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Effect of Systolic Blood Pressure on Left Ventricular Structure and Function

A Mendelian Randomization Study

Tom Hendriks, M. Abdullah Said, Lara M.A. Janssen, M. Yldau van der Ende,
Dirk J. van Veldhuisen, Niek Verweij, Pim van der Harst

See Editorial, pp 747–748

Abstract—We aimed to estimate the effects of a lifelong exposure to high systolic blood pressure (SBP) on left ventricular (LV) structure and function using Mendelian randomization. A total of 5596 participants of the UK Biobank were included for whom cardiovascular magnetic resonance imaging and genetic data were available. Major exclusion criteria included nonwhite ethnicity, major cardiovascular disease, and body mass index >30 or <18.5 kg/m^2. A genetic risk score to estimate genetically predicted SBP (gSBP) was constructed based on 107 previously established genetic variants. Manual cardiovascular magnetic resonance imaging postprocessing analyses were performed in 300 individuals at the extremes of gSBP (150 highest and lowest). Multivariable linear regression analyses of imaging biomarkers were performed using gSBP as continuous independent variable. All analyses except myocardial strain were validated using previously derived imaging parameters in 2530 subjects. The mean (SD) age of the study population was 62 (7) years, and 52% of subjects were female. Corrected for age, sex, and body surface area, each 10 mm Hg increase in gSBP was significantly ($P<0.0056$) associated with 4.01 g (SE, 1.28; $P=0.002$) increase in LV mass and with 2.80% (SE, 0.97; $P=0.004$) increase in LV global radial strain. In the validation cohort, after correction for age, sex, and body surface area, each 10 mm Hg increase in gSBP was associated with 5.27 g (SE, 1.50; $P<0.001$) increase in LV mass. Our study provides a novel line of evidence for a causal relationship between SBP and increased LV mass and with increased LV global radial strain. **(*Hypertension*. 2019;74:826-832. DOI: 10.1161/HYPERTENSIONAHA.119.12679.)** • **Online Data Supplement**

Key Words: biomarker ■ blood pressure ■ body surface area ■ cardiovascular disease ■ hypertrophy

Hypertension, traditionally defined as a systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg,[1] and in 2017 redefined by the American Heart Association as an SBP ≥130 mm Hg or DBP ≥80 mm Hg,[2] is a highly prevalent condition which plays an essential role in the etiology of a wide range of cardiovascular diseases. In 2011 to 2014, the prevalence of hypertension in adults in the United States, according to the most recent definition, was estimated at 45.6%.[3] When left untreated, a high blood pressure can lead to adverse left ventricular (LV) remodeling, such as LV hypertrophy, which is associated with an increased incidence of heart failure and cardiovascular death.[4–6] However, high blood pressure tends to cluster with other cardiovascular risk factors, such as obesity and smoking, making it difficult to identify independent effects of blood pressure on the structure and function of heart. Genome-wide association studies have successfully identified genetic variants associated with blood pressure and hypertension.[7–12] Individuals with more blood pressure–raising alleles, and therefore, a higher genetic risk of developing hypertension, are at higher risk of developing coronary artery disease.[13] It is yet unknown whether the relationship between increased blood pressure and adverse LV remodeling is of a causal nature. This study aimed to assess the causality of previously established associations between increased blood pressure and adverse LV remodeling by determining the effect of genetically predicted SBP (gSBP) on LV structure and function.

Methods

The data for this study is publicly available to registered investigators of the UK Biobank. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the UK Biobank at https://www.ukbiobank.ac.uk/. Analyses were performed using individuals included in the cardiovascular magnetic resonance imaging (CMR) substudy of the UK Biobank resource[14] with available short-axis cine images and genetic data (N=5596).[15] Townsend deprivation index, an area-based proxy for socioeconomic status, was calculated by the UK Biobank at baseline visit and inverse rank normalized. Body surface

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area (BSA) was calculated as proposed by DuBois and DuBois.[16] Blood pressure was calculated as the mean value of 2 automated or manual measurements and was adjusted for the use of an automated device using a previously described algorithm.[17] Physical activity was calculated using answers from touchscreen questions and classified into moderate-intensity (3.0–6.0 metabolic equivalents) or vigorous-intensity physical activity (>6.0 metabolic equivalents).[18] Medical history was defined using self-reported answers from questionnaires and hospital episode statistics. Several diseases were additionally defined by medication use: hypertension (oral β blocker, ACE (angiotensin-converting enzyme) inhibitor, angiotensin II receptor antagonist, thiazide diuretic, and calcium channel blocker), hyperlipidemia (cholesterol-lowering medication), and diabetes mellitus (oral antidiabetic and insulin). Subjects with unavailable SBP measurements (n=40), unavailable height measurements (n=6), nonwhite ethnicity (n=162), body mass index <18.5 or >30 kg/m^2 (n=1078), a medical history of coronary artery disease, heart failure, cardiomyopathy, cardiac surgery, percutaneous cardiac intervention, peri-/myocarditis, cardiac arrhythmia, heart valve disease, pulmonary hypertension, use of oral anticoagulants, noncoronary arterial disease, stroke, thromboembolism, malignancy, and renal failure (N=1101) were excluded from analyses. Nonwhite ethnicity (3% of the study population) was excluded to improve the homogeneity of the study population and because effects of genetic variants might vary across ethnicities. Subjects with major cardiovascular disease, active malignancy, renal failure, and obesity were excluded because their effect on LV structure and function has been reported and might dilute the observed effect of gSBP. After applying exclusion criteria, 3209 subjects remained in the study population.

Genotyping in the UK Biobank

The genotyping and imputation process in the UK Biobank has been described in more detail previously.[15] Briefly, individuals were genotyped using either the custom UK Biobank Axiom array that included 820 967 genetic variants (N=452 713; here N=2906) or the UK Biobank Lung Exome Variant Evaluation Axiom array that included 807 411 genetic variants (N=49 949; here N=303). Both arrays have insertion and deletion markers and have >95% common content. UK Biobank provided imputed genotype data based on merged UK10K and 1000 Genomes phase 3 panels.

Mendelian Randomization

A genetic risk score (GRS) for SBP was constructed in all remaining participants to quantify gSBP using variants reported in literature. When this study was designed in June 2017, we identified 128 previously discovered genetic variants for SBP in previously reported genome-wide association studies,[7–12] of which 126 were available in the UK Biobank, as listed in Table S1 in the online-only Data Supplement and described in Said et al.[19] Because some studies reported multiple correlated variants in the same genetic locus, the linkage disequilibrium clumping procedure (at $R^2<0.01$) implemented in PLINK version 1.9 was used to select 107 independent single nucleotide polymorphisms (SNPS), based on the lowest reported *P* value. For these 107 genetic variants, we used reported effect sizes that were estimated in the largest sample size that did not include UK Biobank data, for example, from the replication sample, to prevent circular inference and avoid overestimation of the effect. The GRS was constructed by summing the number of blood pressure–raising alleles (0, 1, or 2) for each individual after multiplying the alleles with the reported effect size of the genetic variant on SBP. Figure 1 highlights the association between gSBP and phenotypic SBP (pSBP). To optimize the statistical power of the study, participants with the lowest and highest GRS values were selected for further CMR postprocessing analyses and were allocated to a low gSBP (N=150, 4.8% of study population) and high gSBP (N=150) group, respectively. Image quality was assessed by observers blinded to study group, based on presence of artifacts, axis alignment, and short-axis coverage of LV. In case of insufficient image quality (N=15), subjects were excluded from analyses and replaced by subjects with subsequent highest or lowest GRS values to keep 150 subjects in both groups. GRS thresholds used to select the final study groups were <4.45 mm Hg for the low gSBP group and >13.16 mm Hg for the high gSBP group (Figure 2).

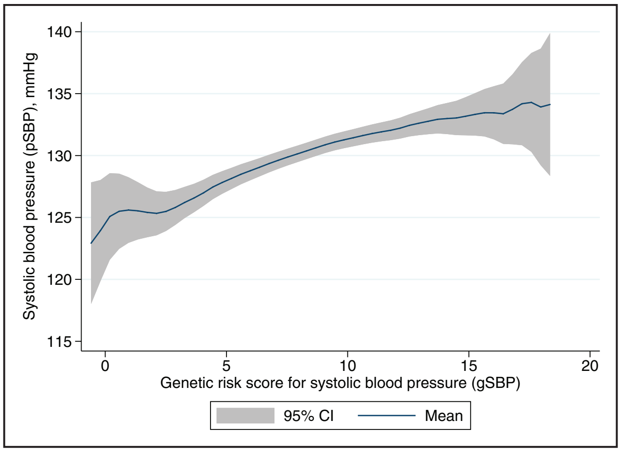

Figure 1. Association between genetically predicted systolic blood pressure (gSBP) and phenotypic systolic blood pressure (pSBP). Presented is a local polynomial smooth plot with 95% CI, using the Epanechnikov kernel function and 50 smoothing points.

CMR Postprocessing

Postprocessing analyses were performed by 2 experienced observers using cvi42 version 5.6.4 (Circle Cardiovascular Imaging, Calgary, Alberta, Canada), blinded to patient characteristics and study group. Epicardial and endocardial LV contours were traced at end-diastolic and end-systolic phases according to contemporary guidelines in short-axis cine series to determine LV mass, LV end-diastolic volume, and LV end-systolic volume.[20] Papillary muscles and trabeculae were included in the LV cavity. LV mass was determined at the end-diastolic phase. LV mass to volume ratio was calculated by dividing LV mass by LV end-diastolic volume. Myocardial strain measurements were done using the cvi42 tissue tracking plugin (Figure S1). Peak global circumferential and radial strain were measured in the short-axis cine series. Peak global longitudinal strain was measured by manually tracing endocardial and epicardial contours at end-diastolic phase in 3 long-axis cine series (2-chamber view, 3-chamber view, 4-chamber view) and calculating mean values. In case of insufficient quality of the 4-chamber view (N=9), 3-chamber view (N=6), or 2-chamber view (N=2) series due to severe artifacts or very poor axis alignment, measurements were excluded and mean values of the remaining measurements were used.

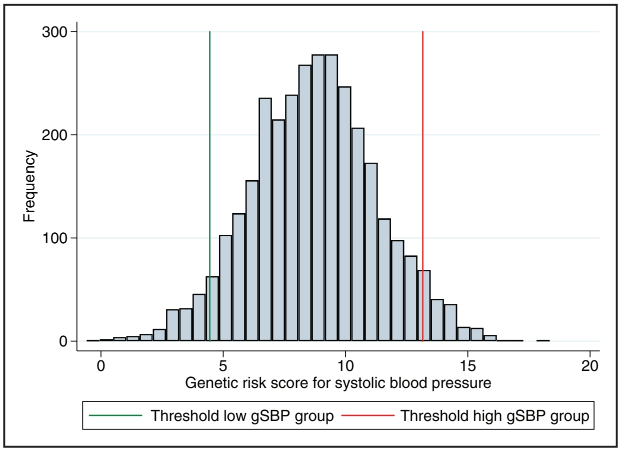

Figure 2. Distribution of genetic risk score for systolic blood pressure in UK Biobank population after initial exclusion criteria (N=3209). gSBP indicates genetically predicted systolic blood pressure.

Validation cohort

To validate our results observed in a population with extreme GRS values, we used imaging parameters previously derived by Petersen et al,[21,22] which were available in 2530 subjects out of 3209 subjects that remained in the study after applying inclusion and exclusion criteria and excluding our study population. LV myocardial strain measurements were not available and could not be validated.

Statistical Analyses

Baseline characteristics of the study population are presented by study group. Continuous variables are presented as mean with SD when normally distributed and as median with interquartile range in case of a non-normal distribution. Categorical and dichotomous variables are presented as number with percentage. Differences between groups were compared using ANOVA for normally distributed continuous variables, Wilcoxon rank-sum for non-normally distributed continuous variables, and Pearson χ^2 for categorical and dichotomous variables.

To determine intraobserver and interobserver variability in imaging parameters, intraclass correlation coefficients for derived imaging biomarkers were calculated in a subset of the study population in which postprocessing analyses were repeated. Linear regression analyses were performed on derived imaging biomarkers using GRS (as an estimate of gSBP) as a continuous independent variable, adjusted for genotyping chip used and the first 5 principal components (to adjust for population structure). First, basic univariate linear regression analyses were performed. Next, multivariable linear regression analyses were performed to correct for the effects of possible confounders, using 2 models of covariates. A basic model of covariates (model 1) included age and sex. In addition to age and sex, Model 2 also included BSA, which is widely used for indexation of LV volumes, LV mass, and cardiac output, to reduce variation related to body size.[21,23,24] The ratio between the variance of the imaging biomarker and the variance of pSBP explained by gSBP (R^2) was determined using univariate linear regression analysis and reported. Interaction analyses were performed to test for the presence of interactions between gSBP, age, and sex, using model 2. Linear regression analyses were repeated in the validation cohort on all available imaging biomarkers. To compare results of gSBP with effects of the phenotype, linear regression analyses were repeated using pSBP as a continuous independent variable. Unstandardized effect sizes on imaging biomarkers were reported per 10 mm Hg gSBP and pSBP. A Bonferroni correction was applied to reduce the chance of type I error; a significance level of 0.05/9=0.0056 was adopted as statistically significant. All aforementioned statistical analyses were conducted with STATA version 15.1 (StataCorp LP, College Station, TX).

Mendelian randomization assumes that (1) the instrumental variable is associated with the risk factor of interest, (2) the instrumental variable is independent of confounders, and (3) the instrumental variable does not affect the outcome except through the risk factor. The first assumption was assessed by linear regression of pSBP against gSBP. The second assumption was assessed by adding baseline characteristics that were significantly different ($P<0.05$) between study groups (possible confounders) to linear regression analyses. The third assumption was assessed by including pSBP as a covariate to linear regression analyses with gSBP.

If a significant effect of gSBP on a specific imaging parameter was observed after multivariable adjustment with model 2, statistical tests were performed to assess the presence of pleiotropy or heterogeneity of the observed effect estimates. Individual SNP effect sizes on SBP were determined in all UK Biobank participants with available genetic information and no CMR assessment performed, using the same cutoff values for GRS as the study population (<4.45 and >13.16 mm Hg). Individual SNP effect sizes on imaging parameters were determined using linear regression, corrected for confounders using model 2, and visualized using Forest plots and scatter plots. Results from inverse-variance–weighted fixed-effects meta-analyses of effect size on imaging parameters were reported. Mendelian randomization–Egger intercepts were determined; a $P<0.10$ was considered evidence for pleiotropic bias. A Cochran Q test was performed; a heterogeneity $P<0.05$ was considered evidence for heterogeneity. Heterogeneity and pleiotropy tests were performed using the MR Base package (https://mrcieu.github.io/TwoSampleMR/) in R version 3.3.2.

Results

Population Characteristics

Baseline characteristics of the study population are presented in Table 1. The mean (SD) age of the study population was 62 (7) years, and 52% of subjects were female. The difference in median gSBP between study groups was 10.34 mm Hg, whereas the difference in mean pSBP between groups was 7.56 mm Hg. The observed difference in mean pSBP was largely due to a difference in pulse pressure of 5.11 mm Hg and to a lesser extent due to a difference in DBP of 2.45 mm Hg. The overlap in pSBP between study groups is displayed in Figure 3. In the high gSBP group, 47 subjects (31%) were diagnosed with hypertension, of which 41 (27%) used antihypertensive medication. In the low gSBP group, 26 subjects (17%) were diagnosed with hypertension, of which 18 (12%) used antihypertensive medication. Other significant baseline differences between groups not directly related to blood pressure were Townsend deprivation index (P=0.010), hours of moderate physical activity per week (P=0.033), and smoking status (P=0.008).

Mendelian Randomization: Effect of gSBP on LV Structure and Function

Interobserver and intraobserver variability in determining imaging parameters was above 0.90 in all investigated parameters except LV mass to volume ratio and LV ejection fraction (Table S2). Results from regression analyses with gSBP are presented in Table 2. We observed a significant ($P<0.0056$) association between gSBP and LV mass and LV global radial strain. Corrected for age, sex, and BSA, each 10 mm Hg increase in gSBP was associated with 4.01 g (SE, 1.28; P=0.002) increase in LV mass and with 2.80% (SE, 0.97; P=0.004) increase in LV global radial strain.

Mendelian Randomization: Testing Assumptions

In our study population (N=300), gSBP was significantly associated with pSBP ($P<0.001$) and explained 5.5% of its variance. Adding baseline characteristics that were significantly different ($P<0.05$) between study groups (Townsend deprivation index, moderate physical activity, smoking status) to linear regression analyses did not change the observed effect of gSBP on LV mass and global radial strain from significant to nonsignificant. Adding pSBP to linear regression analyses changed the associations between gSBP and both LV mass and LV global radial strain from significant to nonsignificant (P=0.10 and P=0.030, respectively).

Mendelian Randomization: Pleiotropy and Heterogeneity

Pleiotropy and heterogeneity analyses were performed for observed associations between gSBP and LV mass and LV peak global radial strain. Forest plots and scatter plots with meta-analyzed results are presented in Figure S2 and Figure S3, respectively. Results from inverse-variance–weighted fixed-effects meta-analyses, Mendelian randomization–Egger

Table 1. Baseline Characteristics

Characteristic	Low gSBP (N=150)	High gSBP (N=150)	*P* Value
Genetic risk score for systolic blood pressure, mm Hg	3.52 (2.85–4.10)	13.86 (13.43–14.45)	<0.001
Age, y	61.31 (7.54)	62.13 (6.98)	0.33
Sex (male)	76 (50.7%)	69 (46.0%)	0.42
Townsend deprivation index at recruitment, inverse rank normalized	0.02 (0.94)	−0.27 (0.99)	0.010
Average total household income before tax, visit 2			
<18 000	27 (19.6%)	13 (9.2%)	0.13
18 000–30 999	36 (26.1%)	37 (26.2%)	
31 000–51 999	32 (23.2%)	42 (29.8%)	
52 000–100 000	34 (24.6%)	36 (25.5%)	
>100 000	9 (6.5%)	13 (9.2%)	
Weight, kg	72.30 (10.96)	71.83 (10.81)	0.71
Height, cm	169.26 (8.77)	169.13 (8.82)	0.89
Body mass index, kg/m^2	25.15 (2.64)	25.04 (2.68)	0.71
Body surface area, m^2	1.83 (0.17)	1.82 (0.17)	0.76
Waist hip ratio	0.85 (0.08)	0.84 (0.07)	0.27
Systolic blood pressure, mm Hg	125.09 (16.57)	132.65 (15.94)	<0.001
Diastolic blood pressure, mm Hg	76.83 (8.15)	79.28 (8.12)	0.009
Pulse pressure, mm Hg	48.26 (11.90)	53.37 (12.20)	<0.001
Mean arterial pressure, mm Hg	92.92 (10.22)	97.07 (9.78)	<0.001
Total moderate physical activity, h/wk	6.35 (3.08–14.38)	9.33 (3.71–16.05)	0.033
Total vigorous physical activity, h/wk	1.38 (0.19–3.50)	1.44 (0.38–3.42)	0.33
Smoking behavior			
Nonsmoker	78 (52.0%)	105 (70.0%)	0.008
Past smoker	62 (41.3%)	42 (28.0%)	
Active, occasional smoker	5 (3.3%)	2 (1.3%)	
Active, daily smoker	5 (3.3%)	1 (0.7%)	
Alcohol intake, UK Units/wk	9.60 (3.20–16.10)	9.60 (3.20–18.80)	0.88
Hypertension	26 (17.3%)	47 (31.3%)	0.005
Antihypertensive medication use	18 (12.0%)	41 (27.3%)	<0.001
Diabetes mellitus	5 (3.3%)	11 (7.3%)	0.12
Hyperlipidemia	27 (18.0%)	37 (24.7%)	0.16

gSBP indicates genetically predicted systolic blood pressure.

intercepts and heterogeneity *P* values from Cochran *Q* test are presented in Table S3. There was no evidence for pleiotropic bias or heterogeneity in any of the investigated associations.

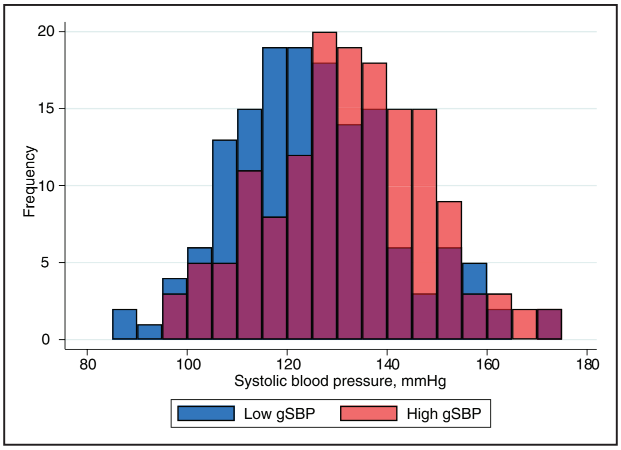

Figure 3. Distribution of systolic blood pressure at imaging visit per study group. gSBP indicates genetically predicted systolic blood pressure.

Interactions Between gSBP, Age and Sex

There was a significant interaction between gSBP and age on LV global radial strain (P=0.031), suggesting a difference in effect of gSBP on radial strain with varying age. An additional interaction was observed between gSBP and sex on LV end-systolic volume (P=0.030), suggesting a reduction of LV end-systolic volume with increasing gSBP in males, but not in females.

Validation Using Previously Derived Imaging Parameters

We attempted to validate the observed results by repeating linear regression analyses with gSBP on LV mass, volumes, mass to volume ratio, cardiac output, and ejection fraction in 2530 independent subjects with previously derived imaging parameters (Table 3). As in the study cohort, we observed a significant (P<0.0056) association between gSBP and LV mass in the validation cohort; all other associations were nonsignificant. Corrected for age, sex, and BSA, a 10 mm Hg increase in gSBP was associated with an increase of 5.27 g (SE, 1.50; P<0.001) in LV mass. The interaction between gSBP and sex on LV end-systolic volume could not be reproduced in the validation cohort (P>0.05). LV myocardial strain measures were not available in the validation cohort.

Discrepancies With Phenotype Associations

Results from regression analyses of pSBP are reported in Table S4. Corrected for age, sex, and BSA, we observed significant associations (P<0.0056) between pSBP and LV mass (β, 2.87±0.46 g/10 mm Hg; P<0.001) and LV global radial strain (β, 1.07±0.37 %/10 mm Hg; P=0.004). Associations that were significant for the phenotype but not for the genotype were associations between pSBP and LV mass to volume ratio (β, 0.0138±0.0032 /10 mm Hg; P<0.001) and cardiac output (β, 0.20±0.04 L/10 mm Hg; P<0.001).

Discussion

We investigated CMR-derived measures of LV structure and function in 300 individuals with extremes of gSBP. The main findings of our study were observed associations between gSBP and increased LV mass and LV global radial strain, providing evidence for a causal relationship between gSBP and adverse LV remodeling.

Table 2. Linear Regression Analyses of gSBP on Imaging Biomarkers (N=300)

Imaging Biomarker	Univariate		Model 1		Model 2		R^2/R^2_{SBP}
	β±SE	*P* Value	β±SE	*P* Value	β±SE	*P* Value	
LV mass (g)	2.90±2.01	0.15	4.37±1.40	0.002	4.01±1.28	0.002	0.16
LV end-diastolic volume (mL)	0.10±3.59	0.98	2.74±2.82	0.33	2.05±2.62	0.44	0.00
LV end-systolic volume (mL)	−1.47±2.06	0.47	−0.10±1.70	0.95	−0.36±1.66	0.83	0.03
LV mass to end-diastolic volume ratio	0.0177±0.0094	0.060	0.0194±0.0087	0.025	0.0191±0.0087	0.028	0.27
LV cardiac output (L/min)	0.04±0.13	0.78	0.12±0.11	0.29	0.10±0.11	0.37	0.01
LV ejection fraction (%)	1.00±0.66	0.13	0.81±0.64	0.21	0.79±0.65	0.22	0.14
LV peak global circumferential strain (%)	−0.79±0.28	0.005	−0.66±0.27	0.014	−0.66±0.27	0.014	0.49
LV peak global radial strain (%)	3.24±1.02	0.002	2.80±0.97	0.004	2.81±0.97	0.004	0.62
LV peak global longitudinal strain (%)	−0.03±0.25	0.91	−0.06±0.25	0.80	−0.06±0.25	0.82	0.00

Reported are unstandardized coefficients and SEs per 10 mm Hg increase of gSBP (genetic risk score). Model 1 consists of covariates age and sex. Model 2 consists of covariates age, sex, and body surface area. All analyses are adjusted for the genotyping chip used and the first 5 principal components. gSBP indicates genetically predicted SBP; LV, left ventricular; and SBP, systolic blood pressure.

Hypertension does generally not lead to symptoms,[6] meaning that individuals who are affected often do not visit a medical professional until a symptomatic comorbidity, such as myocardial ischemia due to coronary artery disease, has manifested. Hypertension is the leading risk factor for deaths caused by cardiovascular diseases, causing >40% of cardiovascular deaths.[25] Even small increases in blood pressure from thresholds of 115 mm Hg SBP and 75 mm Hg DBP have been associated with an increased risk of cardiovascular events.[26] Therefore, more recently, the American Heart Association's 2017 guideline has suggested lower thresholds for stage 1 hypertension at SBP values between 130 and 139 mm Hg and DBP values between 80 and 89 mm Hg.[2] The association between raised SBP and increased risk of cardiovascular disease has been shown repeatedly,[1,2] resulting in its inclusion in commonly used prediction models, such as the Framingham risk score.[27]

Magnetic resonance analyses using GRSs can provide evidence for causal relationships. This is especially valuable in studying processes with a multifactorial cause such as LV remodeling. gSBP has been previously associated with increased risk of cardiovascular diseases, such as coronary heart disease, atrial fibrillation, and stroke.[10,13,28] To our knowledge, the present study is the first to report the association between gSBP and changes in CMR-derived measurements of LV structure and function. The current study provides evidence for a causal relationship between SBP and adverse LV remodeling. We observed a large effect of gSBP on LV mass. These findings are in line with an earlier study that showed a significant association between gSBP using 29 genetic variants and increased LV wall thickness as measured by echocardiography.[29] Similar associations for pSBP have been reported before.[30] LV mass and concentricity are known to be strong predictors of incident cardiovascular events.[31] Although CIs somewhat overlapped, point estimates of the effect size of gSBP were larger compared with pSBP. The observed effect sizes are likely underestimated because the GRS for SBP was based on the estimated effect size of SBP-raising genetic variants, and differences in GRS between groups were larger than differences in measured SBP. Larger effects of gSBP on LV mass compared with pSBP is an expected result, as pSBP is a snapshot at a specific moment in time, affected by many confounding factors (such as white coat hypertension), whereas gSBP is stable and its effects are cumulative over a whole lifetime.

We observed a strong association between gSBP and increased LV radial strain, which was also observed for pSBP, but to a much lesser extent. Previous studies have mostly reported associations between hypertension and impaired LV longitudinal strain and in some cases also impaired circumferential

Table 3. Replication of gSBP Effect Size in Previously Determined Imaging Biomarkers by Petersen et al[21,22] (N=2530)

Imaging Biomarker	Univariate		Model 1		Model 2		R^2/R^2_{SBP}
	β±SE	*P* Value	β±SE	*P* Value	β±SE	*P* Value	
LV mass, g	7.14±2.25	0.001	5.90±1.63	<0.001	5.27±1.50	<0.001	0.29
LV end-diastolic volume, mL	7.54±3.23	0.020	5.75±2.56	0.025	4.82±2.38	0.043	0.15
LV end-systolic volume, mL	4.75±1.82	0.009	3.84±1.54	0.013	3.42±1.48	0.021	0.18
LV mass to end-diastolic volume ratio	0.0157±0.0110	0.15	0.0146±0.0105	0.16	0.0140±0.0105	0.18	0.06
LV cardiac output, L/min	0.11±0.11	0.34	0.07±0.10	0.47	0.04±0.10	0.66	0.03
LV ejection fraction, %	−0.70±0.59	0.24	−0.59±0.58	0.31	−0.57±0.58	0.33	0.03

Reported are unstandardized coefficients and SEs per 10 mm Hg increase of gSBP (genetic risk score). Model 1 consists of covariates age and sex. Model 2 consists of covariates age, sex, and body surface area. All analyses are adjusted for the genotyping chip used and the first 5 principal components. gSBP indicates genetically predicted SBP; LV, left ventricular; and SBP, systolic blood pressure.

strain.[32,33] Other studies observed that LV myocardial strain is most significantly impaired in subjects with both obesity and hypertension,[34] and we investigated a population free of obesity. As a prolonged exposure to high blood pressure can eventually progress into heart failure, we suspect that these studies have investigated individuals that had already suffered hypertension-related injury to the myocardium. We hypothesize that in a general population, blood pressure is associated with increased LV contractility and myocardial strain, whereas in more severe stages of hypertension, it is associated with strain impairment.

Future Perspectives

Our study indicates that gSBP is strongly related to increased LV mass, and radial strain indicating that long-term exposure to higher blood pressure directly impacts cardiac structure and function. Future studies will have to reveal whether a genetically predicted risk of hypertension also has additional value in predicting and preventing cardiovascular risk. GRSs are a potential detection tool that can be used for the prevention of cardiovascular disease, starting from an early stage in life. Because genetic variants are present from conception, they will have a cumulative burden on the cardiovascular system during one's lifetime. However, not only genetic composition but also lifestyle is strongly associated with risk of developing hypertension and future (cardiovascular) events.[19] The effect of lifestyle on cardiovascular disease, as well as the effect of lifestyle on pSBP are independent from the effects of gSBP.[19,35] Risk stratification based on genetic composition as well as lifestyle might eventually lead to clinical trial designs where individuals at high genetic risk receive early antihypertensive lifestyle or pharmacological interventions. Future studies could aim at determining whether hypertensive individuals with a large genetic component respond differently to pharmacological treatment.

Strengths and Limitations

This study is the first to perform Mendelian randomization analyses of SBP on CMR-derived imaging biomarkers of LV structure and function. Major strengths of this study were the use of CMR data, balanced GRS-based groups, and the comparison between genotype and phenotype.

A limitation of our study that should be considered is that we investigated subjects with extreme GRS values and, therefore, did not cover the full range as is usually done in magnetic resonance analyses. We were, however, able to validate some of our results in a large subset of UK Biobank participants with previously derived imaging parameters and a normal distribution of genetic risk. A second limitation is that we have selected a relatively healthy population, free of obesity, and therefore, our results might not be generalizable.

Perspectives

By investigating associations between genetically predicted higher SBP and imaging parameters derived from CMR, our study provides evidence supporting a causal relationship between SBP and increased LV mass and increased LV global radial strain. These results further improve our understanding of pathophysiology in hypertensive heart disease. As more genetic variants related to blood pressure are being discovered, genetic variants more strongly associated with adverse cardiac remodeling, such as concentric hypertrophy, could provide potential targets for therapy.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Mendelian randomization analyses of systolic blood pressure on cardiovascular magnetic resonance imaging–derived biomarkers of left ventricular structure and function, and comparisons with the phenotype.
- Genetically predicted systolic blood pressure was associated with increased left ventricular mass and left ventricular global radial strain.

What is Relevant?

- Evidence for causal links between systolic blood pressure and increased left ventricular mass and increased left ventricular global radial strain.

Summary

Performing a Mendelian randomization analysis of systolic blood pressure on imaging biomarkers of left ventricular structure and function resulted in evidence for causal links between systolic blood pressure and increased left ventricular mass and increased left ventricular global radial strain.