

Familial Correlation and Heritability for Cardiovascular Risk Factors

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The goal of this study was to describe the overall genetic contribution of phenotypic variation to cardiovascular disease. The study population included 7,589 family members of 1,891 families, derived from Korean Medical Insurance Corporation. The risk factors considered were systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and high serum cholesterol. The levels of cardiovascular disease risk factors were adjusted for age, gender, smoking and alcohol drinking. Heritability was estimated from the slope of the line linear regression of offspring on mid-parent.

All risk factors showed positive familial correlations, and correlations were generally lower for spouses than for parent-offspring pairs. Spouse correlations showed increasing patterns with age. Parents-offspring correlations showed little variation with age, suggesting that the observed correlations with CVD risk factors were primarily due to genetic influences rather than environmental effects. Estimated heritabilities were 26% for BMI, 26% for high serum cholesterol, 19% for SBP, and 9% for DBP. These results highlight the importance of considering genetic factors in studies of cardiovascular risk factors.

Key Words: Correlation, heritability, CVD risk factor

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INTRODUCTION

Despite the decline in mortality from cardiovascular disease since 1970 in most industrialized countries, cardiovascular disease (CVD) and coronary heart disease in particular, are still the leading causes of death. In Korea, cardiovascular disease was responsible for 23.3% of all deaths in 1999.¹

Familial aggregations of cardiovascular disease can be largely accounted for by a clustering of cardiovascular risk factors.²⁻⁵ Almost all studies have demonstrated that there is a familial aggregation of cardiovascular risk factors, although there is some debate over the extent to which this observed aggregation is due to genetic rather than environmental causes. One strategy for identifying the genes that influence CVD risk, is to identify the genes that influence the intermediate traits associated with atherosclerosis, i.e., traits such as dyslipidemia, obesity, and hypertension. Although the literature on this topic is abundant, no study has been conducted upon cardiovascular risk factors in Korea. Most studies have investigated only a small number of cardiovascular risk factors, though a variety of statistical methods have been applied. Few studies have investigated both familial correlation and the heritability of CVD risk factors.

This study reports upon the familial correlations and heritabilities of body mass index, systolic and diastolic blood pressure, and serum cholesterol using data from the Korea Medical Insurance Corporation study.

MATERIALS AND METHODS

The Korea Medical Insurance Corporation (KMIC) provides health insurance to government employees, teachers and their dependents. In 1990, of the entire Korean population consisting of approximately 43 million people, 4,603,361 (11%) were insured by KMIC, including 1,213,594 workers and their 3,389,767 dependants. All insured workers are required to participate in biennial medical examinations conducted by KMIC.⁶ In 1992, it was reported that 94% completed biennial examinations.

The KMIC family study is designed to assess the effect of the genetic variance of CVD risk factors in Korean men and women. In the present analysis, only families with three or more members were included. Families in which only one member had valid data were not included. After exclusion, this data set consisted of 7,589 individuals in 1,891 families.

Data collection

KMIC biennial examinations are conducted in a standardized fashion by medical staff at local hospitals. Biennial examinations were carried out in 1992 and 1994 for the insured, and for dependants similarly examinations were conducted in 1993 and 1995. The biennial medical examination included measurements of weight, height, and serum cholesterol. A fasting blood specimen was drawn and analyzed for total cholesterol. Each hospital that participated in the examination followed internal and external quality control procedures as directed by the Korean Association of Laboratory Quality Control. Body mass index (BMI) was defined as weight/height² (Kg/m²).

Statistical analysis

Using univariate analyses, we examined the distribution of CVD risk factors. Familial correlations of cardiovascular risk factors were estimated using the Fcor program in S.A.G.E. (Statistical Analysis for Genetic Epidemiology, 1997).⁷ Heritability estimates from regression of offspring on parents were estimated. The sloping line is the linear regression of offspring on mid-parent. The slope of this line is an estimate of the heritability; and equal to the standard error: $h^2 = b \text{ op (offspring-parents)}$. The data are presented in the form of parents measurements - one or the mean of the two, and the mean of their offspring.^{8,9}

RESULTS

Study population

The mean age of subjects was 59.8 years (males 59.0 and females 60.4 years), with a wide range (40-85 years). Height was distributed normally and ranged from 150.7 to 177.5 cm, with a mean of 159.2 cm (females 154.3 and males 168.0 cm). SBP ranged from 89.5 to 161.8 mmHg in the entire sample, with a mean of 123.6 mmHg (females 122.3 and males 124.4 mmHg); this distribution was slightly positively skewed (coefficient of skewness 0.02). Serum cholesterol ranged from 122.2 to 162.0 mg/dl, with a mean of 190.7 mg/dl (females, 192.7 and males, 187.5 mg/dl). (Table 1)

Familial correlations of CVD risk factors

Table 2 shows the estimated familial correlations of CVD risk factors. These risk factors

Table 1. Means (SD) of Characteristics for the 7,589 Persons in the 1,891 Families

	Female Mean	SD	Male Mean	SD
Age (years)	35.41	21.93	34.01	21.23
Height (cm)	154.32	5.82	168.06	5.84
Weight (kg)	55.22	7.72	65.93	8.92
Systolic BP (mmHg)	122.36	18.13	124.43	14.55
Diastolic BP (mmHg)	77.32	11.58	80.02	9.33
Cholesterol (mg/dl)	192.71	38.86	187.51	35.56

BP, blood pressure; SD, standard deviation.

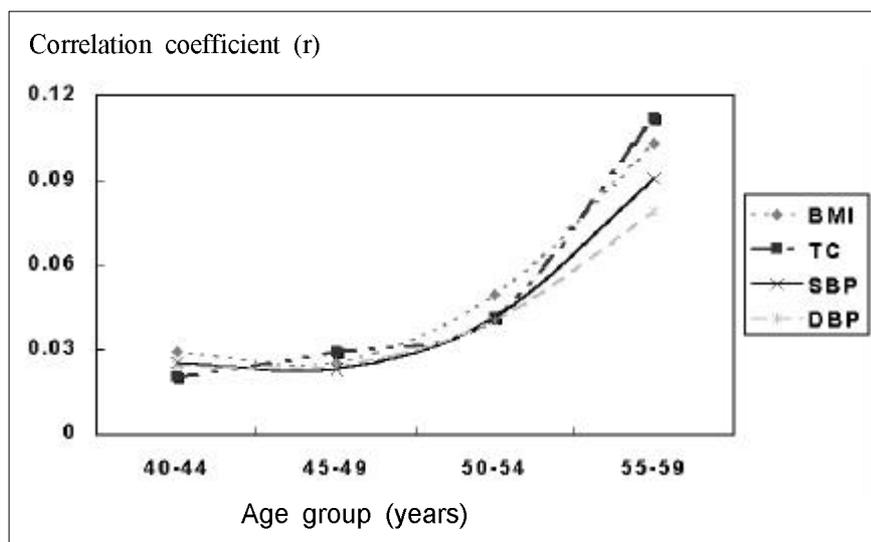


Fig. 1. Spouse correlation with Age group. The average age of both parents.

Table 2. Correlation Coefficient for Cardiovascular Risk Factors

	Number of pairs	Correlation Coefficient		DBP	TC
		BMI	SBP		
Spouse	2269	0.06	0.05	0.06	0.08
Parents-offspring	4848	0.14	0.12	0.17	0.09
Mother-son	2472	0.13	0.12	0.13	0.10
Mother-daughter	433	0.11	0.09	0.14	0.03
Father-son	1996	0.25	0.11	0.25	0.05
Father-daughter	367	0.12	0.11	0.12	0.08
Siblings (intra class)	3396	0.10	0.06	0.07	0.08
Sister-sister	1070	0.05	0.05	0.05	0.10
Brother-brother	560	0.08	0.10	0.09	0.09
Sister-brother	1630	0.21	0.10	0.21	0.04

showed correlation patterns consistent with genetic control, i.e., a low spouse (mother-father) correlation and a high parent-offspring correlation. Parent-offspring correlations in this study were estimated to be 0.2 for BMI, 0.11 for SBP and 0.17 for DBP. Spouse correlations tended to increase with age suggesting that the observed correlations of CVD risk factors are more likely due to be cohabitational effects rather than being due to genetic influence (Fig. 1).

Heritabilities of CVD risk factors

Table 3 shows estimates of the genetic variances and heritabilities for this population. The genetic variance estimate includes only the additive

genetic variance and is significantly greater than zero for all the risk factors. Heritabilities in this study were estimated to be 26.0% for BMI, 19% for SBP, and 18% for DBP. For serum cholesterol, the size of the genetic effect was 49.9 mg/dl, and this accounted for 26% of the heritability.

DISCUSSION

In this family study of the Korean population, we found that CVD risk factors showed familial aggregation. Overall, heritabilities were estimated to be 26% for BMI, 19% for SBP, and 26% for serum cholesterol.

The parent-offspring correlations were all

Table 3. Heritability for Cardiovascular Risk Factor

	Estimate	SE	Variance Mid-parent	Son	Heritability
Body mass index	0.26	0.011	6.62	5.76	26 ± 1.0
Systolic BP (mmHg)	0.19	0.014	159.78	168.55	19 ± 1.0
Diastolic BP (mmHg)	0.09	0.008	68.6	76.77	9 ± 0.8
Cholesterol (mg/dl)	0.26	0.011	887.59	903.67	26 ± 1.0

SE, standard error.

greater than 0.1, an observation suggesting that individuals who share genes tend to be more alike in terms of cardiovascular risk factors levels. Correlations for most of the risk factors did not show significant differences between father-son and mother-son. The magnitude of these correlations was similar to that previously observed overseas. The lack of significant differences between sex-specific and non-sex-specific parent-offspring relationships for blood pressure was also observed in a large Norwegian study.¹⁰ A review of the results obtained for cholesterol conducted in 1982 found similar correlations for all (sex-specific) parent-offspring combinations,¹¹ and a Framingham study also found similar correlations for all (sex-specific) sibling combinations for cholesterol.⁴

In general, increasing trends in spouse were found correlations with duration of marriage suggesting that the observed correlation between spouses for CVD risk factors is primarily due to cohabitational effects rather than assortative mating.¹² However, in the current study, the duration of marriage was not available, though we found a correlation between the of ages of mid parents and phenotypes. Heritability represents the additive effects of genes only, and assumes no Interaction between alleles at a single locus (i.e., no dominance effects) or between different loci (i.e., no epistatic effects). The estimates of heritability for SBP and DBP were 19% and 18%, respectively. These heritabilities were lower than the estimates of a large Norwegian study,¹⁰ which found both heritabilities to be 29%. Our heritability estimate for cholesterol was 26%, which is generally lower than other studies. A review of several twin and family studies¹³ found the heritability of cholesterol to be around 55%, and an analysis of data from nine Lipid Research Clinic

Centers found heritabilities ranging from 31% to 55%¹⁴ suggesting a large genetic influence in the familial aggregation of cholesterol. There are difficulties in comparing heritabilities across studies because the denominator of the heritability ratio includes all sources of variability.¹⁵ Some studies have used a single measurement of the risk factor, whereas others have used an average of two or more measures taken minutes, days, or even years apart. Other studies have been based on a random sample of families, whereas others have been upon selected families. Exclusion criteria vary from study to study; for example, some studies on blood pressure omit persons receiving treatment for hypertension. Finally, although most estimation methods are adjusted for the effects of age and sex on the risk factors, other studies have adjusted for other variables. These differences affect the total observed risk factor variation and thus affect the estimate of heritability. The absolute size of the genetic component of variance is not influenced by many of these differences, and therefore, it is perhaps a more relevant quantity for comparison purpose. For this reason we report the magnitude of the genetic component of variance as was done in a previous study.^{15,16}

The strengths of the KMIC family study, include, the repeated measures of several exposures (total serum cholesterol, weight and height) and its large, national sample. In terms of heritability estimation, a large data set was necessary to obtain familial correlations. And in terms of this objective, the study population was well constituted. Another aspect of the study population also deserves comment, as the KMIC family study participants tend to be middle-class, employed individuals. However, KMIC populations were similar for important health indices, such as blood

pressure, total cholesterol, body mass index and smoking status.¹⁷ Although this study has potential limitations, its large size (>1800 families) provides sufficient statistical power. Random error would tend to diminish the study's power to detect associations. However, the consistency of our findings, i.e. of a strong familial correlation with CVD risk factors, suggest that major errors related to the measurements of risk factors are unlikely.

Thus the nuclear family should be considered as a point of intervention in the application of preventive measures aimed at modifying risk factors through non-genetic approaches, thereby reducing morbidity and mortality from CVD in the population.

In conclusion, this study shows a clear familial correlation with four CVD risk factors, specifically BMI, SBP, DBP, and serum cholesterol.

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