

University of Groningen

Effect of Systolic Blood Pressure on Left Ventricular Structure and Function A Mendelian Randomization Study

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

Published in:
Hypertension

DOI:
[10.1161/HYPERTENSIONAHA.119.12679](https://doi.org/10.1161/HYPERTENSIONAHA.119.12679)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hendriks, T., Said, M. A., Janssen, L. M. A., van der Ende, M. Y., van Veldhuisen, D. J., Verweij, N., & van der Harst, P. (2019). Effect of Systolic Blood Pressure on Left Ventricular Structure and Function A Mendelian Randomization Study. *Hypertension*, 74(4), 826-832. <https://doi.org/10.1161/HYPERTENSIONAHA.119.12679>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

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/m². 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 mmHg 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 mmHg 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 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg,¹ and in 2017 redefined by the American Heart Association as an SBP ≥ 130 mmHg or DBP ≥ 80 mmHg,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 resource¹⁴ 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

Received January 17, 2019; first decision February 3, 2019; revision accepted May 18, 2019.

From the Department of Cardiology, University of Groningen, University Medical Center Groningen, the Netherlands.

The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.119.12679>.

Correspondence to Pim van der Harst, HPC AB 43, PO Box 30.001, 9700 RB Groningen, the Netherlands. Email p.van.der.harst@umcg.nl

© 2019 The Authors. *Hypertension* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial License](#), which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited and is not used for commercial purposes.

Hypertension is available at <https://www.ahajournals.org/journal/hyp>

DOI: 10.1161/HYPERTENSIONAHA.119.12679

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/m² (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 820967 genetic variants (N=452 713; here N=2906) or the UK Biobank Lung Exome Variant Evaluation Axiom array that included 807411 genetic variants (N=49949; 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

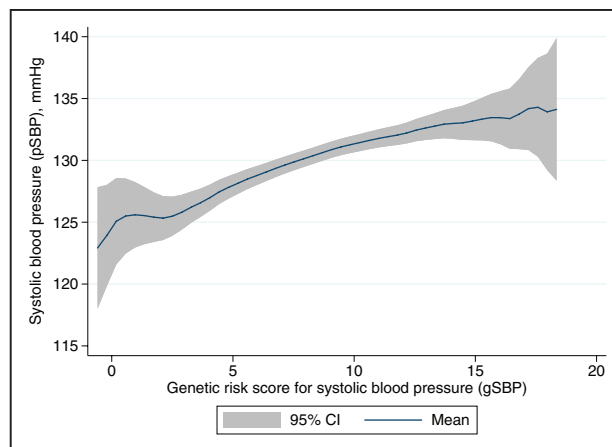


Figure 1. Association between genetically predicted systolic blood pressure (gSBP) and phenotypic systolic blood pressure (pSBP). Presented is a local polynomial smooth plot with 95% CI, using the Epanechnikov kernel function and 50 smoothing points.

to keep 150 subjects in both groups. GRS thresholds used to select the final study groups were <4.45 mmHg for the low gSBP group and >13.16 mmHg for the high gSBP group (Figure 2).

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.

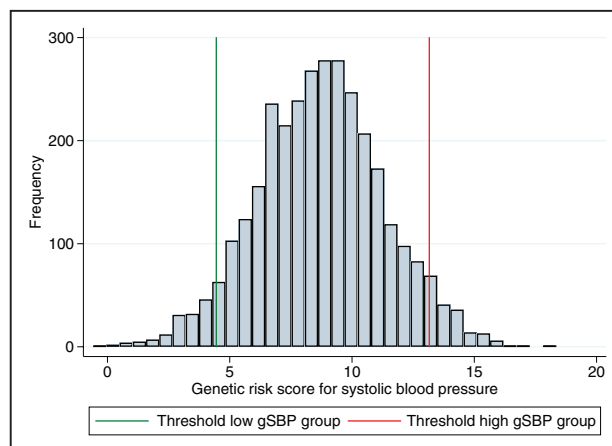


Figure 2. Distribution of genetic risk score for systolic blood pressure in UK Biobank population after initial exclusion criteria (N=3209). gSBP indicates genetically predicted systolic blood pressure.

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 mmHg 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 mmHg). 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 mmHg, whereas the difference in mean pSBP between groups was 7.56 mmHg. The observed difference in mean pSBP was largely due to a difference in pulse pressure of 5.11 mmHg and to a lesser extent due to a difference in DBP of 2.45 mmHg. 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 mmHg 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.

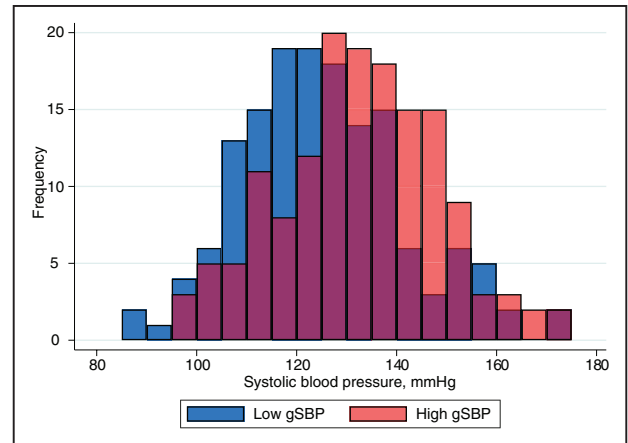


Figure 3. Distribution of systolic blood pressure at imaging visit per study group. gSBP indicates genetically predicted systolic blood pressure.

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 mmHg 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 mmHg; $P<0.001$) and LV global radial strain (β , 1.07 ± 0.37 %/10 mmHg; $P=0.004$). 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 mmHg; $P<0.001$) and cardiac output (β , 0.20 ± 0.04 L/10 mmHg; $P<0.001$).

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}
	$\beta \pm SE$	P Value	$\beta \pm SE$	P Value	$\beta \pm SE$	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 mmHg 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 mmHg SBP and 75 mmHg 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 mmHg and DBP values between 80 and 89 mmHg.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}
	$\beta \pm SE$	P Value	$\beta \pm SE$	P Value	$\beta \pm SE$	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 mmHg 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.

Acknowledgments

This research has been conducted using the UK Biobank Resource under Application Number 12010. We thank Ruben N. Eppinga, MD, Yordi J. van de Vegte, BSc, Yanick Hagemeyer, MSc, and Jan-Walter Benjamins, BEng, University of Groningen, University Medical Center Groningen, Department of Cardiology, for their contributions to the extraction and processing of data in the UK Biobank. None of the mentioned contributors received compensation, except for their employment at the University Medical Center Groningen. All authors made substantial contributions and have read and approved the final version.

Sources of Funding

This work was supported by the Netherlands Heart Foundation (grant 2018B017). The funder had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the article; or decision to submit the article for publication.

Disclosures

None.

References

- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2159–2219. doi: 10.1093/eurheartj/eh151
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248. doi: 10.1016/j.jacc.2017.11.006
- Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation*. 2018;137:109–118. doi: 10.1161/CIRCULATIONAHA.117.032582
- Garg S, de Lemos JA, Ayers C, Khouri MG, Pandey A, Berry JD, Peshock RM, Drazner MH. Association of a 4-tiered classification of LV hypertrophy with adverse CV outcomes in the general population. *JACC Cardiovasc Imaging*. 2015;8:1034–1041. doi: 10.1016/j.jcmg.2015.06.007
- Velagaleti RS, Gona P, Pencina MJ, Aragam J, Wang TJ, Levy D, D'Agostino RB, Lee DS, Kannel WB, Benjamin EJ, Vasan RS. Left ventricular hypertrophy patterns and incidence of heart failure with preserved versus reduced ejection fraction. *Am J Cardiol*. 2014;113:117–122. doi: 10.1016/j.amjcard.2013.09.028
- Drazner MH, Rame JE, Marino EK, Gottdiener JS, Kitzman DW, Gardin JM, Manolio TA, Dries DL, Siscovick DS. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2004;43:2207–2215. doi: 10.1016/j.jacc.2003.11.064
- Ehret GB, Ferreira T, Chasman DI, et al; CHARGE-EchoGen consortium; CHARGE-HF Consortium; Wellcome Trust Case Control Consortium. The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet*. 2016;48:1171–1184. doi: 10.1038/ng.3667
- Hoffmann TJ, Ehret GB, Nandakumar P, Ranatunga D, Schaefer C, Kwok PY, Iribarren C, Chakravarti A, Risch N. Genome-wide association analyses using electronic health records identify new loci influencing blood pressure variation. *Nat Genet*. 2017;49:54–64. doi: 10.1038/ng.3715
- Surendran P, Drenos F, Young R, et al; CHARGE-Heart Failure Consortium; EchoGen Consortium; METASTROKE Consortium; GIANT Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study; Wellcome Trust Case Control Consortium; Understanding Society Scientific Group; EPIC-CVD Consortium; CHARGE+ Exome Chip Blood Pressure Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; ExomeBP Consortium; CHD Exome+ Consortium. Trans-ancestry meta-analyses identify rare and common variants associated with

- blood pressure and hypertension. *Nat Genet.* 2016;48:1151–1161. doi: 10.1038/ng.3654
10. Warren HR, Evangelou E, Cabrera CP, et al; International Consortium of Blood Pressure (ICBP) 1000G Analyses; BIOS Consortium; Lifelines Cohort Study; Understanding Society Scientific group; CHD Exome+ Consortium; ExomeBP Consortium; T2D-GENES Consortium; GoT2DGenes Consortium; Cohorts for Heart and Ageing Research in Genome Epidemiology (CHARGE) BP Exome Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; UK Biobank CardioMetabolic Consortium BP working group. Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. *Nat Genet.* 2017;49:403–415. doi: 10.1038/ng.3768
 11. Liu C, Kraja AT, Smith JA, et al; CHD Exome+ Consortium; ExomeBP Consortium; GoT2DGenes Consortium; T2D-GENES Consortium; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia; CKDGen Consortium. Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. *Nat Genet.* 2016;48:1162–1170. doi: 10.1038/ng.3660
 12. Kato N, Loh M, Takeuchi F, et al; BIOS-consortium; CARDIoGRAMplusC4D; LifeLines Cohort Study; InterAct Consortium. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. *Nat Genet.* 2015;47:1282–1293. doi: 10.1038/ng.3405
 13. Lieb W, Jansen H, Loley C, et al; CARDIoGRAM. Genetic predisposition to higher blood pressure increases coronary artery disease risk. *Hypertension.* 2013;61:995–1001. doi: 10.1161/HYPERTENSIONAHA.111.00275
 14. Petersen SE, Matthews PM, Francis JM, Robson MD, Zemrak F, Boubertakh R, Young AA, Hudson S, Weale P, Garratt S, Collins R, Piechnik S, Neubauer S. UK Biobank's cardiovascular magnetic resonance protocol. *J Cardiovasc Magn Reson.* 2016;18:8. doi: 10.1186/s12968-016-0227-4
 15. Bycroft C, Freeman C, Petkova D, et al. *Genome-Wide genetic Data on ~500,000 UK Biobank Participants.* *BioRxiv.* Cold Spring Harbor Laboratory Press, NY; 2017.
 16. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition.* 1989;5:303–311; discussion 312–313.
 17. Stang A, Moebus S, Möhlenkamp S, Dragano N, Schermund A, Beck EM, Siegrist J, Erbel R, Jöckel KH; Heinz Nixdorf Recall Study Investigative Group. Algorithms for converting random-zero to automated oscillometric blood pressure values, and vice versa. *Am J Epidemiol.* 2006;164:85–94. doi: 10.1093/aje/kwj160
 18. ODPHP. 2008 Physical Activity Guidelines for Americans [Internet]. Accessed January 10, 2018. <https://health.gov/paguidelines/2008/>.
 19. Said MA, Verweij N, van der Harst P. Associations of combined genetic and lifestyle risks with incident cardiovascular disease and diabetes in the UK biobank Study. *JAMA Cardiol.* 2018;3:693–702. doi: 10.1001/jamacardio.2018.1717
 20. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, Kim RJ, von Knobelsdorff-Brenkenhoff F, Kramer CM, Pennell DJ, Plein S, Nagel E. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. *J Cardiovasc Magn Reson.* 2013;15:35. doi: 10.1186/1532-429X-15-35
 21. Petersen SE, Aung N, Sanghvi MM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. *J Cardiovasc Magn Reson.* 2017;19:18.
 22. Petersen SE, Sanghvi MM, Aung N, Cooper JA, Paiva JM, Zemrak F, Fung K, Lukaschuk E, Lee AM, Carapella V, Kim YJ, Piechnik SK, Neubauer S. The impact of cardiovascular risk factors on cardiac structure and function: Insights from the UK Biobank imaging enhancement study. *PLoS One.* 2017;12:e0185114. doi: 10.1371/journal.pone.0185114
 23. Le Ven F, Bibeau K, De Larochellière É, Tizón-Marcos H, Deneault-Bissonnette S, Pibarot P, Deschepper CF, Larose É. Cardiac morphology and function reference values derived from a large subset of healthy young caucasian adults by magnetic resonance imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:981–990. doi: 10.1093/ehjci/jev217
 24. Chuang ML, Gona P, Hautvast GL, Salton CJ, Breeuwer M, O'Donnell CJ, Manning WJ. CMR reference values for left ventricular volumes, mass, and ejection fraction using computer-aided analysis: the framingham heart Study. *J Magn Reson Imaging.* 2014;39:895–900. doi: 10.1002/jmri.24239
 25. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes Endocrinol.* 2014;2:634–647.
 26. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913. doi: 10.1016/s0140-6736(02)11911-8
 27. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837–1847. doi: 10.1161/01.cir.97.18.1837
 28. He L, Culminskeya I, Loika Y, Arbeev KG, Bagley O, Duan M, Yashin AI, Kulminski AM. Causal effects of cardiovascular risk factors on onset of major age-related diseases: a time-to-event mendelian randomization study. *Exp Gerontol.* 2018;107:74–86. doi: 10.1016/j.exger.2017.09.019
 29. Ehret GB, Munroe PB, Rice KM, et al; International Consortium for Blood Pressure Genome-Wide Association Studies. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature.* 2011;478:103–109.
 30. Lieb W, Gona P, Larson MG, Aragam J, Zile MR, Cheng S, Benjamin EJ, Vasani RS. The natural history of left ventricular geometry in the community: clinical correlates and prognostic significance of change in LV geometric pattern. *JACC Cardiovasc Imaging.* 2014;7:870–878. doi: 10.1016/j.jcmg.2014.05.008
 31. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol.* 2008;52:2148–2155. doi: 10.1016/j.jacc.2008.09.014
 32. Tadic M, Cuspidi C, Celic V, Ivanovic B, Pencic B, Grassi G. The influence of sex on left ventricular strain in hypertensive population. *J Hypertens.* 2019;37:50–56. doi: 10.1097/HJH.0000000000001838
 33. Fung MJ, Thomas L, Leung DY. Left ventricular function and contractile reserve in patients with hypertension. *Eur Heart J Cardiovasc Imaging.* 2018;19:1253–1259. doi: 10.1093/ehjci/jex338
 34. Tadic M, Cuspidi C, Pencic B, Andric A, Pavlovic SU, Iracek O, Celic V. The interaction between blood pressure variability, obesity, and left ventricular mechanics: findings from the hypertensive population. *J Hypertens.* 2016;34:772–780. doi: 10.1097/HJH.0000000000000830
 35. Pazoki R, Dehghan A, Evangelou E, Warren H, Gao H, Caulfield M, Elliott P, Tzoulaki I. Genetic predisposition to high blood pressure and lifestyle factors: associations with midlife blood pressure levels and cardiovascular events. *Circulation.* 2018;137:653–661. doi: 10.1161/CIRCULATIONAHA.117.030898

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.