ISCHEMIC HEART DISEASE IN DEATH-DISCORDANT TWINS

A Study on 205 Male and Female Pairs with Special Reference to Hereditary Factors

ULF DE FAIRE
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From January 1971 to March 1973 all twin pairs in the Swedish Twin Registry below the age of 70, who became death-discordant, were continuously recorded. A total of 205 (78%) of the surviving cotwins were examined with respect to different manifestations of ischemic heart diseases (IHD) and several "environmental" and "biometric" risk factors. Among the death-discordant pairs, the cause of death was IHD in 57 pairs and other than IHD in 148 pairs. Analyses revealed that the prevalence rate of myocardial infarction, angina pectoris, pathologic Q-wave, and ST depressions in connection with exercise, were significantly higher among the surviving cotwins whose partners had died from IHD than those whose partners had died from other causes. The same trends were seen for most of the risk factors measured both singly and in combination, although not very pronounced. The results indicate a substantial genetic influence in the development of IHD. The genetic influence is possibly transmitted not only through some of the risk factors measured, but also through other factors, still unknown.

The present study on ischemic heart disease (IHD) in death-discordant twin pairs derives from the Swedish Twin Registry. The Registry was set up in the years 1959-1961 when it contained about 11,000 twin pairs covering 95% of all Swedish same-sexed twins born in the country between 1886-1925 and with both members living when the Registry was formed. The compilation procedure and the demographic structure of the twin series have been described in detail by Cederlöf in 1966. The Swedish twins have been followed for mortality since 1962. From January 1971, information on deceased twins has been available every month, thereby permitting clinical examination of the surviving cotwins reasonably soon after death of the partners.

One of the main objectives of this investigation was to evaluate the genetic influence in IHD by seeing if an association exists between the occurrence of IHD in the surviving cotwins and the cause of death of the partners (IHD or not IHD).

MATERIAL AND METHODS

The mortality among the twins has been established in the following way. The total Twin Registry is matched regularly against a total death registry for Sweden at the Central Bureau of Statistics. Since 1971 this has been done once a month. This matching provides access to the death certificates and the name of the physician who signed it. Then, hospital records, autopsy protocols, information from general practitioners, and other pertinent information, are collected. The causes of death are established from all these records and the cause of death is then classified according to the 1965 (the 8th) revision of International Statistical Classification (ISC) of Diseases, Injuries, and Cause of Death, which has been used since 1969 in Sweden.

During the period January 1971 to March 1973, 262 male and female twin pairs 46-70 years old, became death-discordant, i.e., one of the members in an unbroken pair died during the period mentioned above. About two or three months after death had occurred, the surviving cotwins were invited to a thorough health check-up at Serafimer Hospital in Stockholm. A total of 205 (78.2%) of the surviving cotwins could be examined on average about 5 months after the death of the partner. The zygosity diagnoses were exclusively based on the diagnoses earlier made by the aid of similarity questions contained in a questionnaire (Cederlöf 1966).

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Table. *Distribution of death discordant pairs (by sex and zygosity) according to cause of death of partner*

	Number of death-discordant twins							
	Males				Females			
	MZ	DZ	XZ	Total	MZ	DZ	XZ	Total
All causes	35	67	6	108	38	57	2	97
IHD, total	10	25	5	40	8	9	0	17
Myocardial infarction	8	18	4	30	3	5	0	8
Other IHD	0	0	0	0	1	1	0	2
Sudden death	2	7	1	10	4	3	0	7
Not IHD, total	25	42	1	68	30	48	2	80
CVD	2	4	0	6	2	5	0	7
Malignant tumors	9	18	0	27	19	21	2	42
Uremia	1	0	0	1	0	2	0	2
Diabetes mellitus	0	1	0	1	0	1	0	1
Suicides	2	3	0	5	1	2	0	3
Accidents	1	6	0	7	1	5	0	6
Other causes	10	10	1	21	7	12	0	19

The distribution of the examined cotwins according to the cause of death of the partner is shown in the table 1. There were 57 (28%) whose partners had died from IHD, i.e., 40 of the 108 male pairs (37%) and 17 of the 97 female pairs (18%). Sudden death caused 17 of the 57 IHD deaths.

All the surviving, respondent cotwins were examined in the same way according to standardized methods. A sociologic and medical history was taken, using questionnaires. The diagnosis of angina pectoris was established by interview (Rose 1962). Myocardial infarction was considered established when it had been verified at hospital. Blood pressure determinations, anthropometric measurements, and X-ray of the heart and lungs were performed, as well as ECG, before, during and after an ergometer test. Blood samples were drawn after an overnight's fast for determination of cholesterol, triglycerides, uric acid, and blood sugar. Erythrocyte sedimentation rate, hemoglobin, and hematocrite were also determined. The urine was tested for proteinuria and glucosuria. Information about environmental background variables on both deceased and surviving twins was obtained through questionnaires mailed to all members of the Swedish Twin Registry in 1967 and 1970. The variables included were: smoking habits, physical inactivity, extra work, change of place of work, education, and place of residence. To permit combination of the most important "risk factors", certain defined "risk levels" were chosen: relative weight $\geq$ 110 according to a weight-height index, basal systolic blood pressure $\geq$ 160 mm Hg and/or basal diastolic blood pressure $\geq$ 95 mm Hg, cholesterol $\geq$ 250 mg/100 ml and/or triglycerides $\geq$ 150 mg/100 ml, a history of clinical diabetes mellitus, cigarette smoking as elucidated from a mailed questionnaire in 1967/1970, physical inactivity during 25-50 years of age as elucidated from a mailed questionnaire in 1967/1970, regular extra work beside the ordinary job as elucidated from a mailed questionnaire in 1967/1970.

RESULTS AND DISCUSSION

The distribution of different manifestations of IHD is given in Fig. 1.

Myocardial infarction had occurred in 15% of the surviving male cotwins whose partners had died from IHD (3 or 30% of the MZ cotwins and 3 or 12% of the DZ cotwins) as compared to only 3% of the surviving cotwins whose partners had died from other causes than IHD. Only one of the female cotwins had myocardial infarction. When angina perctoris, pathologic Q-wave and segmental ST depressions $\geq$ 0.5 mm in connection with exercise had been successively included in the criteria of IHD, both male and female cotwins (pooled zygosity groups) whose partners had died from IHD displayed these signs significantly ($p < 0.05$) more often than those whose partners had died from other causes. In the males, but not in the females, the difference was significant already when ST depressions $\geq$ 1.0 mm was included in the criteria of IHD. Similarly, the male MZ cotwins whose

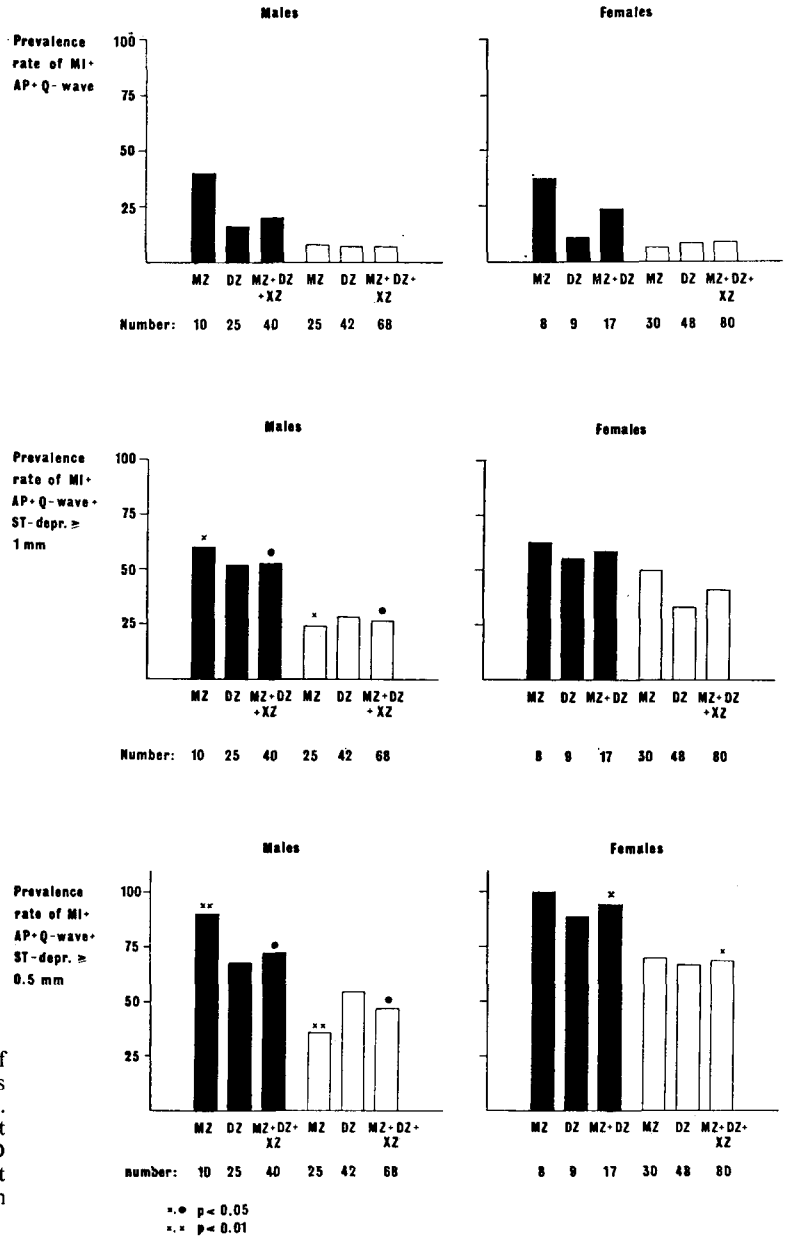

Fig. 1. Prevalence rate of some IHD manifestations among respondent cotwins. Dark columns indicate that the partners died from IHD and white columns that the partners died from other causes.

partners died from IHD displayed significantly more IHD manifestations ($p < 0.05$ with ST depressions ≥ 1.0 mm, and $p < 0.01$ with ST depressions ≥ 0.5 mm) than the MZ cotwins whose partners had died from other causes.

Most of the biometric risk factors measured as relative weight, skinfold thickness, blood pressure, lipids and uric acid showed somewhat higher mean values for the cotwins whose partners died from IHD compared to those whose partners died from other reasons. The differences found were non-

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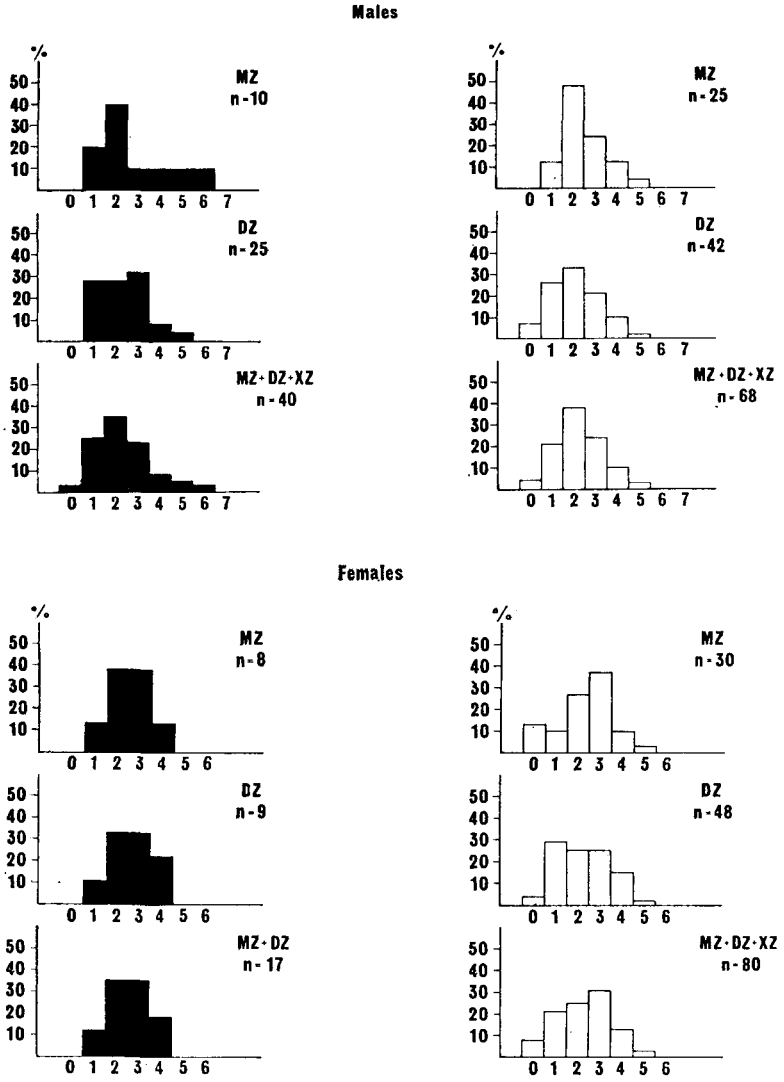

Fig. 2. Distribution of cotwins according to number of biometric and environmental « risk factors ». Black columns indicate that the partners died from IHD and white columns that the partners died from other causes.

significant except for casual blood pressures in females ($p < 0.05$ between the pooled zygosity groups). Overt diabetes mellitus showed about the same prevalence among the surviving cotwins irrespective of cause of death of the partner (IHD or not IHD).

Information earlier obtained through mailed questionnaires about environmental factors as smoking habits, physical inactivity, extra work, change of place of work, education, and place of residence, showed similar distributions among the surviving cotwins, irrespective of the cause of death of the partner (IHD vs. not IHD). When the biometric risk factors (for definition see methods) overweight, elevated blood pressure, hyperlipidemia and overt diabetes mellitus were combined, it was found that the surviving cotwins whose partners died from IHD had on average a somewhat higher number of risk factors than those whose partners had died from other causes. The same trends were seen when also environmental risk factors (cigarette smoking, physical inactivity and extra work) were included

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in the possible combination of risk factors (Fig. 2). The inclusion of the environmental factors contributed proportionally less to the number of risk factors among the females, especially the MZ cotwin

To judge from the present study a considerable genetic influence seems to operate in the development of IHD. Although different manifestations of IHD have been measured and other approaches have been adopted, the twin studies by Cederlöf at al. (1967), Harvald and Hauge (1970), and Liljefors (1970) also point to the importance of hereditary factors in the pathogenesis of IHD.
It is well-known that the genetic influence is trasmitted through many of the biometric risk factors. However, from the present investigation, the risk factors measured, singly and in combination, seem to explain only part of the difference in IHD manifestations between the surviving cotwins whose partners died from IHD and those whose partners died from other causes. The genetic mechanisms are therefore probably transmitted not only through the risk factors measured, but also through factors still unknown. The prevention of IHD demands that the carriers of predisposing traits are properly identified, so that prophylactic measures can be instituted in these people. In doing so, we must probably go beyond the common risk-factor concept. Epstein (1964) has proposed that if one could identify and measure all of the predisposing traits as underlying biologic disturbances in terms of metabolic or other defects, then it probably emerge that they are more common than the prevalence of disease would suggest and show more clear-cut distributions among family members.

REFERENCES

Cederlöf R. 1966. The Twin Method in Epidemiological Studies on Chronic Disease. Stockholm: Karolinska Institutet.

Cederlöf R., Friberg L., Jonsson E. 1967. Hereditary factors and « angina pectoris ». A study on 5,877 twin pairs with the aid of mailed questionnaires. Arch. Environ. Health, 14: 397.

Epstein F.H. 1964. Hereditary aspects of coronary heart disease. Am. Heart J., 67: 445.

Harvald B., Hauge M. 1970. Coronary occlusion in twins. Acta Genet. Med. Gemellol. (Roma), 19: 248.

Liljefors I. 1970. Coronary heart disease in male twins. Hereditary and environmental factors in concordant and discordant pairs. Acta Med. Scand. [Suppl.], 511.

Rose G. 1962. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bull. WHO, 27: 645.

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