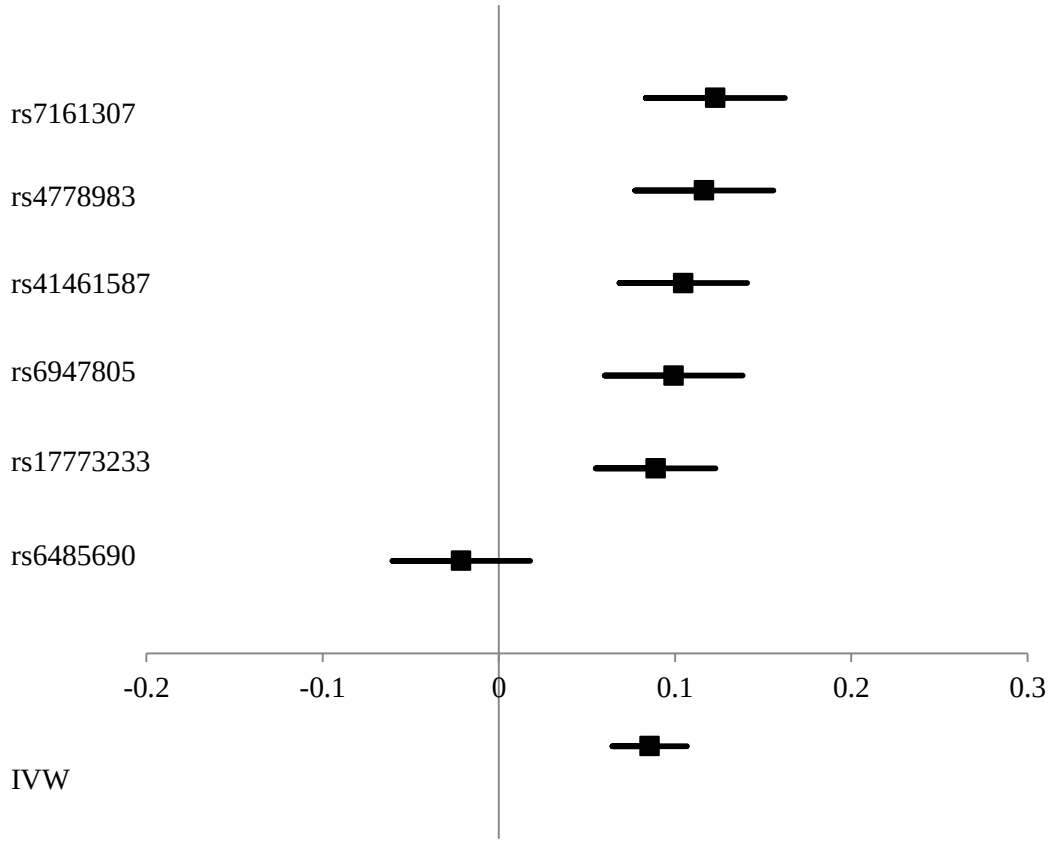
SBP=systolic blood pressure; DBP=diastolic blood pressure; PP=pulse pressure; AP=augmentation pressure; PWV=pulse wave velocity; LVOT=left ventricular outflow tract; SV=stroke volume; CO=cardiac output; SVR=systemic vascular resistance. Bars represent 95% confidence intervals.

Figure 3 (A): Forest plot of 2 sample Mendelian randomisation (MR) with systolic blood pressure (SBP) as the outcome (single nucleotide polymorphisms are ordered according to strength of association).



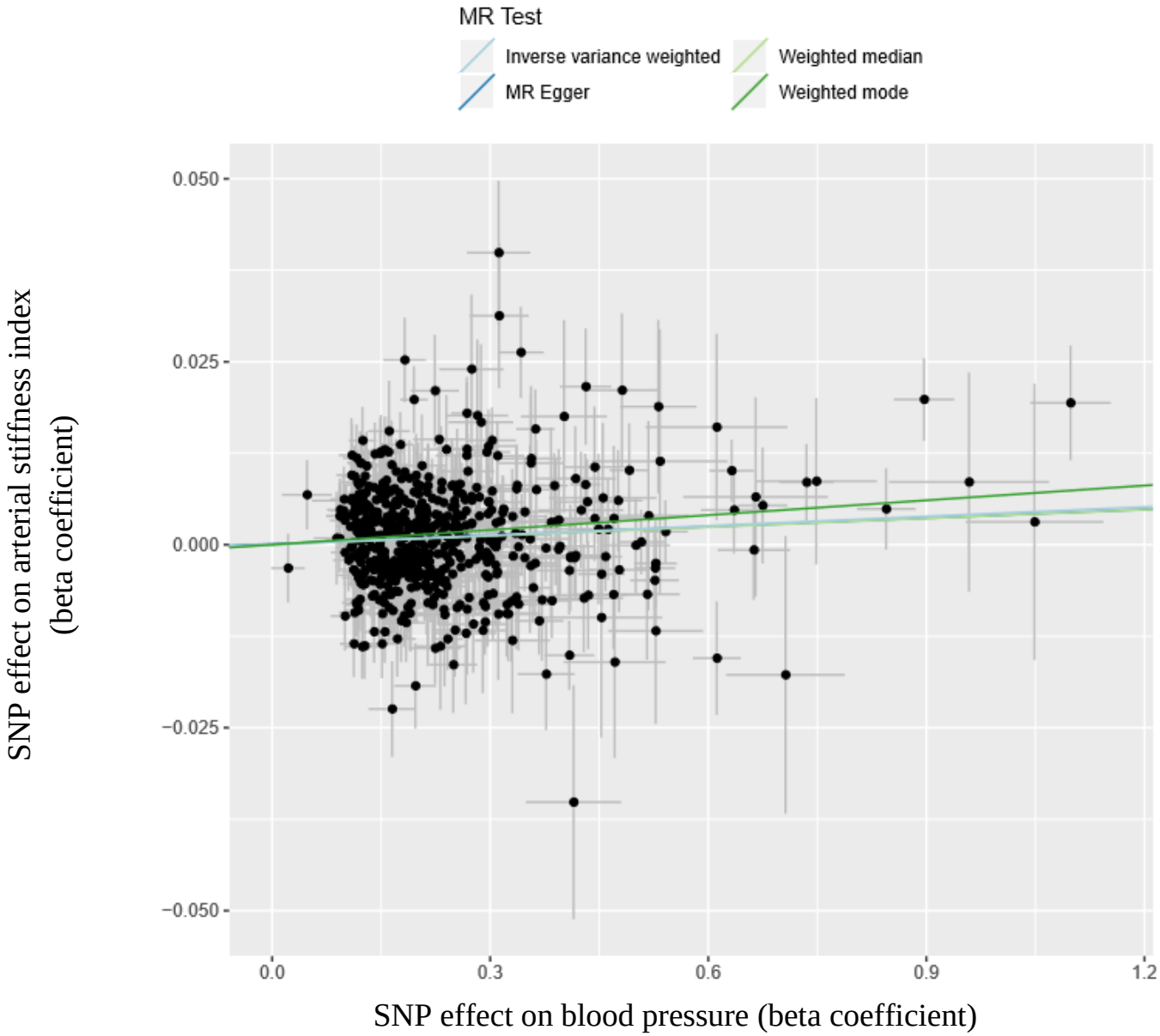
Method	beta	Standard error	P-value
Weighted median	0.1092	0.0333	0.001
Inverse variance weighted (IVW)	0.1094	0.04488	<0.02

Figure 3B. Forest plot of 2 sample Mendelian randomisation (MR) with diastolic blood pressure (DBP) as the outcome (single nucleotide polymorphisms are ordered according to strength of association).



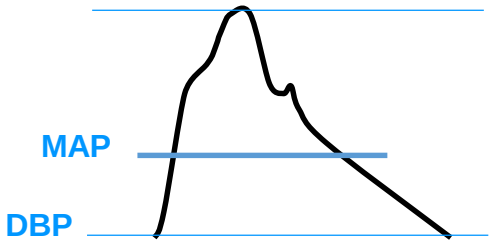
Method	beta	Standard error	P value
Weighted median	0.09997	0.02223	<0.0001
Inverse variance weighted (IVW)	0.0856	0.02111	<0.0001

Figure 4. The association between the effect of blood pressure associated single nucleotide polymorphisms (SNPs) on the arterial stiffness index (y-axis) plotted against the effect of blood pressure associated SNPs on blood pressure (x-axis). The slope of the regression line represents the causal association estimated using different regression methods.



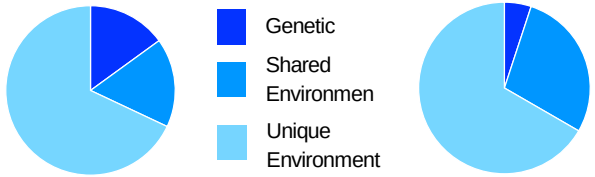
Figure

Mean arterial pressure/ Diastolic blood pressure



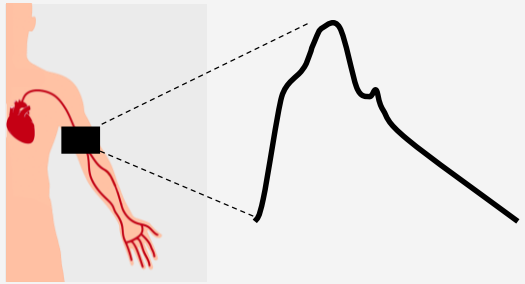
Cardiac Output

Vascular Resistance



High Blood Pressure

(>900 associated SNPs)



BP associated Genetic variants

One sample MR – 56 SNP (Twins UK)

Two-sample MR- 575 SNPs (Biobank UK)

BP

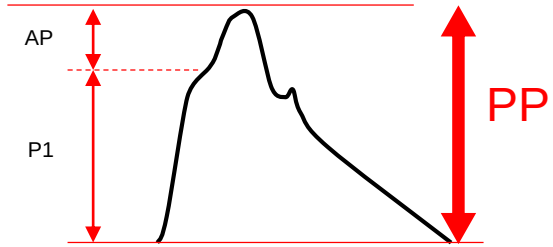
Stiffness

One sample MR – 2 SNP (Twins UK)

Two-sample MR - 6 SNP (Biobank UK)

Stiffness associated Genetic variants

Pulse Pressure



Aortic Stiffness

Low heritability

High environmental determinants

Bi-directional causality

Blood Pressure ⇄ Stiffness

Using Mendelian Randomisation

High heritability

Pleiotropic effect of blood pressure SNPs

SUPPLEMENTARY MATERIAL

METHODS

Genotyping

Genotyping was performed using Infinium 317K and 610K assay (Illumina, San Diego, California, USA) [1]. For quality control, single nucleotide polymorphism (SNPs) were excluded if they had a call rate <97%for SNPs with minor allele frequency (MAF) ≥5% or if the call rate was less than 99% for SNPs with MAF between 1% and 5%. SNPs were also excluded if MAF was less than 1% and Hardy-Weinberg equilibrium P values were less than 10^{-6}. Participants were removed if genotyping failed in >2% of the SNPs. Imputation of genotypes was carried out using IMPUTE V2 software using HAPMAP2 as the reference panel.

Blood Pressure and Hemodynamic Measurements

All hemodynamic measurements were performed in succession during a single visit. Brachial BP was measured with the participants in a supine position using a validated oscillometric method (Omron 705CP, Omron Health Care, Japan). Measurements were made in triplicate and the average taken for statistical analysis. Radial blood pressure waveforms were obtained using applanation tonometry using the Sphymocor system (Atcor, West Ryde, Australia) and transformed into a corresponding central blood pressure waveforms using a validated inbuilt transfer function calibrated to mean arterial pressure (MAP) and diastolic blood pressure (DBP) [2]. BP components derived from the central pressure waveform included central systolic blood pressure (cSBP), central pulse pressure (cPP) and pressure at the first systolic shoulder of the central pressure waveform (P1). P1 represents the pressure at the first systolic peak or peak and corresponds to the time of peak myocardial wall stress[3]. Augmentation pressure (AP), measured as the difference between cSBP and P1 (Figure 1) [4], refers to the portion of central systolic pressure arising after wall stress has flow peaked but pressure continues to rise. We

have previously shown that these two components of central pressure, P1 and AP, relate to different cardiovascular properties [4, 5].

Pulse wave velocity (PWV) between the carotid and femoral arteries, a measure of large artery stiffness, was obtained using the Sphygmocor system [6]. Carotid and femoral pressure waveforms were recorded sequentially in reference to an electrocardiogram. The distance between the recording sites was estimated using surface measurements between the sternal-notch and femoral artery (at the point of applanation). PWV was then calculated by dividing distance by time (difference in time of pulse arrival between the carotid and femoral arteries). All measurements were made in triplicate and mean values used for analysis [6].

The left ventricular outflow tract (LVOT), was visualised using 2–dimensional echocardiography from a long-axis parasternal view using Siemens CV70 (Acuson-Siemens Corp., California) or Vivid-7 (General Electric Healthcare, UK) ultrasound system and a 4-MHz cardiac transducer [5]. Diameter of the LVOT was measured proximal to the aortic valve. Velocity time integral was obtained using continuous Doppler at the same level as the LVOT from the apical 5-chamber view and stroke volume (SV), was calculated by multiplying the velocity-time integral by the cross-sectional area of the LVOT estimated from diameter measurements. Cardiac output (CO), was calculated by multiplying the SV by heart rate. Systemic vascular resistance (SVR) was calculated using the formula (80 x MAP)/CO ($dyn \cdot s \cdot cm^{-5}$) [7].

Heritability

Genetic contributions are partitioned into those that are additive and describe the total sum of individual alleles influencing the phenotype. Environmental influences are partitioned into

those that are shared between twins and therefore make them more similar (e.g. raised in same household); and those that are unique to individuals and result in differences between twins (and which includes measurement error). Shared environment is assumed to correlate perfectly for both monozygotic (MZ) and dizygotic (DZ) twins while unique environment is assumed to be uncorrelated in twins (Supplementary Figure 1).

For heritability analysis, intraclass correlation coefficients and their 95% confidence intervals were calculated for MZ and DZ twins to compare twin resemblance for cardiovascular phenotypes as previously described [8]. A greater correlation in MZ compared to DZ twins indicates a genetic influence. The intra-class correlation coefficient difference between MZ and DZ twins was less than half for these phenotypes indicating an additive genetic difference is more likely than a dominant genetic model. Heritability analysis for cardiovascular phenotypes was performed using Mx software (University of Virginia) using structural equation modelling. For this analysis, phenotypic variation was assumed to derive from an additive genetic component (A), shared environmental component (C) and unique environmental component (E) forming an ACE model. The unique environmental component also includes measurement error. Correlation between additive genetic factors is assumed to be complete (r=1.0) in MZ twins and incomplete (r=0.5) in DZ twins. Shared environmental factors are assumed to correlate (r=1.0) in both MZ and DZ twins, whereas unique environmental factors are assumed to be uncorrelated (r=0) between twins. The fit of the genetic models was compared to a 'saturated model' which fully describes the data without making any assumptions. Parameters of the saturated and ACE model were estimated using maximum likelihood. The significance of the ACE parameters was tested by constraining each individual parameter to zero and comparing the fit to the full ACE model using a likelihood ratio chi-squared (χ^2) test. A non-significant χ^2 value indicates the most parsimonious model is the one omitting the parameter in

question. Variables that appeared to deviate from a normal distribution were transformed either using a log or square root transformation. All variables were age-adjusted. Because CO, SV, and SVR are size dependent we further adjusted heritability estimates for height. Sensitivity analysis excluding individuals on antihypertensive medication was performed.

The extent to which the correlation between different traits (BP components and hemodynamic properties) can be attributed to overlapping genetic influence was examined using bivariate heritability analysis for which all variables were standardised. For this analysis the variance-covariance matrices, with cross-twin, cross-trait correlations, were specified in terms of the ACE parameters and the additive genetic correlation (r_g), shared environmental correlation (r_c) and unique environmental correlation (r_e), parameters estimated using maximum likelihood. An r_g of 1 indicates that the genes that influence the two traits completely overlap, whereas an r_g value of 0 indicates that the two traits are influenced by completely different genes.

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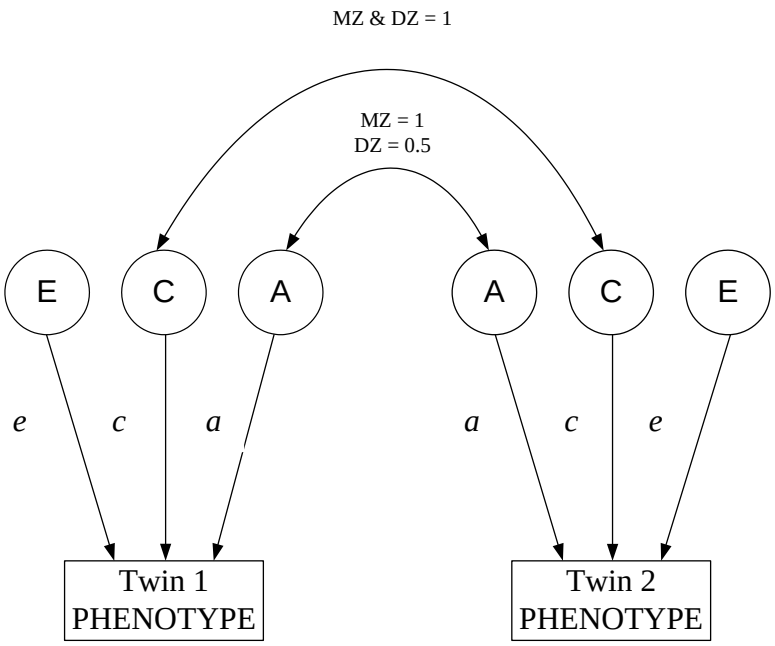
Figure 1. Path diagram of the ACE model.



Influence of genetic factors (A) and environmental factors in the ACE twin model. Environmental influences are partitioned into those that are shared between twins (C) and therefore make them more similar (e.g. raised in same household); and those that are unique to individuals (E) and result in differences between twins (and which includes measurement error). Shared environment is assumed to correlate perfectly for both monozygotic and dizygotic twins while unique environment is assumed to be uncorrelated in twins. Environmental factors represent the totality of all factors whether measured or unmeasured. Single headed arrows show the effect of latent variables on the phenotype where a, c and e are path coefficients. Double headed arrows represent correlations between latent variables for monozygotic (MZ) and dizygotic (DZ) twin pairs. Correlation for A is 1.0 for MZ and 0.5 for DZ twins. Correlation for C is 1.0 for both MZ and DZ twins, and E is uncorrelated in twins. Structural equation modeling incorporates the relationships in this diagram.

Table 1. Intra-class correlation coefficients for cardiovascular phenotypes for monozygotic and dizygotic twins

Phenotype	r_{MZ} (95% CI)	r_{DZ} (95% CI)
Peripheral SBP (mm Hg)	0.82 (0.80-0.84)	0.49(0.41-0.56)
Peripheral DBP (mm Hg)	0.74(0.71-0.77)	0.27(0.33-0.50)
Peripheral PP (mm Hg)	0.82(0.79-0.84)	0.55(0.48-0.61)
Central SBP (mm Hg)	0.84(0.82-0.86)	0.53(0.46-0.60)
Central DBP (mm Hg)	0.74(0.70-0.77)	0.44(0.35-0.51)
Central PP (mm Hg)	0.85(0.82-0.86)	0.62(0.55-0.67)
AP (mm Hg)	0.84(0.82-0.86)	0.62(0.55-0.67)
P1 (mm Hg)	0.80(0.77-0.82)	0.56(0.49-0.62)
PWV (m/sec)	0.88(0.86-0.90)	0.73(0.69-0.77)
LVOT diameter (mm)	0.71(0.64-0.77)	0.57(0.45-0.67)
SV (ml)	0.51(0.39-0.61)	0.41(0.24-0.54)
CO (l/min)	0.50(0.38-0.60)	0.40(0.22-0.54)
SVR (dyn□s□cm^{-5})	0.36(0.20-0.49)	0.37(0.18-0.52)

Table 2. Univariable model fitting estimates for cardiovascular measures by structural equation modelling (adjusted for age).

Phenotype	Model	Proportion of variance (95% CI)			Model Fit	
		A	C	E	χ^2	P-Value
SBP (mm Hg)	ACE	0.63 (0.58-0.66)	0.00 (0.00-0.04)	0.37 (0.34-0.41)	6.8*	0.077*
	AE	**0.63 (0.58-0.66)**	**-**	**0.37 (0.34-0.41)**	**0.00**	**$**
DBP (mm Hg)	ACE	0.58 (0.49-0.62)	0.00 (0.00-0.08)	0.42 (0.38-0.46)	7.8*	0.050*
	AE	**0.58 (0.54-0.62)**	**-**	**0.42 (0.38-0.46)**	**0.00**	**$**
PP (mm Hg)	ACE	0.60 (0.51-0.64)	0.00 (0.00-0.08)	0.40 (0.36-0.44)	3.2*	0.360*
	AE	**0.60 (0.56-0.64)**	**-**	**0.40 (0.36-0.44)**	**0.00**	**$**
AP (mm Hg)	ACE	0.53 (0.39-0.64)	0.08 (0.00-0.21)	0.39 (0.35-0.43)	5.4*	0.146*
	AE	**0.61 (0.57-0.65)**	**-**	**0.39 (0.35-0.43)**	**1.5**	**0.22**
P1 (mm Hg)	ACE	0.60 (0.47-0.64)	0.00 (0.00-0.12)	0.40 (0.37-0.44)	3.621	0.305*
	AE	**0.60 (0.56-0.64)**	**-**	**0.40 (0.36-0.44)**	**0.00**	**$**
PWV (m/sec)	ACE	0.65 (0.52-0.71)	0.02 (0.00-0.15)	0.33 (0.29-0.36)	7.8*	0.050*
	AE	**0.67 (0.64-0.71)**	**-**	**0.33 (0.29-0.36)**	**0.12**	**0.726**
LVOT diameter (mm)	ACE	0.17 (0.00-0.42)	0.38 (0.15-0.56)	0.45 (0.38-0.52)	1.32*	0.725*
	CE	**-**	**0.52 (0.46-0.58)**	**0.48 (0.42-0.54)**	**1.98**	**0.159**
Cardiac Output (l/min)	ACE	0.15 (0.00-0.41)	0.17 (0.00-0.36)	0.68 (0.58-0.36)	12.2*	0.007*
	CE	**-**	**0.29(0.21-0.37)**	**0.71 (0.63-0.79)**	**0.896**	**0.344**
SVR (dyn□s□cm^{-5})	ACE	0.05 (0.00-0.37)	0.28 (0.01-0.40)	0.66 (0.57-0.76)	7.1*	0.069*
	CE	**-**	**0.32 (0.24-0.40)**	**0.68 (0.60-0.76)**	**0.1**	**0.727**

Values in brackets are 95% confidence intervals. A=standardized additive gentic influence; C= standardized shared environmental influence; E=standardized non-shared environmental influence. * Compared to saturated model. $ Incalculable due to a lack of a change in fit statistics. Non-significant *p* values indicate that there is no significant deterioration in model fit compared to the saturated model or full ACE model. Results highlighted in bold indicate the most parsimonious models. SBP=systolic blood pressure (log); DBP=diastolic blood pressure; PP=pulse pressure; AP=augmentation pressure (square root); PWV=pulse wave velocity; LVOT=left ventricular outflow tract; SVR=systemic vascular resistance (log).

Table 3. Sensitivity analysis of heritability estimates for cardiovascular measures by structural equation modelling (adjusted for age and excluding individuals on HT treatment).

Phenotype		Proportion of variance (95% CI)			Model Fit	
	Model	A	C	E	χ^2	P-Value
SBP (mm Hg)	**ACE**	0.68 (0.62-0.72)	0.00 (0.00-0.05)	0.32 (0.28-0.36)	11.6	<0.001
	AE	0.68 (0.64-0.72)	-	0.32 (0.28-0.36)	0.00	$
DBP (mm Hg)	**ACE**	0.61 (0.50-0.66)	0.00 (0.00-0.10)	0.39 (0.34-0.43)	7.5	0.058
	AE	0.61 (0.57-0.66)	-	0.39 (0.34-0.43)	0.00	$
PP (mm Hg)	**ACE**	0.64 (0.50-0.68)	0.00 (0.00-0.12)	0.36 (0.32-0.41)	1.7	0.646
	AE	0.64 (0.59-0.68)	-	0.36 (0.32-0.41)	0	1
AP (mm Hg)	**ACE**	0.60 (0.43-0.68)	0.03 (0.00-0.18)	0.36 (0.32-0.41)	3.26	0.353
	AE	0.64 (0.59-0.68)	-	0.36 (0.32-0.41)	0.14	0.71
P1 (mm Hg)	**ACE**	0.58 (0.41-0.67)	0.06 (0.00-0.21)	0.37 (0.32-0.41)	0.25	0.97
	AE	0.64 (0.59-0.68)	-	0.36 (0.32-0.41)	0.486	0.486
PWV (m/sec)	**ACE**	0.68 (0.53-0.72)	0.00 (0.00-0.15)	0.32 (0.28-0.36)	12.4	<0.001
	AE	0.68 (0.64-0.72)	-	0.32 (0.28-0.36)	0.00	$
LVOT diameter (mm)	**ACE**	0.30 (0.00-0.57)	0.29 (0.00-0.53)	0.45 (0.38-0.54)	3.74	0.291
	CE	-	0.50 (0.43-0.57)	0.50 (0.43-0.57)	3.25	0.071
Stroke volume (ml)	**ACE**	0.00 (0.00-0.28)	0.31 (0.07-0.40)	0.69 (0.59-0.78)	6.056	0.109
	CE	-	0.31 (0.22-0.40)	0.69 (0.60-0.78)	0.00	$
Log SVR (dyn□s□cm⁻	**ACE**	0.10 (0.00-0.43)	0.24 (0.00-0.40)	0.67 (0.56-0.78)	10	0.019
	CE	-	0.31 (0.22-0.40)	0.69 (0.60-0.78)	0.28	0.598

Values in brackets are 95% confidence intervals. A=standardized additive gentic influence; C= standardized shared environmental influence; E=standardized non-shared environmental influence. * Compared to saturated model. $ Incalculable due to a lack of a change in fit statistics. Non-significant *p* values indicate that there is no significant deterioration in model fit compared to the saturated model or full ACE model. Results highlighted in bold indicate the most parsimonious models. SBP=systolic blood pressure (log); DBP=diastolic blood pressure; PP=pulse pressure; AP=augmentation pressure (square root); PWV=pulse wave velocity; LVOT=left ventricular outflow tract; SVR=systemic vascular resistance (log).

Table 4. Bivariate heritability showing the proportion of phenotypic correlation explained by common genetic factors.

	Augmentation Pressure			Blood Pressure at P1			Pulse Wave Velocity		
	r	**r_g**	**%**	**r**	**r_g**	**%**	**r**	**r_g**	**%**
pSBP (mm Hg)	0.65	0.67	59.7	0.79	0.84	61.7	0.59	0.67	57.9
pDBP (mm Hg)	0.31	0.45	81.7	0.28	0.49	93.4	0.36	0.58	79.0
pPP (mm Hg)	0.66	0.64	52.6	0.94	0.94	54.1	0.56	0.57	47.7
AP (mm Hg)	-	-	-	0.49	0.50	54.1	0.38	0.17	19.6
P1 (mm Hg)	-	-	-	-	-	-	0.55	0.60	48.9

r = phenotypic correlation; r_g = genetic correlation; %= Percentage of the phenotypic correlation attributed to overlapping genetic influence (Bivariate heritability); pSBP = peripheral systolic blood pressure; pDBP = peripheral diastolic blood pressure; pPP = peripheral pulse pressure; AP = augmentation pressure; P1 = pressure at the first systolic shoulder.

Table 5. Single-nucleotide polymorphisms identidief by LASSO regression to associate with BP in the TwinsUK Cohort.

SNP number	BP trait replicated association
rs4980515	DBP
rs8016306	DBP/SBP/PP
rs2390258	DBP/SBPPP
rs2178452	DBP
rs4553000	DBP/SBP/PP
rs10923038	DBP
rs3184504	DBP/SBP/PP
rs17287293	DBP
rs10842991	DBP
rs3745318	DBP
rs28621435	DBP/SBP/PP
rs11248862	DBP
rs11909120	DBP
rs4443403	DBP/SBP/PP
rs4424827	DBP
rs1906672	DBP
rs72765298	DBP
rs62380354	DBP
rs1215469	DBP
rs12374077	DBP
rs10474346	DBP
rs10732433	DBP
rs11008355	DBP
rs3741378	DBP
rs67976715	DBP
rs11021221	DBP
rs3742182	DBP
rs9526707	DBP
rs2289261	DBP
rs1378942	DBP
rs33063	DBP
rs1529744	DBP/SBP
rs11681462	DBP/SBP/PP
rs11701033	DBP
rs11923667	DBP/SBP/PP
rs73171158	DBP
rs262986	DBP
rs16998073	DBP
rs1347345	DBP

rs286809	DBP/SBP/PP
rs62373688	DBP
rs157678	DBP
rs6867399	DBP/SBP/PP
rs13179413	DBP
rs6875372	DBP
rs7763294	DBP
rs504691	DBP
rs1004558	DBP
rs6963105	DBP
rs7009170	DBP
rs4582532	DBP
rs9888615	SBP
rs1055144	SBP
rs4810332	SBP
rs1126464	SBP
rs9860290	PP