Familial Aggregation of Resting Blood Pressure and Heart Rate in a Sedentary Population

The HERITAGE Family Study

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The familial aggregation of resting systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) was assessed in 98 white families, who participated in the HERITAGE Family Study, and were selected to be sedentary, and primarily nonobese and normotensive. In the present study, 522 family members were sedentary at baseline examination, and resting SBP, DBP, and HR measured during this examination were investigated. If physical activity level is a potent environmental factor, then we expected that the relative contribution of environmental factors to the familial aggregation of blood pressure (BP) would be somewhat reduced, because activity was controlled for in this study. Using a familial correlation model, maximal heritabilities were estimated to be 54%, 41%, and 32% for resting SBP, DBP, and HR, respectively, in these families; and they were 51%, 42%, and 34% for resting SBP, DBP, and HR, respectively, when the data were adjusted for body mass index. The estimates are somewhat higher for BP but similar for HR to those reported in previous family studies, suggesting that the distribution of the underlying etiologic factors in these sedentary families may be similar to those in the general population. There was substantial spouse resemblance in this study, which may be explained by a higher concordance for correlated lifestyle factors including diet, similar activity levels, or by assortative mating for relative weight or dietary preferences. Am J Hypertens 1999;12:264–270 © 1999 American Journal of Hypertension, Ltd.

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It is known that elevated resting blood pressure (BP) and heart rate (HR) are associated with cardiovascular diseases (CVD),[1-3] and there is considerable interest in understanding the role of genetic and familial environmental contributions to the variation in these risk factors. According to the review by Williams et al,[4] who combined data from five studies, including twin and adoption designs, Pearson correlations for BP were 0.06 to 0.08 in spouse pairs, 0.14 to 0.18 in offspring-parents and sibling pairs, 0.25 to 0.27 in dizygotic (DZ) twins, and 0.55 to 0.58 in monozygotic (MZ) twins. Estimates of genetic heritability for BP ranged from 44% to 60% in twins and from 17% to 38% in pedigrees. Estimates of the heritability of resting SBP, DBP, and HR based on other family studies are generally in the range of 15% to 35%.[5-9] However, none of these previous family studies controlled for the contribution of physical activity level, which is correlated with resting BP and HR,[7,10-15] and is characterized as a risk factor for CVD.

Physical activity level was controlled for in The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study by requiring all participants to be sedentary at baseline, ie, having not engaged in regular vigorous physical activity over the previous 6 months. A battery of measurements of CVD and non-insulin-dependent diabetes mellitus (NIDDM) risk factors were collected before a 20-week endurance exercise training regimen and after the training period.[12] The primary goal of the current investigation was to assess the role of genetic and familial environmental factors on resting BP and HR levels measured at baseline. This study is unique in that the contribution of physical activity level to phenotypic variability is minimized, as the HERITAGE Family Study participants were uniformly sedentary at entry.

MATERIALS AND METHODS

Sample A total of 528 individuals in 98 two-generation families of white descent (257 men, 265 women) were analyzed in this study. Four subjects with incomplete resting BP and HR information, one member of a MZ twin pair, and one single offspring were dropped from the sample. Families of black American descent also were recruited and tested, but are not reported here. Recruitment of families was based on extensive media publicity and advertisements from four participating clinical centers.

The following criteria were applied to screen subjects for participation. First, individuals were required to be between the ages of 17 and 65 years (17 to 40 years of age for children and ≤65 years of age for parents). Second, all participants were required to be sedentary at baseline. Third, individuals with a body mass index (BMI) > 40 kg/m^2 were excluded unless they were able to meet the demands of the exercise tests and exercise training program. Fourth, resting BP levels could not exceed 159 mm Hg for SBP and 99 mm Hg for DBP. Antihypertension drug therapy was also a cause for exclusion. Finally, participants were required to be in good physical health and to complete the 20-week exercise program. Further details can be found in Bouchard et al.[12]

Measurements Each individual was examined for a battery of measurements before engaging in the 20-week standardized exercise program. Multiple resting BP and HR measurements were made on two separate days before the start of exercise training. Resting BP measurements were obtained before 11:00 AM with patients having no caffeine-containing beverages or tobacco products for at least 2 h before measurements. Measurements were performed in a quiet room at neutral ambient temperature (24° to 25°C) with the lights dimmed after participants rested for at least 5 min in a reclining chair with legs elevated and the chair's back support reclined at about 45° from the ground. The BP was determined using a properly fitted cuff connected to a Colin STBP-780 automated unit (San Antonio, TX).[12] Resting HR was obtained from the Colin STBP-780 using three lead electrodes attached to the skin (CM-5 configuration) and connected to the electrocardiogram (ECG) input connector. The printout value is the average of heart rate during the BP measurements. At least four BP and HR readings were taken after an initial 5-min rest period, with 2-min intervals between readings. The first measurement, although recorded on the paper form, was discarded. The three valid measurements taken on each of the 2 days were averaged for further analyses.[14]

Age Adjustment Resting SBP, DBP, and HR were adjusted for age using a stepwise multiple regression procedure. Briefly, phenotypes were regressed on up to a cubic polynomial in age within four gender-generation groups (fathers, mothers, sons, and daughters). The resulting squared residuals were similarly adjusted for age effects on variance[16]; the final adjusted phenotypes were standardized to a mean of zero and a SD of one. In addition, resting BP and HR were also adjusted for age and BMI to assess BMI influence on estimates of heritability.

Familial Correlation Model A gender-specific familial correlation model was used to investigate whether there was evidence of familial factors underlying the variation in each of the age-adjusted SBP, DBP, and HR phenotypes. The computer program SEGPATH[17] was used to fit the model directly to the family data using the method of maximum likelihood under the assumption that the phenotypes within a

TABLE 1. MODEL-FITTING SUMMARY

Model	df	Resting SBP			Resting DBP			Resting HR		
		χ^2	P	AIC	χ^2	P	AIC	χ^2	P	AIC
Age adjusted										
(1) General model	0	—	—	1434.91	—	—	1433.13	—	—	1487.23
(2) No gender differences in offspring (fs=fd, ms=md, ss=dd=sd)	4	4.26	.372	1431.17	7.06	.133	1432.19	2.17	.705	1481.40
(3) No gender differences in parents or offspring (fs=fd=ms=md, ss=dd=sd)	5	4.27	.511	1429.18	8.13	.149	1431.26	3.17	.674	1480.40
(4) No gender, no generation differences (fs=fd=ms=md=ss=dd=sd)	6	8.56	.200	1431.47	8.17	.226	1429.30	3.54	.739	1478.77
(5) No sibling resemblance (ss=dd=sd=0)	3	49.90	<.001	1478.81	28.26	<.001	1455.39	16.95	<.001	1498.18
(6) No parent-offspring resemblance (fs=fd=ms=md=0)	4	16.18	.003	1443.09	19.48	<.001	1444.61	9.30	.054	1488.53
(7) No spouse resemblance (fm=0)	1	11.55	<.001	1444.46	13.95	<.001	1445.08	8.05	.005	1493.28
(8) Single correlation (fm=fs=fd=ms=md=ss=dd=sd)	7	9.59	.213	1430.50	10.82	.147	1429.95	5.56	.592	1478.79
Parsimonious models										
Model (3)	5	4.27	.511	1429.18						
Model (4)	6				8.17	.226	1429.30	3.54	.739	1478.77
Models (4) and (6)	6							11.15	.084	1486.38
Age and BMI adjusted										
(1) General model	0	—	—	1435.26	—	—	1429.46	—	—	1480.21
(2) No sex differences in offspring	4	4.43	.351	1431.69	9.04	.060	1430.50	2.45	.654	1474.66
(3) No sex diff. in parents, offspring	5	4.52	.477	1429.78	9.89	.078	1429.35	3.17	.674	1473.38
(4) No sex, no generation differences	6	8.23	.222	1431.49	9.89	.129	1427.35	3.60	.731	1471.81
(5) No sibling resemblance	3	47.01	<.001	1476.27	25.90	<.001	1449.36	17.99	<.001	1492.20
(6) No parent-offspring resemblance	4	16.13	.003	1443.39	20.40	<.001	1441.86	9.96	.041	1482.17
(7) No spouse resemblance	1	8.03	.005	1441.29	11.04	<.001	1438.50	8.01	.005	1486.22
(8) Single correlation	7	8.35	.303	1429.61	11.48	.119	1426.94	5.47	.603	1471.68
Parsimonious models										
Model (8)	7	8.35	.303	1429.61	11.48	.119	1426.94	5.47	.603	1471.68

AIC, Akaike's Information Criterion; f, fathers; m, mothers; s, sons; d, daughters; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

family jointly follow a multivariate normal distribution. The general model was based on the four groups of individuals referred to above (fathers [f], mothers [m], sons [s], and daughters [d]), giving rise to eight correlations in three familial classes (one spouse [fm], four parent-offspring [fs, fd, ms, md], and three sibling [ss, dd, sd]). Null hypotheses were also evaluated. Each null hypothesis was tested by a comparison to the general model using the likelihood ratio test, which is the difference in minus twice the log-likelihood (−2 ln L) obtained under the two models. The likelihood ratio is approximately distributed as a χ^2, with the degrees of freedom being equal to the difference in the number of parameters estimated in the two models. In addition to the likelihood ratio test, Akaike's Information Criterion (AIC),[18] which is −2 ln L plus twice the number of estimated parameters, was used to compare nonnested models. The best model is the one with the smallest AIC.

Two general series of null hypotheses were tested on age-adjusted, and age- and BMI-adjusted data (Table 1). Sex and generation differences were tested in the first series (models 2 to 4). The second series of null hypotheses examined the significance of various components of the familial resemblance (models 5 to 7). Finally, a single correlation was fit to the data by equating all eight correlations (model 8). A parsimonious model was derived by combining the nonrejected hypotheses into a single test. Maximal heritability was computed using the familial correlations from the most parsimonious model (see Rice et al[16] and footnote of Table 2 for equation). This estimate includes both polygenic and familial environmental sources of variance, and is adjusted for the degree of spouse resemblance. In the absence of genetic effects, this simply includes familial environmental effects. And, in the absence of familial environmental effects, maximal heritability indicates the extent

TABLE 2. PARAMETER ESTIMATES AND STANDARD ERRORS FOR GENERAL AND MOST PARSIMONIOUS MODELS

Parameters	Resting SBP		Resting DBP		Resting Heart Rate	
	General	Most Parsimonious	General	Most Parsimonious	General	Most Parsimonious
Age adjusted						
fm	0.34 ± 0.09	0.34 ± 0.09	0.37 ± 0.08	0.37 ± 0.08	0.29 ± 0.09	0.30 ± 0.09
fs	0.30 ± 0.08	0.24 ± 0.06	0.27 ± 0.09	0.23 ± 0.05	0.24 ± 0.08	0.17 ± 0.04
fd	0.21 ± 0.09	[0.24]	0.26 ± 0.07	[0.23]	0.13 ± 0.08	[0.17]
ms	0.21 ± 0.10	[0.24]	0.18 ± 0.09	[0.23]	0.13 ± 0.10	[0.17]
md	0.26 ± 0.09	[0.24]	0.20 ± 0.07	[0.23]	0.09 ± 0.08	[0.17]
ss	0.44 ± 0.10	0.37 ± 0.06	0.39 ± 0.09	[0.23]	0.27 ± 0.09	[0.17]
dd	0.44 ± 0.09	[0.37]	0.50 ± 0.10	[0.23]	0.13 ± 0.11	[0.17]
sd	0.30 ± 0.08	[0.37]	0.21 ± 0.07	[0.23]	0.15 ± 0.08	[0.17]
Maximal heritability*		54% ± 12%		41% ± 10%		32% ± 8%
Age and BMI adjusted						
fm	0.29 ± 0.09	0.29 ± 0.04	0.34 ± 0.09	0.23 ± 0.04	0.29 ± 0.09	0.18 ± 0.04
fs	0.29 ± 0.09	[0.29]	0.22 ± 0.09	[0.23]	0.25 ± 0.08	[0.18]
fd	0.24 ± 0.09	[0.29]	0.28 ± 0.07	[0.23]	0.12 ± 0.08	[0.18]
ms	0.20 ± 0.10	[0.29]	0.18 ± 0.09	[0.23]	0.15 ± 0.10	[0.18]
md	0.25 ± 0.09	[0.29]	0.21 ± 0.07	[0.23]	0.10 ± 0.08	[0.18]
ss	0.43 ± 0.10	[0.29]	0.38 ± 0.09	[0.23]	0.27 ± 0.09	[0.18]
dd	0.45 ± 0.09	[0.29]	0.03 ± 0.10	[0.23]	0.13 ± 0.11	[0.18]
sd	0.28 ± 0.09	[0.29]	0.18 ± 0.08	[0.23]	0.16 ± 0.08	[0.18]
Maximal heritability*		51% ± 8%		42% ± 8%		34% ± 8%

* *Maximum heritability computed as* $[(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2*r_{spouse}*r_{parent\text{-}offspring})]$, *including both genetic and familial environmental sources of variance, and adjusted for the degree of spouse resemblance.*

Abbreviations as in Table 1.

of genetic effects. In reality, it likely includes both sources.

RESULTS

In this study, coefficients of variations (CV) for repeated measures are 4%, 6%, and 8% for resting SBP, DBP, and HR, respectively, and intraclass correlations (ICC) are 0.84, 0.79, and 0.73 for resting SBP, DBP, and HR, respectively. Means, ranges, and SD of the unadjusted resting SBP, DBP, and HR are presented in Table 3. Skewness is 0.06, 0.02, and 0.38 for resting SBP, DBP, and HR, respectively, and kurtosis excess is −0.11, 0.09, and 0.66 for resting SBP, DBP, and HR, respectively. Significant ($P < .05$) age terms and percentages of variance accounted for in each of the gender by generation groups are as follows. For resting SBP, age[3] accounted for 5.57% of the mean variation in mothers, whereas no age terms were significant for

TABLE 3. MEANS, RANGES, AND STANDARD DEVIATIONS (SD) FOR UNADJUSTED DATA

Variables	Fathers			Mothers			Sons			Daughters		
	N	Mean (range)	SD	N	Mean (range)	SD	N	Mean (range)	SD	N	Mean (range)	SD
Age (years)*	97	53.5 (44.4–63.8)	5.1	94	52.1 (42.4–65.2)	5.0	160	25.4 (16.9–40.2)	6.1	171	25.3 (17.1–40.8)	6.2
SBP (mm Hg)	97	122.1† (96.3–151.7)	13.1	94	116.9† (85.7–152.5)	11.9	160	119.2† (93.0–147.3)	8.7	171	110.5† (91.7–127.5)	7.9
DBP (mm Hg)*	97	72.9† (50.0–95.7)	8.7	94	67.7† (50.7–84.2)	6.8	160	65.6† (44.5–85.8)	8.4	171	61.9† (43.5–79.3)	6.3
HR (beats/min)*	97	63.9† (48.5–84.2)	7.7	94	66.7† (50.3–93.0)	8.8	160	61.1† (42.8–83.7)	8.7	171	67.1† (44.0–105.3)	8.6

* *Significant ($P < .05$) mean differences for father–son or mother–daughter (within gender) comparisons.*

† *Significant ($P < .05$) mean differences for father–mother or son–daughter (within generation) comparisons.*

fathers or offspring. For resting DBP, age accounted for 12.12% of the mean variation for sons, and age^3 accounted for 4.44% of the mean variation for daughters, and there were no significant age terms for parents. For resting HR, age accounted for 3.89% of the mean variation for sons, but was not significant in any other group. For age and BMI adjustment for resting SBP, BMI accounted for 8.71% in fathers and age^3 accounted for 18.65% in mothers, of the mean variation; for resting DBP, BMI accounted for 14.9% in fathers, age accounted for 12.87% in sons, and BMI-age^3 accounted for 9.22% in daughters, of the mean variation; for resting HR, BMI accounted for 8.38% of the mean variation in sons. No other age or BMI terms were significant in any other groups. No age or BMI effects in the variance (ie, heteroscedasticity) were detected.

The model-fitting results are presented in Table 1. For resting SBP, none of the tests for no-sex and no-generation differences in the correlations was significant (models 2 to 4, $P > .05$). The hypothesis on a single correlation (model 8, $P > .05$) also was not rejected. However, the familial correlations were significantly different from zero (models 5 to 7), suggesting significant familial resemblance. For the most parsimonious hypothesis, while any of the no-sex and no-generation difference models fit the data, the AIC suggested that model 3 (no sex differences in parents or offspring) provides the most parsimonious fit ($\chi^2_5 = 4.27$, $P = 0.511$, AIC = 1429.18). For the age-BMI-adjusted data, none of the sex and generation tests were significant, and the correlations were significantly different from zero. Therefore, model 8 (a single correlation) is the most parsimonious ($\chi^2_7 = 8.35$, $P = 0.303$, AIC = 1429.61).

For resting DBP, the results show an identical pattern. There were no sex and no generation differences, and the familial correlations were significantly different from zero ($P < .001$), suggesting significant familial resemblance. Based on the AIC, the most parsimonious hypothesis was given by model 4 (no sex and no generation differences, $\chi^2_4 = 8.17$, $P = .226$, AIC = 1429.30). For the age-BMI-adjusted data, there were no sex and no generation differences, and the correlations were significant, and thus model 8 (a single correlation) is the most parsimonious model by AIC ($\chi^2_7 = 11.48$, $P = .119$, AIC = 1426.94).

For resting HR, none of the models testing sex and generation differences was rejected. Each of the familial correlations was significantly different from zero, except that the evidence for no parent-offspring resemblance (model 6) was borderline ($\chi^2_4 = 9.30$, $P = .054$). The likelihood ratio tests suggest no sex and no generation differences, and no parent-offspring resemblance. Whereas the combined test of these hypotheses (models 4 and 6, fs = fd = ms = md = 0, ss = dd = sd) was not rejected by likelihood ratio test ($\chi^2_6 = 11.15$, $P = .084$), the AIC (1486.38) was not acceptable. Therefore, the parent-offspring correlations were added back to the model, leaving hypothesis 4 as the most parsimonious ($\chi^2_6 = 3.54$, $P = .739$, AIC = 1478.77). For the age-BMI-adjusted data, none of the no-sex and no-generation difference hypotheses were rejected, and the correlations were significantly different from zero. Model 8 (a single correlation) is the most parsimonious ($\chi^2_7 = 5.47$, $P = .603$, AIC = 1471.68).

Parameter estimates (correlations ± SE) are given in Table 2 under both the general and the most parsimonious models for each of the phenotypes. The maximal heritability estimates, which include both genetic and familial environmental sources of variance, were 54% for resting SBP, 41% for resting DBP, and 32% for resting HR. After age and BMI adjustment, they were 51%, 42%, and 34% for resting SBP, DBP, and HR, respectively.

DISCUSSION

The HERITAGE Family Study provides an opportunity to assess the familiality of resting BP and HR in a uniformly sedentary sample. To the extent that physical activity levels affect variation in these phenotypes, we expected the overall variability to be reduced and, as a consequence, the estimated heritability may be higher. Although the CV for mean resting BP and HR in this sample is consistently smaller when compared with other samples,[6,7,9,19,20] including both active and inactive participants, we observed levels of familial resemblance for resting BP and HR in these sedentary families to be consistent with the findings of most other studies.[6-9,19] The heritability estimates for resting BP, especially resting SBP, in these inactive families (41% to 54%) are at least as high as those reported in the Québec Family Study (QFS, genetic heritabilities of about 50% in offspring and 8% to 18% in parents, and cultural or familial environmental heritabilities of 30% to 40% in both generations),[8] the Framingham Family Study (genetic heritability of 31% for SBP),[9] and a large Brazilian family study (genetic heritabilities of 41% in offspring and 14% in parents for SBP, and 34% in both generations for DBP).[6] However, the estimate of heritability for resting HR (32%) in this inactive sample is quite similar to the estimate of 33% obtained by Pérusse et al[7] in the Canada Fitness Survey sample, which includes 4000 participating families.

A pattern of higher sibling resemblance than that predicted under a pure polygenic model was observed for resting BP, and again it is in agreement with other studies.[6,8] This noteworthy pattern suggests possible dominance effects in the genetic components or genetic developmental effects (age-specific genetic ef-

fects), ie, the genetic effect may be relatively greater in childhood than in adulthood, may decrease as individuals reach their adulthood, and may be affected by various environmental exposures. Alternatively, a higher sibling resemblance than parent-offspring correlation could be due to the fact that siblings share more similar environments with each other than they do with their parents.

In the current study, the spouse resemblance is significant and substantial for all the traits assessed. In fact, for the age-adjusted measures, the spouse correlation was generally as high, or higher, than the remaining familial correlations. One explanation is that of shared environments, including such factors as diet, salt and alcohol consumption, and limited regular physical activity. It would be reasonable to expect that spouse concordance for inactivity would also result in greater spouse similarity for other lifestyle factors. However, Knuiman et al[20] studied the pattern of spouse resemblance in SBP and DBP (among other variables) as a function of marriage duration, and found a decreasing trend in the magnitude of the correlations for both BP measures, which is contrary to the hypothesis that shared environments can account for substantial spouse resemblance. This finding, according to Knuiman, may suggest assortative mating as a more plausible explanation. It is interesting to note that Allison et al[21] found evidence of assortative mating for relative weight. Given that resting BP and HR are correlated with body mass or body composition,[22-24] the spouse resemblance observed in the present study may be a function of assortative mating for body size in addition to the possibility of shared environments. These data were therefore adjusted for the effects of BMI. We expected that if the spouse correlations were due to assortative mating for BMI, then they would be decreased after adjustment. In general, the spouse correlations were reduced to the same magnitude as the remaining familial correlations.

However, the remaining familial correlations did not significantly change, nor did the resulting heritability estimates after BMI adjustment. Thus, the high spouse correlation in these data may be due in part to assortment on a correlated trait (BMI). Given that the spouse correlations are still rather high after BMI adjustment, there may still be assortment on other factors, such as dietary preferences.[4] Alternatively, these strong spouse correlations may reflect in whole or in part some familial environmental factors. It was also interesting to note that after BMI adjustment, the gender or generation differences for BP were eliminated, suggesting an interaction between body size and gender on the familial effects of BP.

Regular physical activity, particularly endurance exercise training, is known to affect HR.[14] Using a large general population sample of the Canada Fitness Survey, Pérusse et al[7] reported a heritability for resting HR of 33%. Although it is reasonable to expect a higher heritability estimate for resting HR from the sedentary families in the current study, our result (32%) is very close to Pérusse's finding. Consistent with this finding is the possibility that there was a low proportion of individuals in the Canada Fitness Survey who were sufficiently endurance trained so as to affect the relative importance of environmental factors influencing the resting HR. In any case, these results suggest that the hereditary mechanisms affecting resting HR appear to be comparable in these two studies.

In summary, our study results suggest that resting BP and HR levels are moderately heritable in sedentary families. The novel finding from the present study is that the familial effects for resting BP are somewhat higher in these sedentary families than those reported in other studies that include both physically active and inactive families, probably reflecting the effect of physical inactivity on resting BP and an ensuing reduction in phenotypic variation in the HERITAGE Family Study, as compared with other samples.

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