Familial Resemblance for Coronary Heart Disease Risk: The HERITAGE Family Study

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The objective of this study was to quantify familial resemblance for coronary heart disease risk in 260 Black and 427 White participants in the HERITAGE Family Study. Coronary heart disease risk was estimated using a coronary heart disease risk index (CHDRI) computed from the revised Framingham Heart Study algorithm, based on age, LDL-cholesterol, HDL-cholesterol, blood pressure, diabetes, and smoking status. Using a familial correlation model to test hypotheses regarding familial aggregation, significant familial resemblance was detected in both Blacks and Whites. There were significant sibling correlations in both Blacks and Whites, while spouse correlations were significant only in the White sample. The maximal heritabilities, which have to be interpreted cautiously in light of negligible parent-offspring correlations, were 34% and 53% in Whites and Blacks, respectively. Thus, the maximal heritability, which includes both genetic and non-genetic sources of variation, is higher in Blacks than Whites, and explains a significant proportion of the total phenotypic variance. The results indicate that risk of coronary heart disease runs along family lines, and common environmental effects are important in explaining the observed familial resemblance. (*Ethn Dis.* 2000;10:138–147)

Key Words: Blood Lipids, Blood Pressure, Coronary Heart Disease, Family Study, Genetic, Risk Factors

Introduction

The prevention of coronary heart disease (CHD) is a public health priority, as more lives are lost to CHD in North America than to any other single cause.[1,2] Further, relatives of individuals with CHD are at an increased risk of having the disease themselves.[3–5] For example, in a sample of African-American families, the risk of CHD among parents and offspring of CHD patients was 5.3 times the general population risk.[6] Important risk factors for CHD include cigarette smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, physical inactivity, and a family history of premature CHD.[7–9] Given that many of the major CHD risk factors are partly modifiable through changes in physical activity, diet and lifestyle, the study of the genetic and environmental influences on CHD risk factors is currently of major interest.

There is ample evidence that many of the individual risk factors for CHD aggregate within families. For example, significant familial resemblance for body fat,[10–18] blood

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lipids,[19-24] blood pressure,[25-33] physical activity and lifestyle,[34,35] and plasma insulin and glucose levels[36-38] have been demonstrated. However, with a few notable exceptions,[6,39-45] there is a paucity of data regarding the familial influences on CHD risk factors in Blacks. The recent research recommendations of the US National Heart, Lung and Blood Institute Working Group on Research on CHD in Blacks indicates that, "When considering CHD in Blacks, however, research on the interaction of environmental, biological, and genetic factors is especially important."[46] Thus, studies of the familial resemblance for CHD risk that include black subjects are particularly timely and valuable.

The recently revised algorithm for CHD risk from the Framingham Heart Study, based on risk factor categories,[47] was designed to aid clinicians in defining a patient's risk of future CHD. To our knowledge, the degree to which the Framingham CHD risk index (CHDRI) aggregates within families has not been explored. Designed to complement and expand upon the research on the family history of CHD and the genetics of risk factors described above, the purpose of this study was to examine the familial factors influencing the CHDRI. To this end, the familial aggregation for CHD risk was quantified in Black and White families of the HERITAGE Family Study using a familial correlation model.

Methods

Sample

The HERITAGE Family Study was designed to investigate the genetics of cardiovascular, metabolic, and hormonal responses to aerobic exercise training and the contribution of regular exercise to changes in risk factors for cardiovascular disease and type 2 diabetes. The aims and design of the HERITAGE Family Study were previously described in detail.[48] Briefly, the participating research centers consisted of four clinical centers and a data coordinating center. Recruitment of participants was based on extensive publicity and advertisements at the clinical centers. The essential criteria for participation in the HERITAGE Family Study included being between the ages of 17 and 65 years, healthy but sedentary (no regular physical activity over the previous six months), BMI under 40 $kg \cdot m^{-2}$, and systolic/diastolic blood pressures less than 159/99 mm Hg. Further, individuals with confirmed or possible CHD, chronic or recurrent respiratory problems, and uncontrolled endocrine and metabolic disorders (including diabetes and the use of lipid-lowering drugs) were also excluded from the study. The sample considered here includes 260 Black participants from 113 families, and 427 White participants from 99 families, all of whom were 20 years of age and older and for whom the appropriate measures were available. Although the HERITAGE Family Study includes participants as young as 17 years of age, the CHDRI was computed only on those participants 20 years of age and older who completed the necessary measurements (see Methods). The HERITAGE Family Study involved a 20-week exercise training program; however, only data collected during the baseline (sedentary state) visit are considered here. Sample sizes by race, sex and generation are provided in Table 1.

Measures

The study personnel were centrally trained on all aspects of recruitment and measurement protocols using a specially prepared manual of procedures. Data quality was assured through an extensive quality control program.[49]

Resting systolic and diastolic blood pressures were measured twice on separate days in the morning (before 11:00 a.m.) in the post-absorptive state. Measurements were made in a quiet room with the participant reclined at a 45° angle, with legs elevated. Blood pressure was determined after a 5-

Table 1.—Descriptive statistics of age, BMI and risk factors in each of the race, sex and generation groups in the HERITAGE Family Study

Variable	Fathers			Mothers			Sons			Daughters		
	N	M	SD	*N*	M	SD	*N*	M	SD	*N*	M	SD
Blacks												
Age (years)	29	50.0	7.2	53	46.3	6.6	64	29.2	5.9	114	29.5	6.9
BMI (kg/m^2)	29	27.5	5.2	53	29.5	5.4	64	27.9	4.7	114	28.4	6.8
LDL-cholesterol (mmol/L)	29	3.3	0.8	53	3.1	0.7	64	3.0	0.8	114	2.7	0.7
HDL-cholesterol (mmol/L)	29	1.0	0.5	53	1.2	0.3	64	1.0	0.2	114	1.1	0.3
Systolic blood pressure (mm Hg)	29	127	13	53	129	13	64	125	9	114	120	12
Diastolic blood pressure (mm Hg)	29	77	9	53	78	8	64	72	6	114	71	9
CHDRI	29	4.6	2.4	53	3.3	5.0	64	0.1	2.0	114	−7.2	4.7
Whites												
Age (years)	95	53.6	5.2	87	52.1	4.9	118	27.5	5.2	127	27.6	5.6
BMI (kg/m^2)	95	28.3	4.5	87	27.2	4.4	118	26.2	5.0	127	23.9	4.5
LDL-cholesterol (mmol/L)	95	3.5	0.8	87	3.3	0.7	118	2.9	0.8	127	2.8	0.7
HDL-cholesterol (mmol/L)	95	0.9	0.2	87	1.2	0.3	118	0.9	0.2	127	1.1	0.3
Systolic blood pressure (mm Hg)	95	122	13	87	117	12	118	119	9	127	110	8
Diastolic blood pressure (mm Hg)	95	73	9	87	67	7	118	67	8	127	63	6
CHDRI	95	5.2	1.9	87	4.3	4.0	118	0.2	2.0	127	−9.5	3.5

minute rest period using a Colin STBP-780 automated unit while the technician wore ear phones to confirm the readings. The first measurements were discarded and up to three valid measurements were made during each assessment. The average of the valid blood pressure measurements (up to six) was used as the measure of blood pressure in the present analysis.

Fasting (12 hour) blood samples were obtained from an antecubital vein and collected into vacutainer tubes containing EDTA. For women, samples were obtained in the early follicular phase of the menstrual cycle. Plasma was ultracentrifuged and the top fraction containing VLDL was quantitatively recovered. The LDL in the ultracentrifuged bottom fraction was precipitated with heparin and $MgCl_2$[50,51] and the HDL was obtained in the supernatant. The concentrations of cholesterol[52] in the lipoprotein fractions were measured by autoanalyzer (Technicon RA-500) using enzymatic reagents obtained from Miles Laboratories.

A coronary heart disease risk index (CHDRI) was computed using the recently modified algorithms derived from Framingham Heart Study follow-up data.[47] The algorithm estimates CHD risk from age, plasma levels of LDL-C, HDL-C, blood pressure, presence or absence of diabetes, and smoking status, using separate prediction equations for males and females. The algorithm was developed from 12-year follow-up data on 2489 men and 2856 men (Caucasian), 30–74 years of age, in the Framingham Heart Study and utilizes the fifth Joint National Committee (JNC-V) blood pressure[53] and National Cholesterol Education Program (NCEP) cholesterol[54] categories. Participants were assigned a score for each: age, LDL-C, HDL-C, blood pressure, diabetes status, and smoking status (from a personal history questionnaire). One of the exclusion criteria for the HERITAGE Family Study was diabetes requiring medication for blood glucose control, so all participants were assigned a zero score for this variable. Although developed on adults 30–74 years of age, the algorithm was applied to all adults over the age of 20 years in the present study, and 20–29 year olds were assigned the same age score as 30–34 year olds. In males, those with a CHDRI of less than −3 have a 1%, 10-year risk of CHD, while someone with a score of 14 and above has a greater than 56%, 10-year CHD risk. In females, someone with a CHDRI of less than −2 has a 1%, 10-year risk of CHD, while someone with a CHDRI above 17 has a greater than 32% 10-year risk of CHD.[47]

Age adjustments

The CHDRI was adjusted for the effects of age in both the mean and variance separately in each of the eight race-by-sex-by-generation groups using regression procedures. In summary, the CHDRI was regressed on up to a cubic polynomial in age in a forward stepwise manner, retaining terms significant at the 5% level. The CHDRI was then examined for heteroscedasticity by regressing the squared residuals on up to another cubic polynomial in age. The final phenotype was then standardized to a mean of zero and unit variance within each of the eight groups. Briefly, age accounted for 32%, 33%, and 12% of the variance in Black fathers, White fathers, and White sons, respectively, while age^2 accounted for 20% of the variance in Black sons. In Black and White mothers, age and age^3 accounted for 54% of the variance in Black mothers, while age^2 accounted for 35% of the variance in White mothers. In Black daughters, age and age^2 accounted for 55% of the variance, while age^2 and age^3 accounted for 29% of the variance in White daughters. No heteroscedasticity was found in any of the age regressions.

Familial correlation model

An ANOVA comparing the between-family to within-family variances was used to verify the hypothesis that the CHDRI ag-

Table 2.—Summary of hypothesis tests

Hypothesis	Parameter Constraints
1. General model	All 8 correlations estimated
2. No sex differences in offspring	FS = FD, MS = MD, SD = SS = DD
3. No sex differences in offspring or parents	FS = FD = MS = MD, SD = SS = DD
4. No sex or generation differences	FS = FD = MS = MD = SD = SS = DD
5. All correlations equal (environmental model)	FM = FS = FD = MS = MD = SD = SS = DD
6. No spouse resemblance	FM = 0
7. No sibling resemblance	SD = SS = DD = 0
8. No parent-offspring resemblance	FS = FD = MS = MD = 0
9. No familial resemblance	All 8 correlations are zero
10. Most parsimonious model	Combination of non-rejected hypotheses above

FM, father-mother; FS, father-son; MS, mother-son; FD, father-daughter; MD, mother-daughter; SD, son-daughter; SS, son-son; DD, daughter-daughter.

gregates within families. The familial correlation model is based on four types of individuals (fathers [F], mothers [M], sons [S], daughters [D]) giving rise to eight types of correlations (one spouse [FM]: four parent-offspring [FS, MS, FD, MD], and three sibling [SS, SD, DD]). The maximum likelihood computer program SEGPATH[55] fits the model directly to the family data under the assumption that the CHDRI in a family follows a multivariate normal distribution. Hypotheses regarding the familial aggregation of the CHDRI were tested using the likelihood ratio test, which is the difference in minus twice the log-likelihoods (-2 ln L) obtained under two different nested models. The likelihood ratio is distributed approximately as a χ^2, with degrees of freedom being the difference in the number of parameters estimated under the opposing models. In addition to the likelihood ratio test, Akaike's Information Criterion (AIC),[56] which is -2 ln L plus twice the number of estimated parameters, was used to judge the overall fit of the non-nested models. The "best" model is the one with the lowest AIC.

A general model (model 1) in which all 8 correlations were estimated was fit to the data, as were a series of nested models (Table 2). The tested hypotheses included no sex differences in offspring (model 2: FS = FD, MS = MD, DS = SS = DD), no sex differences in offspring or parents (model 3: FS = FD = MS = MD, SD = SS = DD), no sex or generation differences (model 4: FS = FD = MS = MD = SD = SS = DD), all correlations equal (model 5), no sibling resemblance (model 5: SD = SS = DD = 0), no parent-offspring resemblance (model 6: FS = FD = MS = MD = 0), no spouse resemblance (model 7: FM = 0), and no familial resemblance (model 8: all correlations equal 0). The most parsimonious model was derived from combining all non-rejected hypotheses.

Table 3.—Results of ANOVAs for familial aggregation of the coronary heart disease risk index (CHDRI) in Black and White families of the HERITAGE Family Study

	R^2	F	P
Blacks	0.61	2.06	<.0001
Whites	0.37	1.96	<.0001

Results

The CHDRI significantly aggregates within families, as evidenced by the significant ANOVAs (Table 3). The F-ratios indicate that there is between 1.96 and 2.06 times the variance between families than within families for the CHDRI. A comparison of R^2 values indicates that family membership accounts for 61% of the variation in the CHDRI in the Black sample

Table 4.—Summary of results for hypothesis tests for the coronary heart disease risk index (CHDRI)

Model	Blacks		Whites	
	*P**	AIC†	*P**	AIC†
1. General model		24.00		24.00
2. No sex differences in offspring	.65	18.48	.77	17.80
3. No sex differences in offspring or parents	.59	17.69	.86	15.93
4. No sex or generation differences	.70	15.86	.75	15.45
5. All correlations equal (environmental model)	.78	13.98	.74	14.35
6. No spouse resemblance	.28	23.18	.02	27.64
7. No sibling resemblance	.02	28.30	.07	30.19
8. No parent-offspring resemblance	.06	25.23	.17	22.35
9. No familial resemblance	.01	28.23	.03	31.61
10. Most parsimonious model Model 5	.78	13.98	.74	14.35

* P from the likelihood ratio χ^2 test; a significant value ($P < .05$) indicates rejection of the hypothesis.

† AIC, Akaikes's Information Criterion; the most parsimonious model is the one with the smallest AIC; we subtracted (−2 ln L) under the general model from the AIC of all the submodels for easy comparison.

Table 5.—Estimates of familial correlations (±S.E.) for the coronary heart disease risk index (CHDRI)

	Blacks	Whites
	General Model	
FM	0.24 ± 0.21	0.25 ± 0.10
FS	0.33 ± 0.38	0.16 ± 0.10
MS	0.48 ± 0.21	0.21 ± 0.09
FD	0.38 ± 0.19	0.11 ± 0.10
MD	0.21 ± 0.15	0.11 ± 0.10
SD	0.12 ± 0.22	0.29 ± 0.11
SS	0.49 ± 0.18	0.15 ± 0.12
DD	0.34 ± 0.13	0.25 ± 0.12
	Most Parsimonious Model	
FM	0.30 ± 0.08	0.18 ± 0.05
FS	[0.30]	[0.18]
MS	[0.30]	[0.18]
FD	[0.30]	[0.18]
MD	[0.30]	[0.18]
SD	[0.30]	[0.18]
SS	[0.30]	[0.18]
DD	[0.30]	[0.18]
Maximal heritability	52.7%	34.1%

Values in brackets are fixed or equal to a preceding value.

FM, father-mother; FS, father-son; MS, mother-son; FD, father-daughter; MD, mother-daughter; SD, son-daughter; SS, son-son; DD, daughter-daughter.

Maximal heritability (h^2) computed as: $(r_{sib} + r_{p\text{-}o})(1 + r_{spouse})/(1 + r_{spouse} + 2r_{spouse}r_{p\text{-}o})$.

and 37% of the variation in the White sample. Thus, a considerable portion of the variation in the CHDRI is accounted for by familial factors, and the estimates of familial aggregation are higher in the Black sample compared to the White sample.

The model fitting results are presented in Table 4. The null hypothesis of no familial resemblance (model 8) was rejected in all cases ($.01<P<.03$), indicating that there is significant familial resemblance in both Blacks and Whites for the CHDRI. None of the models testing for sex differences in the familial correlations were rejected, indicating that there were no significant sex differences. Parent-offspring resemblance in the CHDRI was not detected. On the other hand, there were significant sibling correlations in both Blacks and Whites for the CHDRI. The hypothesis of no spousal resemblance was rejected in the White sample ($P=.02$); however, there was no evidence for spousal resemblance in Blacks ($P=.28$). The most parsimonious model for the CHDRI is model 5 (environmental model) in both the White and Black samples.

Maximum likelihood parameter estimates (± standard errors) are provided in Table 5 for both the general and most parsimonious models, as are the maximal heritabilities computed under the most parsimonious

models. The maximal heritabilities are 34% and 53% in the White and Black samples, respectively. Thus, the maximal heritability of the CHDRI, which includes both genetic and non-genetic causes of familial aggregation, is higher in the Black than the White sample. Caution must be exercised when interpreting the maximal heritabilities since the parent-offspring correlations seem to be small for the most part.

Discussion

The results of this study build upon those of previous studies that have examined the familial aggregation of individual CHD risk factors. Just as CHD risk factors have significant heritable components, so too does the CHDRI. The results of the ANOVAs indicate that there is approximately two times more variance between than within families, and that between 37% and 61% of the variance in the CHDRI was attributable to familial factors. These results are consistent with studies that have shown CHD incidence to aggregate within families.[3-6] In the Framingham Heart Study, the incidence of CHD in men was significantly related to the myocardial infarction experience of their younger brothers, after adjustment for smoking, total cholesterol, and blood pressure.[3] The authors suggested that a family history of disease, which may be genetic, was contributing to the familial resemblance in CHD. The present study could not address this issue further, as CHD risk was computed from traditional risk factors.

The Black sample demonstrated a higher degree of familial resemblance in the CHDRI than did the White sample, based on the familial correlation analyses. Since the CHDRI was developed from CHD followup in a middle-aged White sample (Framingham Heart Study),[47] the utility of the CHDRI as an indicator of CHD risk in Blacks is unknown; however, dyslipidemia, hypertension, and smoking have been shown to be risk factors for CHD in Blacks.[57-59] Further, Rotimi et al[6] demonstrated that among 232 African-American families, the odds ratio for CHD developing in parents and offspring of individuals with CHD was 5.3 times the general population's risk. Taken together, these results suggest that CHD risk does aggregate within Black families.

Derived from nuclear families, the estimates of maximal heritability in the present study include both genetic and non-genetic sources of variation. The maximal heritabilities were 34% in the White sample and 53% in the Black sample; however, the pattern of familial correlations does not provide strong support for a genetic hypothesis. For example, the pattern of significant parent-offspring and sibling correlations coupled with no spousal resemblance (which would suggest a role for genes) was not found in this study. It appears as though a large part of the familial resemblance is driven by shared lifestyles and environments within families.

In summary, the results of the present study indicate that an index of CHD risk significantly aggregates in the Black and White families of the HERITAGE Family Study. The pattern of familial correlations suggests that shared common environments are largely driving the significant maximal heritabilities obtained; however, a genetic hypothesis for CHD risk cannot be discounted. Future genetic studies on the CHDRI should include extended pedigrees and other types of relatives by descent or adoption to better partition genetic from environmental influences on CHD risk, which was not possible in this sample of nuclear families. The CHDRI was designed as a simple tool to estimate risk of future CHD in healthy outpatients.[47] The results of the present study suggest that extending the assessment of the CHDRI to immediate family members may enhance the definition of CHD risk in both Black and White patients.

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