Genetics

Heritability and the Genetic Correlation of Heart Rate Variability and Blood Pressure in >29 000 Families
The Lifelines Cohort Study

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Abstract—Dysregulation of the cardiac autonomic nervous system, as indexed by reduced heart rate variability (HRV), has been associated with the development of high blood pressure (BP). However, the underlying pathological mechanisms are not yet fully understood. This study aimed to estimate heritability of HRV and BP and to determine their genetic overlap. We used baseline data of the 3-generation Lifelines population-based cohort study (n=149 067; mean age, 44.5). In-house software was used to calculate root mean square of successive differences and SD of normal-to-normal intervals as indices of HRV based on 10-second resting ECGs. BP was recorded with an automatic BP monitor. We estimated heritabilities and genetic correlations with variance components methods in ASReml software. We additionally estimated genetic correlations with bivariate linkage disequilibrium score regression using publicly available genome-wide association study data. The heritability (SE) estimates were 15.6% (0.90%) for SD of normal-to-normal intervals and 17.9% (0.90%) for root mean square of successive differences. For BP measures, they ranged from 24.4% (0.90%) for pulse pressure to 30.3% (0.90%) for diastolic BP. Significant negative genetic correlations (all $P<0.0001$) of root mean square of successive differences/SD of normal-to-normal intervals with systolic BP (−0.20/−0.16) and with diastolic BP (−0.15/−0.13) were observed. LD score regression showed largely consistent genetic correlation estimates of root mean square of successive differences/SD of normal-to-normal intervals with systolic BP (range, −0.08 to −0.23) and diastolic BP (range, −0.20 to −0.27). Our study shows a substantial contribution of genetic factors in explaining the variance of HRV and BP measures in the general population. The significant negative genetic correlations between HRV and BP indicate that genetic pathways for HRV and BP partially overlap.

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Heart rate variability (HRV), reflecting beat-to-beat fluctuations in heart rate over time,[1] has emerged as one of the most widely used noninvasive indices of cardiac autonomic nervous system function. The imbalance of the autonomic cardiovascular control plays a key role in the risk for high blood pressure (BP).[2] The modulation of vagal tone helps to maintain the dynamic autonomic function necessary for short-term BP regulation. More specifically, sympathetic inhibition reduces peripheral resistance, while parasympathetic activation attenuates heart rate and contractility. Conversely, sympathetic activation and subsequent parasympathetic inactivation allow the baroreflex to elevate BP.[3] Both cross-sectional[4] and prospective[5,6] studies have shown associations between low HRV and high BP, suggesting an essential role of lower HRV in the development of hypertension.

Besides the established demographic[7] and lifestyle factors[8] that have been reported to explain the individual differences in HRV level at rest, numerous studies have shown that genetic factors contribute substantially to the variance. For example, Sinnreich et al[9] reported heritability estimates of 41% and 39% for SD of normal-to-normal intervals (SDNN) and root mean square of successive differences (RMSSD), respectively, based on 5-minute Holter recordings in the Kibbutzim family study. Recent investigations from the Oman Family Study[10,11] reported heritability estimates of 12.3% to 20.5% from 10-minute ECG recordings in a supine position. In twin studies, the genetic contribution to individual differences in HRV measures can be as high as 74%.[12,13] Likewise, previous studies reported that individual differences in BP traits, such as systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP), could for a large part be accounted for by genetic factors.[14] In a meta-analysis of published twin studies, Wang et al[15] reported that the pooled heritabilities of SBP, DBP, and PP

were 54%, 49%, and 50%, respectively. Family-based studies from Switzerland,[16] Oman,[10,17] and the Seychelles[18] reported heritability estimates ranging from 19% to 24% for SBP, 5% to 25% for DBP, and 18% to 37% for PP.

Although the studies mentioned above have shown the contribution of genetic factors for individual variation in HRV and BP, heritability estimates were from relatively small samples. Moreover, most of these studies did not correctly adjust for the well-known and recently more recognized effect of heart rate on HRV.[19] Thus, large population-based family studies are needed for better understanding of the genetic effects.

Additionally, although an association between HRV and hypertension was found in many epidemiological studies, the underlying pathophysiological mechanisms are not yet fully understood. Given that HRV and BP are both heritable, we hypothesized that shared genetic factors may partly explain the negative association between the 2 traits. In this study, we aimed to (1) determine the genetic contributions to individual differences in both HRV and BP and (2) estimate the magnitude of any potential genetic overlap between HRV and BP. We used data from the population-based Lifelines Cohort Study and Biobank,[20] which with its 3-generation family design, large sample size, and broad age range is ideally suited for this study.

Methods

Data Availability

The data that were used in this study are available from the Lifelines Cohort Study and Biobank (research@lifelines.nl) upon reasonable request. Lifelines is a facility that is open for all researchers; information on application and data access procedures is available on https://www.lifelines.nl/researcher/how-to-apply.

Study Setting and Population

The Lifelines Cohort Study and Biobank with >167 000 participants is a large population-based prospective study in the northern part of the Netherlands, aiming to investigate risk factors for multifactorial diseases. The design and cohort profile of the Lifelines study have been described before.[20,21] In short, baseline data were collected between 2006 and 2013. The recruitment of the Lifelines study was family based by design. Eligible participants between 20 and 50 years of age were invited to participate through their general practitioners. After the inclusion of these individuals, their partner, children, parents, and partner's parents were also invited to participate in the study. In addition, single individuals could register for participation online. In this way, a 3-generation family study was realized. Subsequently, we used the information on family members and information on (anonymized) names and birth dates of parents provided by all participants in questionnaires to define relationships between undefined family members in Lifelines. For instance, 2 sibs could participate in Lifelines and obtained different family IDs, if they were invited by their respective spouses. This process resulted in 40 496 singletons (ie, individuals without any relative in the sample) and 30 914 families (of size ≥2) of up to 4 generations with an average family size of 4.12. The largest family connected 189 participants. Spouses without children were considered as a family of size 2, even though they are genetically unrelated. The Figure shows an example of 23-member Lifelines family extending over 4 generations.

During the baseline visit, ECG recordings were obtained from 153 793 participants (91.8%) aged ≥13 years. From these, HRV could not be calculated in 4586 participants due to excessive noise and ectopic (nonsinus node) beats and 140 were excluded due to extreme values (<5 or >5 SD from the mean) for either HRV or BP measures. In the current analysis, 149 067 individuals (1.03% children; 96.5% European ancestry) with an age range of 13 to 94 years were included, of whom 40 955 were singletons. The remaining individuals belonged to a total of 29 107 families with an average family size of 3.71. The largest family connected 169 participants.

All participants signed an informed consent. The Lifelines cohort study is conducted according to the principles of the declaration of Helsinki and following the research code of University Medical Center Groningen and approved by its Medical Ethical Committee.

Measurements

A 10-second 12-lead resting ECG was recorded while participants were in a supine resting position. For the ECG recording, CardioPerfect software (Welch Allyn DT100 recorder; Welch Allyn, Skaneateles Falls, NY) was used. From the 12 leads, 4 (I, II, V_4, and V_5) were selected to detect R peaks in the ECG. The details of HRV calculation in Lifelines have been published previously.[7] In short, ECG recordings were excluded from HRV calculation if (1) the number of beats were <5, (2) the ratio between maximal and minimal interbeat interval (IBI) exceeded 1.4 indicating a missing trigger or extrasystolic beat, (3) there was extremely low variability (defined as the SD of IBI <1.2 ms), or (4) <60% of the recording time was included in the calculation. In-house software was used to calculate the RMSSD and SDNN as indices of HRV, which are used in the present study. Heart rate has a well-established strong inverse relationship with HRV, which includes a mathematical dependency of the variance in IBI on the mean IBI that is unrelated to the underlying biology. Our group has reintroduced a recommended approach to correct HRV for its dependency on the mean IBI of consecutive R peaks using coefficients of variation.[19,22] The coefficient of variation detects the amount of IBI variability relative to the mean IBI of each participant. We applied this method to additionally calculate HRV values that were corrected for the influence of mean IBI. Heart rate was calculated from the ECG recording using 60 000/(mean IBI).

Simultaneously with the ECG recordings, BP was measured with an automatic BP monitor (DinaMap, PRO 100V2) every minute during 10 minutes while the participant was in a supine resting position. The mean of the last 3 measures was used to calculate SBP and DBP. For participants taking antihypertensive medication (see below), we corrected the measured BP values by adding 15 mm Hg for SBP and 10 mm Hg for DBP.[23] From the adjusted BP values, PP and mean arterial pressure (MAP) were calculated as PP=SBP−DBP and MAP=(2 DBP+SBP)/3.

Medications and diseases that have been reported to influence HRV were included as covariates. Participants self-reported prescription during the baseline visit, which were classified according to the Anatomical Therapeutic Chemical classification, were used to define medications. A list of Anatomical Therapeutic Chemical codes prescribed to treat hypertension, depression, type 2 diabetes mellitus, and cardiovascular diseases in the Netherlands was retrieved from the Dutch Pharmacotherapeutic Compass (https://www.farmacotherapeutischkompas.nl). Participants were considered to have cardiovascular disease if they self-reported one of the following diseases: (1) heart failure, atrial fibrillation, and vascular diseases (myocardial infarction, stroke, and aneurysm) and (2) if participants used medications related to these symptoms (β-blockers, angiotensin-converting enzyme inhibitors, diuretics, vitamin K antagonist, statins, aspirin, and clopidogrel). Any participant who had either self-reported type 2 diabetes mellitus, use of antidiabetes medication(s), a fasting blood glucose ≥7.0 mmol/L, or HbA1c ≥6.5% was considered to have type 2 diabetes mellitus. Hypertension was defined as having SBP ≥140 mm Hg or DBP ≥90 mm Hg or use of antihypertensive medication. Body mass index was calculated as weight/height squared and expressed in kg/m².

Statistical Analysis

The baseline characteristics of participants, stratified by sex, were described as mean and SD for continuous traits and as percentages for categorical variables. A natural logarithmic transformation was computed to achieve approximate normality of HRV indices. ANOVA and χ^2 tests were used to compare any differences between men and women.

Heritability Estimate

Heritability is defined as the proportion of phenotypic variation explained by the genetic differences of individuals in a population.
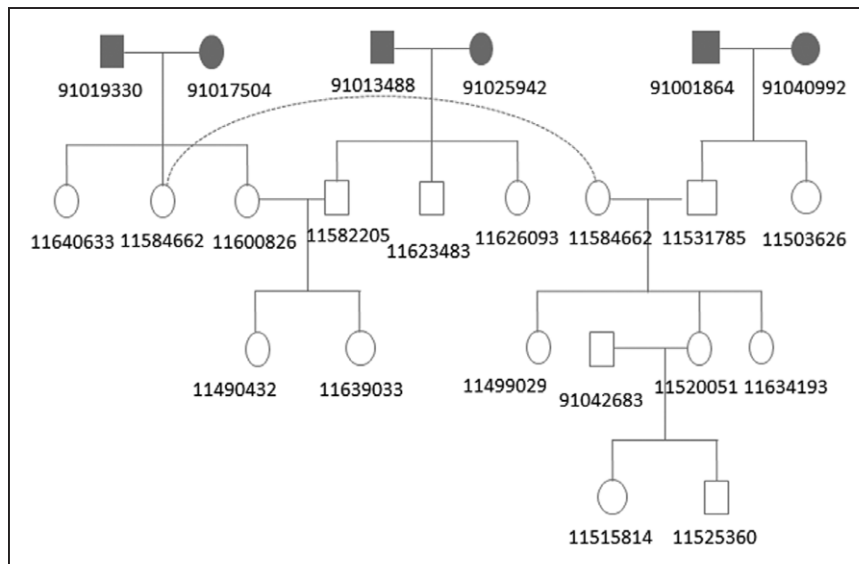
Figure. An example of a 23-member Lifelines pedigree extending over 4 generations. Numbers: Lifelines subject identifications; squares: men; circles: women; gray: founders.

For the univariate analyses, we assumed a linear mixed model for the heritability analysis as follows: $y = Xb + Z_a a + Z_f f + e$, where y is a vector of the response variable (HRV or BP); b, vector of regression coefficients for the fixed effects; a, additive genetic effects with variance $\sigma2_a A$; f, family (shared environment) effects with variance $\sigma2_f I$; and e, residuals (environmental effects) with variance $\sigma2_e I$. X is the design matrix of the fixed effects, Z_a is the design matrix mapping subjects to the genetic kinship (relationship) matrix A, and Z_f is the design matrix for family (group) effects. There are no known genetic relationships between individuals in different families.

Once the total and phenotypic variances were estimated from the linear mixed model, narrow-sense heritability was calculated as

$$h^2 = \sigma_a^2 / \left(\sigma_a^2 + \sigma_f^2 + \sigma_e^2 \right),$$ where σ_a^2 is the additive genetic variance, σ_f^2 is the shared environmental variance, and σ_e^2 is the residual (environmental) variance. The singletons were included in the analysis and contributed to the estimations of variances and phenotypic correlations but not to the genetic correlations.

Genetic Correlation Estimate
The genetic correlations were estimated using the same designs and similar methods as used to estimate heritability in an expanded set of equations (ie, a bivariate model). In the bivariate analyses, the genetic correlations between HRV and BP were obtained from the estimated additive genetic covariance and variance components as

$$r_G = \frac{\sigma_{A_x A_y}}{\sqrt{\sigma_{A_x}^2 \, \sigma_{A_y}^2}},$$ where $\sigma A_x A_y$ is the additive genetic covariance between traits x and y and $\sigma 2A_x$ and $\sigma 2A_y$ is the additive genetic variance for traits x and y, respectively.

To test the significance of the h^2 estimates ($h^2 > 0$) and genetic correlations ($|r_G| > 0$), the model in which all variances and correlations were estimated was compared, using a likelihood-ratio test, to a model in which additive genetic variances and genetic correlations for all measures were constrained to be zero. Similarly, genetic correlations were constrained to be equal to 1 or −1 to test the presence of complete overlap of genetic effects ($|r_G| = 1$).[24] In all analyses, the fixed effects (or covariates) included age, sex, and body mass index. Age squared was also added to the model, to accommodate the curvilinear relationship of HRV with age.[7] In further analyses, heritability estimates of HRV indices were adjusted for a history of diseases (cardiovascular disease, hypertension, and type 2 diabetes mellitus) and antidepressant use. We did not include smoking and alcohol use as additional covariates in our models as we have previously shown that the influence of these lifestyle factors on HRV was negligible.[7] Here we also confirmed for BP that addition of these lifestyle factors as covariates to the model only had minimal impact on heritability estimates (Table S1 in the Data Supplement). We report proportion of variance explained by these covariates. The analyses were performed using ASReml 4.1 software.[25] ASReml is a statistical package that fits the linear mixed models using restricted maximum likelihood to estimate the variance components.

We additionally estimated the genetic correlations using bivariate linkage disequilibrium score regression[26] on the latest publicly available genome-wide association study summary statistics for HRV[27] and BP.[28–30]

Results

Characteristics of the participants are provided in Table 1. Men had a lower heart rate. Means of RMSSD and SDNN were significantly higher in women than in men, and the difference remained significant after correcting the values for mean IBI. In general, all BP measures were significantly higher in men, and women had a lower body mass index. The prevalence of hypertension and type 2 diabetes mellitus was higher in men, but no sex difference was seen for cardiovascular diseases. The proportion of antidepressant use was significantly higher in women.

Table 2 shows the proportion of phenotypic variances explained by additive genetic factors, shared family environment, and covariates for different traits. Heart rate showed a heritability of 22.7%. The univariate narrow-sense heritability estimates for the HRV indices ranged from 13.4% to 17.9%. Correcting them for the mean IBI slightly lowered h^2 estimates for both RMSSD and SDNN. The h^2 estimates for BP measures ranged from 24.4% for PP to 30.3% for DBP. SBP and MAP showed heritability estimates of 28.0% and 30.1%, respectively. In addition to the additive genetic influence, we calculated the proportions of variance explained by shared family environment and covariates of HRV, heart rate, and BP measures. The shared family environment contributed 4.5% of the variance for heart rate. The contribution of familial environmental effects to the variance of HRV was negligible. With regard to BP, we found small effects of the shared family environment that ranged from 0.9% for PP to 3.2% for MAP. The percentage of variance explained by the covariates was 18.4% for SDNN and 19.8% for RMSSD. These contributions even became slightly larger, 20.9%, and 23.7%, respectively, when the effect of mean IBI was taken into account. Similarly,

Table 1. Characteristics of Study Participants and the Distribution of Heart Rate Variability and Blood Pressure Measurements for Men and Women Separately

Variables	Total (N=149 067)	Men (n=61 625)	Women (n=87 442)	P Value*
European ancestry, n (%)	143 892 (96.5)	59 535 (96.6)	84 357 (96.5)	
BMI, kg/m^2	25.99 (4.36)	26.29 (3.74)	25.79 (4.74)	≤0.001
Type 2 diabetes mellitus, n (%)	4221 (2.8)	2153 (3.5)	2068 (2.4)	≤0.001
Hypertension, n (%)	48 602 (32.6)	22 061 (35.8)	26 541 (30.4)	≤0.001
Cardiovascular disease, n (%)	9358 (6.3)	3964 (6.4)	5394 (6.2)	0.238
Antidepressant use, n (%)	7842 (5.3)	1993 (3.2)	5849 (6.7)	≤0.001
Heart rate, bpm	67.30 (11.0)	65.81 (11.18)	68.35 (10.76)	≤0.001
RMSSD, ms	37.31 (31.60)	34.43 (29.87)	39.34 (32.61)	≤0.001
lnRMSSD, ln(ms)	3.35 (0.73)	3.27 (0.73)	3.42 (0.72)	≤0.001
RMSSDc, %	3.97 (3.08)	3.57 (2.86)	4.24 (3.21)	≤0.001
lnRMSSDc, ln(%)	1.15 (0.66)	1.04 (0.66)	1.23 (0.65)	≤0.001
SDNN, ms	36.14 (26.40)	34.69 (25.91)	37.15 (26.73)	≤0.001
lnSDNN, ln(ms)	3.36 (0.67)	3.32 (0.69)	3.40 (0.66)	≤0.001
SDNNc, %	3.91 (2.70)	3.68 (2.62)	4.07 (2.74)	≤0.001
lnSDNNc, ln(%)	1.16 (0.63)	1.09 (0.65)	1.22 (0.62)	≤0.001
SBP,† mm Hg	126.78 (16.76)	131.66 (15.42)	123.34 (16.82)	≤0.001
DBP,† mm Hg	74.59 (10.25)	77.33 (10.36)	72.65 (9.72)	≤0.001
MAP, mm Hg	91.98 (11.61)	95.44 (11.21)	89.55 (11.27)	≤0.001
PP, mm Hg	52.19 (11.41)	54.32 (10.66)	50.69 (11.68)	≤0.001

Means (SD) are shown unless indicated otherwise. BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; ln, logarithmic transformation; lnRMSSDc, log-transformed corrected root mean square of successive differences; lnSDNN, log-transformed SD of normal-to-normal intervals; lnSDNNc, log-transformed corrected SD of normal-to-normal intervals; MAP, mean arterial pressure; PP, pulse pressure; RMSSD, root mean square of successive differences; RMSSDc, corrected root mean square of successive differences; SBP, systolic blood pressure; SDNN, SD of normal-to-normal intervals; and SDNNc, corrected SD of normal-to-normal intervals.

*Age-adjusted P value.

†BP values were corrected for antihypertensive use.

the result showed a substantial contribution of covariates for BP that ranged from 19.0% for PP to 28.3% for SBP. The included covariates explained only 2.6% of the percentage of variance for heart rate.

In Table 3, the bivariate genetic, phenotypic, and environmental correlations between HRV and BP are shown. We found a significant genetic correlation of −0.60 between RMSSD and heart rate and −0.53 between SDNN and heart rate. These correlations were reduced to −0.38 and −0.22, respectively, when HRV values were corrected for the effect of mean IBI. There were negative genetic correlations between RMSSD and BP-related traits with a correlation of −0.20 with SBP, −0.15 with DBP, −0.18 with MAP, and −0.14 with PP that were consistent significantly different from zero. Similarly, there were slightly smaller but significantly consistent correlations between SDNN and the BP measures. However, the correlation between SDNN and PP was not statistically significant. When repeating the analyses with HRV measures corrected for the mean IBI, phenotypically HRV and BP measures still showed negative correlations (ranging from −0.05 to −0.07) with the highest correlation observed between corrected RMSSD and SBP, but they were smaller than for the uncorrected HRV values. Nevertheless, most genetic correlations remained significantly different from zero. All genetic correlations were significantly

different from 1. The bivariate linkage disequilibrium score regression largely confirmed direction and magnitude of our results based on the Lifelines pedigree data with estimates of r$_G$ with RMSSD and SDNN ranging from −0.08 to −0.23 for SBP and −0.20 to −0.27 for DBP (Table 4).

Discussion

In this study, we showed that genetic factors significantly influence the variance in HRV and BP. Our results also show significant negative genetic correlations between HRV and BP measures, which suggests shared genetic factors partly explain the inverse association between these traits.

In the present study, we found similar heritability estimates for RMSSD and SDNN as in the Framingham Heart Study[31] and in recent reports from the Oman Family Study.[10,11] Our results were lower than heritability estimates from the Kibbutzim family study in Israel, 39% for SDNN and 41% for RMSSD.[9] The possible explanation for relatively higher heritability values in the Israel study might be due to an inclusion of more homogenous samples. Our heritability estimates for SDNN and RMSSD remained significant after taking into account the effect of mean heart rate on HRV measures. This finding confirms that the genetic influence in HRV measures is largely independent of the influence of heart rate. Our results also showed substantial

Table 2. Heritability Estimates and Proportion of Variance Due to Shared Family Environment and Covariates of HR, HRV, and BP-Related Measures

Variables	h²*	SE	Variance Due to Shared Family Environment	PVC
HR, bpm	0.227	0.009	0.045	0.026
lnRMSSD, ln(ms)	0.179	0.009	0.006	0.198
lnRMSSDc, ln(%)	0.162	0.009	0.005	0.237
lnSDNN, ln(ms)	0.156	0.009	0.001	0.184
lnSDNNc, ln(%)	0.134	0.009	≈0	0.209
SBP,† mm Hg	0.280	0.009	0.029	0.283
DBP,† mm Hg	0.303	0.009	0.025	0.217
MAP, mm Hg	0.301	0.009	0.032	0.269
PP, mm Hg	0.244	0.009	0.009	0.190

All heritability estimates were adjusted for age, age², sex, and body mass index. Heritabilities for HRV were additionally adjusted for cardiovascular disease, hypertension, type 2 diabetes mellitus, and antidepressant medication use. BP indicates blood pressure; DBP, diastolic blood pressure; HR, heart rate; HRV, heart rate variability; ln, logarithmic transformation; lnRMSSD, log-transformed root mean square of successive differences; lnRMSSDc, log-transformed corrected root mean square of successive differences; lnSDNN, log-transformed SD of normal-to-normal intervals; lnSDNNc, log-transformed corrected SD of normal-to-normal intervals; MAP, mean arterial pressure; PP, pulse pressure; PVC, proportion of variance explained by covariates; and SBP, systolic blood pressure.

*All heritability estimates were significantly different from zero.

†BP values were corrected for antihypertensive use.

heritability of BP measured in supine position ranging from 24.4% for PP to 30.3% for DBP. These findings are slightly higher than heritability estimates reported in previous family studies,[10,16,17] which might be due to the large sample size. A small study in Sweden reported that none of the BP measures were heritable,[32] and another small study conducted in the Seychelles reported a nonsignificant heritability for DBP but a higher one than we found for PP (h²=24.4%).[18] However, both of these studies were likely underpowered (n=260 and 314 participants, respectively). Only one family study from Nigeria[33] reported a heritability estimate for MAP and found a slightly higher heritability compared with our study (36% versus 30%). Differences in heritability estimates could be varying between populations due to different ethnic backgrounds of study participants.

The present study shows consistently significant (from zero) and negative genetic correlations between HRV and BP, particularly with SBP and DBP. This is in line with previous findings from cross-sectional[4,34] and prospective studies[5,6] that reported lower HRV is associated with high BP. This confirms our hypothesis that shared genetic factors might also explain the negative associations between HRV and BP. In agreement with this, the genetic correlations using bivariate linkage disequilibrium score regression on genome-wide association study summary statistics for HRV[27] and BP[28–30] show largely consistent estimates. On the contrary, the Oman Family study[10] recently reported a nonsignificant genetic correlation. However, the authors admittedly recognize that the sample size of their study might have been too small to detect the underlying genetic contributions.

A major strength of our study is that it constitutes the largest family study to date on the subject, providing ample power for precise estimates of heritability and genetic overlap. Unlike previous studies,[9–11] we applied a recommended correction method to adjust the well-known effect of heart rate on HRV to recalculate heritability estimates. Furthermore, familial effects were included in the analysis to minimize overinflation of the heritability estimates due to the common environment shared by family members. Our study, however, acknowledges the following limitations. First, antihypertensive treatments might obscure familial contributions to BP variations.[35] However, we adjusted the measured BP values by adding 15 mm Hg to measured SBP and 10 mm Hg to

Table 3. Bivariate Quantitative Genetic Analyses of HR Variability With HR and Blood Pressure Examining the Genetic, Phenotypic, and Environmental Correlations

Traits	LnRMSSD			LnRMSSDc		
	r_P (SE)	r_G (SE)	r_E (SE)	r_P (SE)	r_G (SE)	r_E (SE)
HR	−0.56 (0.002)	−0.60 (0.02)	−0.54 (0.01)	−0.36 (0.002)	−0.38 (0.03)	−0.34 (0.006)
SBP	−0.10 (0.003)	−0.20 (0.03)	−0.08 (0.01)	−0.07 (0.003)	−0.16 (0.03)	−0.06 (0.007)
DBP	−0.07 (0.003)	−0.15 (0.03)	−0.04 (0.01)*	−0.05 (0.003)	−0.13 (0.03)	−0.03 (0.008)*
MAP	−0.09 (0.003)	−0.18 (0.03)	−0.06 (0.01)	−0.06 (0.003)	−0.16 (0.03)	−0.05 (0.008)
PP	−0.08 (0.003)	−0.14 (0.03)	−0.07 (0.01)	−0.06 (0.003)	−0.10 (0.03)	−0.05 (0.007)
	LnSDNN			LnSDNNc		
HR	−0.40 (0.002)	−0.53 (0.03)	−0.36 (0.01)	−0.15 (0.003)	−0.22 (0.04)	−0.14 (0.007)
SBP	−0.08 (0.003)	−0.16 (0.03)	−0.06 (0.01)	−0.04 (0.003)	−0.11 (0.03)	−0.03 (0.007)*
DBP	−0.06 (0.003)	−0.13 (0.03)	−0.03 (0.01)*	−0.03 (0.003)	−0.11 (0.03)	−0.02 (0.007)*
MAP	−0.07 (0.003)	−0.16 (0.03)	−0.05 (0.01)	−0.04 (0.003)	−0.11 (0.03)	−0.03 (0.007)*
PP	−0.06 (0.003)	−0.10 (0.03)	−0.05 (0.01)	−0.03 (0.003)	−0.05 (0.04)*	−0.02 (0.007)*

Models were adjusted for age, age², sex, and BMI. BMI indicates body mass index; DBP, diastolic blood pressure; HR, heart rate; lnRMSSD, log-transformed root mean square of successive differences; lnRMSSDc, log-transformed corrected root mean square of successive differences; lnSDNN, log-transformed SD of normal-to-normal intervals; lnSDNNc, log-transformed corrected SD of normal-to-normal intervals; MAP, mean arterial pressure; PP, pulse pressure; r_E, environmental correlation; r_G, genetic correlation; r_P, phenotypic correlation; and SBP, systolic blood pressure.

*Nonsignificant genetic correlations (*P*>0.05).

Table 4. Genetic Correlations Between HRV and Blood Pressure as Computed Using Bivariate Linkage Disequilibrium Score Regression Based on Genome-wide Association Study Summary Statistics

Traits	Citation	RMSSD		SDNN	
		r_G (SE)	*P* Value	r_G (SE)	*P* Value
SBP	Ehret et al[28]	−0.230 (0.080)	$6.4×10^{-03}$	−0.204 (0.080)	$8.4×10^{-03}$
	Warren et al[29]	−0.084 (0.063)	$1.8×10^{-01}$	−0.138 (0.065)	$3.2×10^{-02}$
	Evangelou et al[30]	−0.086 (0.046)	$5.9×10^{-02}$	−0.078 (0.044)	$7.9×10^{-02}$
DBP	Ehret et al[28]	−0.271 (0.080)	$4.0×10^{-04}$	−0.267 (0.080)	$4.0×10^{-04}$
	Warren et al[29]	−0.223 (0.061)	$2.0×10^{-04}$	−0.235 (0.056)	$1.7×10^{-05}$
	Evangelou et al[30]	−0.198 (0.048)	$3.4×10^{-05}$	−0.199 (0.041)	$1.4×10^{-06}$

The genome-wide association study summary statistics for HRV traits derive from Nolte et al.[27] DBP indicates diastolic blood pressure; HRV, heart rate variability; r_G, genetic correlation; RMSSD, root mean square of successive differences; SBP, systolic blood pressure; and SDNN, SD of normal-to-normal intervals.

measured DBP level as recommended by Tobin et al.[23] This correction approximates pretreatment BP values and may restore the correct population ranking of BP values to a large extent and optimize estimates of the genetic variance component. Second, because a vast majority (96.5%) of participants are of Caucasian ancestry, the results of this study cannot be generalized to other ethnicities. Finally our study was limited to time-domain parameters SDNN and RMSSD because ultrashort ECG recordings are too short to assess frequency-domain HRV parameters.[1]

To conclude, in this large family study, we showed that the contribution of genetic factors to the variance of HRV (ranging from 15.6% to 17.9%) and BP (ranging from 24.4% to 30.3%) in the general population are substantial. The significant negative genetic correlations between HRV and BP indicate that genes (genetic pathways) for HRV and BP partially overlap.

Perspectives

This implies the need for more studies in the future to identify more genetic variants as the variance explained by known common single-nucleotide polymorphisms discovered in previous genome-wide association studies is still low (0.9%–2.3% for HRV measures and 2.9%–5.7% for BP measures).[27,30] The negative genetic correlations between HRV and BP are in line with a causal effect of cardiac vagal control in the development of hypertension. However, some more discussion is warranted what the results may mean: (1) pleotropic genes, (2) causal effect, or (3) reverse causation, meaning an increase in BP causes compensatory changes in cardiac autonomic nervous system activity that lead to reduced HRV. Mendelian randomization—a statistical approach to test the direction of causality in epidemiologic studies—may be considered in future studies to overcome this problem. If a causal effect was to be confirmed in future studies, this would have potential implications for prevention and treatment of hypertension.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This is the largest family study to date (>29 000 families) to estimate heritability of heart rate variability (HRV) and blood pressure (BP) and determine their genetic overlap.
- We report significant negative genetic correlations between HRV and BP in a family study for the first time.
- We used 2 independent approaches to estimate the genetic correlations showing largely consistent results (familial relationships in pedigree data and linkage disequilibrium score regression models using genome-wide association study data).

What Is Relevant?

- The significant negative genetic correlations between HRV and BP support previous cross-sectional and prospective epidemiological studies that report an association between cardiac autonomic dysregulation and hypertension.

Summary

Our study showed that contributions of genetic factors to the variance of HRV and BP in the general population are substantial. The significant negative genetic correlations between HRV and BP indicate that genes (genetic pathways) for HRV and BP partially overlap.