

# Consanguinity and Family History: Risk Factors of Cardiovascular Diseases

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**Abstract.** The association of consanguinity and family history to the heart diseases, *i.e.* ischemic heart disease (IHD), valvular heart disease (VHD), and cardiomyopathies (CMP), has been investigated in a hospital population. The inbreeding rates among IHD patients were 58.71%, VHD 60.65% and CMP 60.60%. The coefficient of inbreeding (F) calculated for IHD, VHD, CMP and associated cardiovascular diseases (A-CVD) was 0.0313, 0.0357, 0.0269 and 0.017, respectively. The F-value for the whole sample was 0.0306. There were 156 (31.2%) families with positive family history and 344 (68.8%) were with negative family history. Relative risk for cardiovascular disease in positive family history compared to negative family history is 2.106 (CL = 1.97-2.36) and odds ratio was 3.51 (CI = 2.85-4.31). First cousins were significantly ( $P < 0.05$ ) affected with cardiovascular diseases compared to unrelated couples. Majority of the patients from first cousin marriages were diagnosed in the age group between 30 to 39 years (48.75%) and 60 to 69 years age group (49.45%). The study shows that consanguinity and family history are both risk factors for cardiovascular diseases and this risk is enhanced in a patient having positive family history, particularly in the case of affected first degree relatives.

**Key words:** Consanguinity, family history, cardiovascular diseases, Odds ratio, relative risk.

## INTRODUCTION

Family history is a risk for many chronic diseases of public health significance, including coronary heart disease (Kardia *et al.*, 2003), diabetes (Harrison *et al.*, 2003), several cancers (Ziogas and Anton-Culver, 2003). Family history is a useful tool for identifying most prevalent cases of cardiovascular diseases and for population-wide disease-prevention efforts (Hunt *et al.*, 2003). Most early cardiovascular events in a population occur in families with a positive family history of cardiovascular disease. Family history collection is a validated and relatively inexpensive tool for family-based preventive medicine and medical research (Williams *et al.*, 2001).

People from the Indian sub-continent have high rates of cardiovascular disease (Kamath *et al.*, 1999). Close consanguineous unions continue to be extremely common in much of West Asia, including Pakistan (Shami *et al.*, 1990; Hussain and Bittles, 1999). In Pakistan, first cousin marriages are more common than unrelated couples and the rate of inbreeding ranges from 37.8% to 48.9% (Shami *et al.*, 1990).

A family history of a coronary death in parents of Framingham cohort subjects was associated with a 30% independent increased risk of coronary disease. A positive family history predisposed to an early coronary heart disease event, particularly in men, with a risk approximately one and one-half to two-time greater for those with a parental history of coronary heart disease (CHD) (Myers *et al.*, 1990; Goldberg, 1992; Chadha, 1998; Silberg *et al.*, 1998). Various studies have reported a two-to eleven-fold greater risk for acquiring CHD among first-degree relatives of CHD cases than in relatives of controls. The increased risk seems to depend on the sex of the cases, and the age when they experienced the coronary event (Slack and Evans, 1966; Phillips *et al.*, 1974).

The study is aimed to observe the association of consanguinity and family history to the heart diseases including ischemic heart disease (IHD), valvular heart disease (VHD), and cardiomyopathies (CMP).

## MATERIALS AND METHODS

This study is based on 500 cardiovascular disease (CVD) patients. The data were collected from the Federal Government Services Hospital, Islamabad; Pakistan Institute of Medical Sciences, Islamabad; Armed Forces Institute of Cardiology/

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National Institute of Heart Disease, Rawalpindi; and Rawalpindi General Hospital, Rawalpindi. A prior consent of patients and respective Heads of the Cardiology Institute was sought before the start of study. A standard questionnaire was designed and entries were made regarding detailed history, which included age of onset of disease, genetic relationship of couples. The diseases scored in the study comprised ischemic heart disease (IHD), valvular heart disease (VHD), and cardiomyopathies (CMP). The cardiologists of the respective hospitals diagnosed cardiovascular patients.

The statistical analyses carried out were percentages, means, standard deviations, standard errors, student's t-test, odds ratio and chi-square test were applied for comparison. The coefficient of inbreeding (F) was calculated following Wright's method (1922).

## RESULTS

Table I lists the distribution of patients in relation to parental genetic relationships and their F (coefficient of inbreeding) values in the three cardiovascular diseases. Predominance was of those patients coming from first cousin marriages (45.2%), compared to other parental relationships. There are some cardiovascular diseases, which appear in association with IHD *i.e.* IHD + VHD; IHD + CMP and VHD with CMP. These were taken together as Associated Cardiovascular Diseases (ACVD). A higher value of coefficient of inbreeding (F) was seen in the patients diagnosed for IHD (0.0313), and VHD (0.0342) compared to CMP patients (0.028). The F value for the whole sample was 0.0305. The levels of inbreeding for IHD patients were 58.71%, VHD patients 60.65% and in CMP patients 60.60%. An overall inbreeding in the patients for these cardiovascular diseases is 58.4%.

These cardiovascular diseases were traced back in the close relatives of these patients (Table II). There were 156 (31.20%) positive families where the disease was traced back up to the third degree relatives of the patients. There were 344 (68.8%) patients where cardiovascular diseases were not present in any of these relatives indicating negative family history. In these patients sporadic occurrence

of cardiovascular diseases is suggested. Among families with positive family history of the disease there were 98 families (62.82%) in which only first-degree relatives were affected. Nineteen positive family history families (12.18%) have only second-degree relatives with disease and five families (3.20%) are such where only third degree relatives were afflicted with disease. There are 17 (10.90%) families where both first degree and second-degree relatives were affected. In 9 families (5.76%) both first degree and third degree relatives were with the disease. In 3 families (1.92%) second and third degree relatives were affected. There were only 5 families (3.20%) in which first degree, second degree and third degree relatives were diagnosed for cardiovascular disease. Family history of all heart diseases shows that odds ratio associated with positive family history compared to negative family history was 3.51 (CI = 2.85-4.31) and the relative risk for the disease was 2.106 (CI = 1.97-2.36).

Male cardiovascular patients (75.40%) outnumbered the female patients (24.60%). The male to female ratio is 100 females : 306.50 males, which shows that male patients are significantly higher in number compared to the female patients ( $\sum \chi^2_{(1)} = 129.02$ ;  $P < 0.001$ ). There is no difference in age at diagnosis for male and female patients. Both male (48.80%) and female (44.71%) were diagnosed at an age between 40 to 59 years. In majority of patients (48.75%) from first cousin marriages coronary heart disease was diagnosed at an age from 30 to 39 years while those coming from unrelated parents this disease was diagnosed between 50 to 59 years of age.

## DISCUSSION

A strong family history of coronary heart disease (CHD) is the major predisposing factor to the development of CHD. In the Utah population, the risk associated with a positive family history is greater when accounting for number of at risk relatives (Hunt *et al.*, 1986). Family history has been shown to be a risk factor for a majority of chronic diseases of public health significance, including cardiovascular diseases, diabetes, several cancers, osteoporosis and asthma. Most early cardiovascular – related event (coronary heart

**Table I.- Distribution of cardiovascular diseases in different genetic relationships of patients and F (co-efficient of inbreeding) values.**

Disease	Genetic relationships						Total	F
	1 <sup>st</sup> C	1½ C	2 <sup>nd</sup> C	DR	U			
Ischemic heart disease (IHD)	n	173	8	38	73	81	373	0.0313
	%	46.38	2.14	10.18	19.57	21.71		
Valvular heart disease (VHD)	n	33	1	3	14	10	61	0.032
	%	54.09	1.63	4.91	22.95	16.39		
Cardiomyopathies (CMP)	n	13	1	6	4	9	33	0.0282
	%	39.39	3.03	18.18	12.12	27.27		
#Associated cardiovascular disease (A-CVD)	n	7	-	9	7	10	33	0.0172
	%	21.21	-	27.27	21.21	30.30		
Total	n	224	10	56	98	110	500	0.0305
	%	45.2	2	11.2	19.6	22		

\*1<sup>st</sup> C, first cousin; 1½C, first cousin once removed; 2<sup>nd</sup> C, second cousin; DR, Distant relatives; U, unrelated; F, coefficient of inbreeding.

**Table II.- Percentage distribution of patient's close degree relatives with cardiovascular disease.**

Family History	No. of families	No. and percentages of close relative families	1 <sup>st</sup> Degree relatives	2 <sup>nd</sup> Degree relatives	3 <sup>rd</sup> Degree relatives	Total	F
Positive family history	156 (31.20)	98 (62.82)	161	-	-	161	49.85
		19 (12.18)	-	34	-	34	10.52
		5 (3.20)	-	-	5	5	1.55
		17 (10.90)	34	32	-	66	20.43
		9 (5.76)	16	-	11	27	8.36
		3 (1.92)	-	4	3	7	2.17
		5 (3.20)	11	7	5	23	7.12
Total			222 (68.73)	77 (23.83)	24 (7.43)	323	100
Negative family history	344 (38.8)	-	-	-	-	-	-

disease, stroke, hypertension and diabetes) in the population occurs in families with a positive family history of cardiovascular disease (Williams *et al.*, 2001).

This study indicates that both consanguinity and family history are important to look at number of relatives at risk. It was examined in this study that the rate of inbreeding in the first cousin offspring was very high (58.4%) as compared to unrelated couples (22%). In general Pakistani population inbreeding was 35-40% (Shami *et al.*, 1990). Hamamy and Alwan (1994) also observed a 16.5 to 55% rate of inbreeding in the Eastern Mediterranean Region. A higher coefficient of inbreeding (0.0305) for cardiovascular patients was

observed than in general Pakistani population (F=0.028) (Shami *et al.*, 1989). Of the cardiovascular diseases, IHD and VHD, patient's inbreeding coefficient is high, *i.e.* 0.0313 and 0.0342, respectively. The value of F for CMP and associated cardiovascular diseases (A-CVD) is 0.028 and this is nearly equal to that of general population. It is suggested that close relative marriages is one of the factors that encourages the occurrence of cardiovascular diseases in their offspring.

The high prevalence of CHD among relatives (30%) contributes that most, because CHD is more common in males and this is likely that an affected father conferred higher risk than an affected mother

(Silberg *et al.*, 1998). Forde and Thelle (1977) showed that subjects who suffered from myocardial infarction had a considerably high frequency of first-degree relatives with myocardial infarction than those who had not experienced such disease. Slack and Evans (1966) found a seven-fold risk when the relative was a female below 65 years of age and five-fold when relative was a male below 55 years of age.

A positive family history of disease captures the underlying complexities of gene-gene and gene-environment interactions by identify families with combination of risk factors that lead to disease expression. A positive family history also identifies families in the population at highest risk for CVD (Hunt *et al.*, 2003). Williams *et al.* (2001) investigated that in Utah families with positive family history of CHD accounted for 72% of persons with early CHD compared to 14% of the general population. They concluded that most early cardiovascular events in a population occur in families with a positive families history of CVD disease.

Significance of family history is that it is a useful tool for identifying most prevalent cases of CVD and population-wide disease-preventive effects. A positive family history also identifies the relatively small subset of families in the population at highest risk for CVD who may benefit most for targeted screening and intensive interaction. This study, too, signifies the role of consanguineous marriages in the appearance of cardiovascular diseases in their offspring, and also from that of the first degree relatives are at the highest risk for cardiovascular diseases than the other close relatives.

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