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The Increased Risk of Death from Ischaemic Heart Disease in First Degree Relatives of 121 Men and 96 Women with Ischaemic Heart Disease

J. SLACK and K. A. EVANS

From the Medical Research Council, Clinical Genetics Research Unit, Institute of Child Health, London W.C.1

The risks of death from ischaemic heart disease, cerebral haemorrhage, and thrombosis, and the risks of death from all causes have been estimated among the first degree relatives of male and female index patients with ischaemic heart disease. These risks have been compared with the figures published by the Registrar General for England and Wales and with the risks to relatives of a control group. It is considered that the Registrar General's figures provide the best comparison for mortality, but the control series provides useful comparison for morbidity.

There has been much speculation but little concrete evidence about the hereditary aspects of ischaemic heart disease. Gertler and White (1954) studied family histories of 97 male patients with coronary heart disease before 41 years, excluding hypertensive patients, and found an incidence of coronary heart disease which was twice as high amongst fathers of patients compared with controls, but less increase amongst mothers compared with their control sample. Thomas and Cohen (1955) studied family histories of 266 consecutive medical students at Johns Hopkins University and found a 4-fold increase amongst brothers of male patients. In an extensive twin study, Harvald and Hauge (1963) found no difference in concordance rates for the occurrence of coronary occlusion between monozygotic and dizygotic twins of like sex, whereas dizygotic twins of unlike sex showed a significant difference. Rose (1964) has more recently reported on family histories of 100 patients with ischaemic heart disease and found a 3-fold increase in mortality from ischaemic heart disease amongst parents of male patients and a higher mortality at all ages from unrelated illnesses. In these series there have been few female patients studied, and in some there has been a lack of documentary evidence of the causes of mortality of the relatives, and it seems that the lack of evidence still prohibits definite conclusions as to risks to near relatives of patients with ischaemic heart disease.

We have collected pedigrees of nearly equal numbers of men and women with ischaemic heart disease and attempted to obtain documents of confirmation of every cause of death or serious morbidity in first degree relatives.

Subjects and Methods

Index Patients. The patients were 121 men and 96 women who had attended hospital with ischaemic heart disease; this was the only criterion for selection for the series. Diagnosis of ischaemic heart disease was made in each case on clinical evidence supported by ECG changes compatible with ischaemic heart disease. Male patients were all less than 60 years old and female patierts less than 70 at the onset of ischaemic heart disease. The patients were drawn from hospitals serving the central and north London areas and are shown in Table IA. Collection of the series of male patients continued over a period of 7 months at the Central Middlesex Hospital and over a further period of 8 months at the National Heart Hospital. Collection of women patients took longer and was carried out for 7 months at the Central Middlesex Hospital and a further 15 months at the National Heart Hospital and other hospitals in order to collect sufficient numbers for the series.

Controls. The group consisted of 104 men and 105 women. 95 men and 72 women were employees from the London Office of the Prudential Assurance Company; 3 men and 1 woman were hospital patients, 29 controls were wives of the patients, and 6 men and 3 women were medical colleagues (see Table IB). All were within the same age range as the patients. None was aware of having ischaemic heart disease.

Family Histories. Pedigrees were drawn up to include every first degree relative of patients and controls. Permission to verify causes of death was requested

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A

TABLE IA

WHOLE SAMPLE OF INDEX PATIENTS SHOWING THEIR SOURCES AND REASONS FOR EXCLUSION

Patients	National Heart Hospital	Central Middlesex Hospital	The Middlesex Hospital	Elizabeth Garrett Anderson Hospital	Total
Male patients	45	88	7	—	140
less					
(a) non-co-operators	—	6	1	—	7
(b) foreign, etc.	4	6	2	—	12
No. in study	41	76	4	—	121
Female patients	73	29	1	2	105
less					
(a) non-co-operators	—	6	—	—	6
(b) foreign, etc.	2	1	—	—	3
No. in study	71	22	1	2	96

TABLE IB

WHOLE SAMPLE OF CONTROLS, SHOWING THEIR SOURCES AND REASONS FOR EXCLUSION

Controls	Prudential	Hospital Controls	Spouses	Colleagues	Total
Male controls	95	5	—	6	106
less					
(a) non-co-operators	—	1	—	—	1
(b) foreign, etc.	—	1	—	—	1
No. in study	95	3	—	6	104
Female controls	73	1	32	4	110
less					
(a) non-co-operators	1	—	2	—	3
(b) foreign, etc.	—	—	1	1	2
No. in study	72	1	29	3	105

from each person entering the study and if this was withheld or if several relatives were known to be untraceable the subject was excluded from the study. There were 7 male and 6 female patients and 1 male and 3 female controls who were unwilling for us to document causes of death in their relatives. There were 12 male and 3 female patients, and 1 male and 2 female controls who were excluded because the majority of their relatives had died in Eastern Europe or in war-time Germany, and documentary evidence of the causes of death could not be obtained. The cause of death of each relative over 15 years was recorded and verified by death certificates (with the exception of deaths in action during the two Great Wars) and where possible all causes of serious morbidity were confirmed by hospital records or from family doctors. Only limited attempts were made to trace deaths over 80 years and these deaths were not claimed as coronary artery disease unless death certificates were obtained. Table II shows the total numbers of relatives and the success and failure in obtaining confirmatory evidence of death and the reasons for failure.

The number of death certificates obtained was 699, and of these the 397 with any mention of heart disease or cerebral catastrophe were sent to the General Register Office where they were classified by the criteria in use at the time of issue of the certificate. We are much indebted to the Registrar General for this service, because there is no doubt discrepancies would have occurred if we had attempted to classify the certificates ourselves by reference to the headings in the Registrar General's Statistical Review.

TABLE II

NUMBERS OF RELATIVES OF INDEX PATIENTS AND CONTROLS AND DETAILS OF DOCUMENTS CONFIRMING DEATHS

		Total	Relatives				Deaths			
			Not on Tables; Insufficient Evidence of Cause of Death	On Tables			Documented	Not Documented		
				Total	Alive	Dead	Death Certificates	War	Over 80 years	Others
Male patients 121	Fathers	121	6	115	11	104	89	5	3	7
	Brothers	198	1	197	156	41	33	6	0	2
	Mothers	121	3	118	28	90	77	1	4	8
	Sisters	188	1	187	171	16	12	0	0	4
Female patients 96	Fathers	96	6	90	3	87	83	2	1	1
	Brothers	166	1	165	118	47	41	4	0	2
	Mothers	96	3	93	15	78	71	0	5	2
	Sisters	144	2	142	115	27	24	2	0	1
Male controls 104	Fathers	104	0	104	27	77	72	3	2	0
	Brothers	85	0	85	75	10	6	4	0	0
	Mothers	104	0	104	56	48	44	0	2	2
	Sisters	94	1	93	86	7	7	0	0	0
Female controls 105	Fathers	105	3	102	27	75	69	2	2	2
	Brothers	112	0	112	91	21	13	8	0	0
	Mothers	105	1	104	50	54	50	0	2	2
	Sisters	141	0	141	133	8	8	0	0	0

Tables showing years 'at risk' were constructed for every 5 calendar year period from 1930, and divided into 10-year age-groups from 20 years. Relatives were considered in 4 groups, fathers and adult brothers, mothers and adult sisters of male and female patients. Patients were divided into groups by their age at the onset of ischaemic heart disease and separate tables were prepared for each group. Parents were entered on the table at their age at the birth of the index patient, which was the earliest time at which they could be considered to be 'at risk' for purposes of the study. Brothers and sisters were entered at 20 years. Entries were in 5 calendar year groups by date of birth and were scored as entering midway through the appropriate 10-year age period. Deceased relatives left the table midway through the appropriate 10-year age period, and in each case the Registrar General's classification of the cause of death was recorded. Living relatives left the table in 1965 and were scored as leaving halfway through the appropriate 10-year period. Those who reached 75 years and over were allowed a life expectancy corresponding to that given in the National Life Tables instead of a 10-year span. (1930–1945 life expectancy for men 6·4 years and for women 7·4, 1946–1955 for men 6·7 years and for women 8·1, 1956 to 1964 for men 7·1 years and for women 8·8.) In this way it was possible to calculate the number of man years and the calendar years during which the relatives were 'at risk' of dying. Similar tables were constructed for the relatives of male and female controls.

Before 1930, classification and diagnosis of ischaemic heart disease were not sufficiently precise for this study, and, therefore, no use was made, in our calculations, of certificates issued before 1930, and the life experience of relatives before 1930 was excluded. However, details of death before 1930 are given in Appendix II.

The Registrar General's tables were used to calculate the risks of dying from all causes, from ischaemic heart disease, and from cerebrovascular disorders, at 5-yearly intervals from 1930 to the present. The Registrar General's categories used can be seen in Appendix I. Between 1930 and the present day death certificates with special mention of coronary artery disease have been distinguished from other arteriosclerotic heart disease in categories 420 and 94. These categories have been mainly used in this study. For each 5-year period the risks of death in the general population in the categories mentioned were calculated for age-groups 20–34, 35–44, 45–54, 55–64, 65–74, and 75 and over. From the tables then, the expected number of deaths amongst relatives was calculated in each category and at each age-group. The observed number of deaths was compared with the expected number of deaths in each age-group and expressed as a ratio. Tables of years 'at risk' were constructed for controls in the same way. There was no grouping of

TABLE III

RISKS TO MEN AND WOMEN OF DYING FROM ISCHAEMIC HEART DISEASE (REGISTRAR GENERAL'S CATEGORY 420) IN 1962 IN 10-YEAR PERIODS

Age (yr.)	Men	Women
35–44	0·00541	0·00072
45–54	0·02131	0·00358
55–64	0·06391	0·01720
65–74	0·13946	0·06126
75 to expected age at death (see text)	0·17853	0·13500

controls by age, but the life experience of their relatives was considered in the same age-groups.

Risks calculated from the Registrar General's tables for 1962 and set out in Table III show the risks of dying in category 420, encountered by men and women at 10-year age-groups from 35 years. This shows that the risks of dying from ischaemic heart disease in men are similar to those of women who are 10 years older. The risk of dying in category 420 for men becomes about 35/10,000 per year by age 55 years and for women by about 65 years. We have, therefore, divided the male patients and relatives into a 'younger' and 'older' age-group at 55 years and the women patients and relatives at 65 years.

Results

Table IV shows the number of years 'at risk' in each age-group contributed by male and female relatives of male and female patients and controls.

From the years 'at risk' and from the risks of death in the general population in that age-group and in the appropriate secular period, the number of deaths expected amongst relatives of patients is compared with the number observed.

Risks of Death from Ischaemic Heart Disease in Patients' Relatives. Tables VA and VB show, for male and female patients respectively, the number of deaths observed (O) and the expected number of deaths (E) in relatives calculated from the years 'at risk' and the risks from the Registrar General's

TABLE IV

YEARS AT RISK OF RELATIVES OF INDEX PATIENTS (DISTINGUISHED BY AGE OF ONSET) AND CONTROLS

Age of Relative	Patients' Ages at Onset of Ischaemic Heart Disease: Male Patients 35–44	45–49	50–54	55–59	60–64	Total	Male Controls (all ages)
Male relatives							
35–44	288	464	330	440	160	1682	888·5
45–54	238	377	312·5	460·5	160	1548	950
55–64	154	219	209	410	128·5	1120·5	827·5
65–74	64	123	78	230	81	576	460
75 and over	12	25	15·5	46	12	110·5	87·5
Female relatives							
35–44	351	410	479	340	132·5	1712·5	1046·5
45–54	273·5	446·5	436·5	395	175	1726·5	1150
55–64	167·5	322·5	319	365	183·5	1357·5	966
65–74	96	184	186	207·5	158·5	832	652·5
75 and over	21	54	67	67	48	257	183

Age of Relative	Patients' Ages at Onset of Ischaemic Heart Disease: Female Patients 35–44	45–54	55–64	65 and over		Total	Female Controls (all ages)
Male relatives							
35–44	189	584	655·5	7·5		1436	1043·5
45–54	136	492	640	20		1288	1000
55–64	65	284	504	20		873	797
65–74	30	121	211·5	17·5		380	469
75 and over	12	22·5	23·5	0		58	121
Female relatives							
35–44	188·5	458·5	572·5	60		1279·5	1493·5
45–54	172·5	435	567·5	80		1255	1327·5
55–64	102·5	346	504	70		1022·5	1070
65–74	54	176·5	326·5	60		617	591
75 and over	7·5	64	98	19		188·5	199

TABLE VA

OBSERVED NUMBER (O) OF DEATHS CERTIFIED TO BE DUE TO 'ARTERIOSCLEROTIC HEART DISEASE INCLUDING CORONARY DISEASE' (CATEGORIES 420 AND 94) BY AGE IN RELATIVES OF MALE INDEX PATIENTS, COMPARED WITH THE NUMBER EXPECTED (E) FROM THE REGISTER GENERAL'S TABLES

Age of Relative at Death From Ischaemic Heart Disease	'Younger' Patients' Ages at Onset of Ischaemic Heart Disease									'Older' Patients' Ages at Onset of Ischaemic Heart Disease					
	35–44			45–49			50–54			55–59			60 and over		
	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Male relatives															
35–44	2	0·08	25·00	1	0·12	8·33	0	0·06	—	0	0·09	—	0	0·03	—
45–54	1	0·32	3·13	3	0·52	5·77	1	0·45	2·22	2	0·64	3·13	0	0·22	—
55–64	4	0·59	6·78	2	0·81	2·47	2	0·89	2·25	1	1·30	0·77	0	0·52	—
65–74	3	0·61	4·92	2	1·11	1·80	1	0·54	1·85	4	1·55	2·58	0	0·59	—
75 and over	0	0·26	—	1	0·74	1·35	0	0·28	—	3	0·87	3·45	0	0·19	—
Female relatives															
35–44	0	0·01	—	0	0·02	—	0	0·02	—	0	0·01	—	0	—	—
45–54	0	0·06	—	0	0·09	—	1	0·10	10·00	0	0·09	—	0	0·03	—
55–64	0	0·18	—	2	0·28	7·14	0	0·33	—	1	0·30	3·33	0	0·23	
65–74	1	0·43	2·33	1	0·67	1·49	2	0·69	2·90	1	0·61	1·64	1	0·60	1·67
75 and over	0	0·26	—	0	0·75	—	0	0·73	—	3	0·75	4·00	2	0·51	3·92

Tables in categories 420 and 94 (see Appendix I) in each age-group. The third column (O/E) gives the ratio of observed to expected numbers of deaths. The findings are summarized in Table VI.

Tables VA and VB show details of the results and demonstrate a progressively diminishing relative risk to relatives with increasing age of both patients and relatives. The numbers in the small groups are too small to be statistically significant. Table VI, however, with its broader grouping shows that there is a significantly increased risk of death from ischaemic heart disease to first degree relatives of patients. The observed increase is 6½-fold amongst the 'younger' male relatives of the 'younger' female

TABLE VB

OBSERVED NUMBER (O) OF DEATHS CERTIFIED TO BE DUE TO 'ARTERIOSCLEROTIC HEART DISEASE INCLUDING CORONARY DISEASE' (CATEGORIES 420 AND 94) BY AGE IN RELATIVES OF FEMALE INDEX PATIENTS, COMPARED WITH THE NUMBER EXPECTED (E) FROM THE REGISTRAR GENERAL'S TABLES

Age of Relative at Death From Ischaemic Heart Disease	'Younger' Patients' Ages at Onset of Ischaemic Heart Disease									'Older' Patients' Ages at Onset of Ischaemic Heart Disease		
	35–44			45–54			55–64			65 and over		
	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Male relatives												
35–44	1	0·06	16·67	3	0·15	20·00	0	0·11	—	0	0·00	—
45–54	2	0·17	11·77	4	0·73	5·48	3	0·80	3·75	0	0·01	—
55–64	1	0·24	4·17	2	1·52	1·32	4	2·20	1·82	0	0·06	—
65–74	1	0·29	3·45	1	0·87	1·15	6	1·72	3·49	1	0·14	7·14
75 and over	0	0·26	—	2	0·37	5·41	1	0·40	2·50	0	0·00	—
Female relatives												
35–44	0	0·01	—	0	0·02	—	0	0·02	—	0	0·00	—
45–54	1	0·04	25·00	0	0·09	—	0	0·12	—	0	0·02	—
55–64	0	0·13	—	2	0·36	5·56	6	0·51	11·76	0	0·05	—
65–74	0	0·32	—	1	0·58	1·56	1	0·98	1·02	0	0·20	—
75 and over	0	0·09	—	0	0·51	—	2	0·83	2·41	1	0·19	5·26

TABLE VI

SUMMARY OF RISKS OF DEATH FROM ISCHAEMIC HEART DISEASE (REGISTRAR GENERAL'S CATEGORIES 420 AND 94) IN RELATIVES OF PATIENTS

Age of Relative at Death From Ischaemic Heart Disease	Male Patients' Ages at Onset of Ischaemic Heart Disease					
	35–54			55 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	8	1·55	5·16**	2	0·98	2·04
55 and over	15	5·83	2·57*	8	5·02	1·59
Female relatives						
35–64	3	1·09	2·75	1	0·66	1·52
65 and over	4	3·53	1·13	7	2·47	2·83
	Female Patients' Ages at Onset of Ischaemic Heart Disease					
	35–64			65 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	13	2·02	6·44**	0	0·01	—
55 and over	18	7·87	2·29*	1	0·20	5·00
Female relatives						
35–64	9	1·30	6·92**	0	0·05	—
65 and over	4	3·31	1·21	1	0·39	2·56

From the Poisson distribution (Pearson and Hartley, 1954) $p < 0.01$ shown * $p < 0.001$ shown **

TABLE VII

COMPARISON OF RISKS OF DEATH FROM MYOCARDIAL DEGENERATION IN RELATIVES OF PATIENTS AND GENERAL POPULATION USING REGISTRAR GENERAL'S CATEGORIES 93, 421, AND 422

Age of Relative at Death From Ischaemic Heart Disease	Male Patients' Ages at Onset of Ischaemic Heart Disease					
	35–54			55 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	0	0·37	—	0	0·27	—
55 and over	3	3·88	0·77	4	5·27	0·76
Female relatives						
35–64	1	1·36	0·74	2	0·91	2·20
65 and over	1	5·42	0·18	3	4·93	0·61
	Female Patients' Ages at Onset of Ischaemic Heart Disease					
	35–64			65 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	2	0·63	3·17	0	0·01	—
55 and over	8	3·90	2·05	1	0·43	2·33
Female relatives						
35–64	0	1·48	—	0	0·13	—
65 and over	12	7·77	1·54	0	0·85	—

TABLE VIII

COMPARISON OF RISKS OF DEATH FROM CEREBRAL HAEMORRHAGE AND THROMBOSIS IN RELATIVES OF PATIENTS AND GENERAL POPULATION USING REGISTRAR GENERAL'S CATEGORIES 97·1, 82, 83, 331, AND 332

Age of Relative at Death From Cerebral Haemorrhage and Thrombosis	Male Patients' Ages at Onset of Ischaemic Heart Disease					
	35–54			55 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	2	0·53	3·77	0	0·35	—
55 and over	2	3·81	0·52	3	4·27	0·70
Female relatives						
35–64	6	2·31	2·60	1	1·42	0·70
65 and over	5	5·71	0·88	4	4·44	0·90
	Female Patients' Ages at Onset of Ischaemic Heart Disease					
	35–64			65 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	3	0·73	4·11	0	0·01	—
55 and over	8	4·87	1·64	1	0·09	11·11
Female relatives						
35–64	3	2·29	1·31	0	0·16	—
65 and over	12	6·11	1·96	2	0·73	2·74

patients, 7-fold amongst their 'younger' female relatives, and 5-fold amongst the 'younger' male relatives of the 'younger' male patients. These increases are all significant at the 1 in 1000 level (Pearson and Hartley, 1954). Amongst the 'older' male relatives of all the 'younger' patients the risks are doubled ($p = <0·01$), while among the 'younger' female relatives of the 'younger' male patients the risk is doubled, though the figure is not significant.

Risks of Death from Myocardial Degeneration, Cerebrovascular Disorder and All Causes in Patients' Relatives. Table VII shows a summary of deaths observed (O) and expected (E) and the ratio (O/E) from myocardial degeneration, Registrar General's categories 93 in 1931–49 and 421 and 422 from 1950, and shows no indication of any increase in the number of deaths certified in categories 421, 422, and 93 in the female relatives of patients with ischaemic heart disease.

Table VIII shows a similar summary of cerebrovascular disorder in patients' relatives, using the Registrar General's categories 82a and b, and 97·1 in 1931–39, 83a, b, and c in 1940–49, and 331 and 332 from 1950. The expected numbers and observed numbers are too small for significant comparison when considered in four groups divided by sex, but when comparison is made between the sum of the expected (5·86) and observed numbers (14) in the 'younger' relatives of the 'younger' patients there is a more than 2-fold increase which is significant ($p = <0·01$).

Table IX shows a summary of the risks of death from all causes minus deaths from coronary artery disease, Registrar General's categories 94 in 1931–49 and 420 in 1950–present. When the risks of dying from coronary artery disease are subtracted from the risks of dying from all causes, the observed numbers of deaths are not significantly different from the expected numbers.

Risks of Death from Ischaemic Heart Disease and Cerebrovascular Disorders in Relatives of Controls. Table X shows the observed and expected deaths from ischaemic heart disease (Registrar General's categories 420 and 94) and from cerebral harmorrhage and thrombosis (Registrar General's categories 97·1, 82a and b, 83a, b, and c, 331 and 332) in the relatives of controls. The deaths observed from both ischaemic heart disease and cerebrovascular disorder in the relatives of the control series are close to those expected from the incidence in the general population. It is, therefore,

TABLE IX

COMPARISON OF RISKS OF DEATH FROM ALL CAUSES (EXCLUDING DEATHS IN REGISTRAR GENERAL'S CATEGORIES 420 AND 94) IN RELATIVES OF PATIENTS AND GENERAL POPULATION

Age of Relative at Death	Male Patients' Ages at Onset of Ischaemic Heart Disease					
	35–54			55 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	9	10·11	0·89	2	6·51	0·31
55 and over	27	29·02	0·93	31	32·37	0·96
Female relatives						
35–64	14	19·44	0·72	10	11·72	0·85
65 and over	31	27·48	1·13	26	22·58	1·15
	Female Patients' Ages at Onset of Ischaemic Heart Disease					
	35–64			65 and over		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	15	14·17	1·06	0	0·23	—
55 and over	39	39·67	0·93	3	0·83	3·61
Female relatives						
35–64	20	21·51	0·93	0	1·56	—
65 and over	46	34·01	1·35	5	3·72	1·34

TABLE X

COMPARISON OF RISKS OF DEATH IN RELATIVES OF CONTROLS FROM: ISCHAEMIC HEART DISEASE (R.G.'S CATEGORIES 420 AND 94) AND FROM CEREBRAL HAEMORRHAGE AND THROMBOSIS (R.G.'S CATEGORIES 97·1, 82, 83, 331, AND 332

Age at Death	Male Controls (all ages)					
	Deaths of Relatives From Ischaemic Heart Disease			Deaths of Relatives From Cerebral Haemorrhage		
	O	E	O/E	O	E	O/E
Male relatives						
35–54	4	1·20	3·33	0	0·49	—
55 and over	12	9·15	1·31	5	6·61	0·76
Female relatives						
35–64	1	1·17	0·85	1	2·39	0·42
65 and over	6	5·40	1·11	5	7·78	0·64
	Female Controls (all ages)					
	O	E	O/E	O	E	O/E
Male relatives						
35–54	0	1·47	—	0	0·56	—
55 and over	11	6·36	1·73	5	7·00	0·71
Female relatives						
35–64	1	1·31	0·76	2	2·46	0·81
65 and over	7	5·04	1·39	5	7·70	0·65

not unreasonable to compare morbidity in the relatives of the patients with the controls.

Morbidity amongst Living Relatives of Patients and Controls. Table XI shows the incidence of ischaemic heart disease and confirmed diabetes amongst living relatives (all ages included) of patients and controls. The pattern of increased incidence of ischaemic heart disease amongst the living relatives of patients follows closely the pattern of increased risk of death. A higher incidence of diabetes is found amongst the relatives of female patients compared with controls.

TABLE XI

INCIDENCE OF ISCHAEMIC HEART DISEASE AND DIABETES AMONGST LIVING RELATIVES OF PATIENTS AND CONTROLS

	Total	Ischaemic Heart Disease	Diabetes
Male relatives of:			
Male controls	98	1	1
Male patients	162	8	0
Female relatives of:			
Male controls	139	0	1
Male patients	184	1	4
Male relatives of:			
Female controls	110	2	1
Female patients	121	11	6
Female relatives of:			
Female controls	172	0	0
Female patients	110	7	4

Consanguinity in Index Patients and Controls. The parents of 2 unrelated female index patients were first cousins (see Appendix IIB, families 51 and 94). Both index patients had hypercholesterolaemic xanthomatosis. No consanguinity was found amongst the parents of the controls.

Twins. One male index patient has an identical twin who developed ischaemic heart disease 18 months after the onset in his brother. One male index patient has a twin sister who is well (see Appendix IIA, families 102 and 111).

Discussion

Ischaemic heart disease is a common cause of death, especially among men, and the risks have been increasing for men and women over the past 30 years. Male relatives in our series living through the ages 35–54 encountered an average expected risk of death from ischaemic heart disease of 1 in 65 (calculated from the Registrar General's tables categories 420 and 94), and female relatives living through the ages 35–64 encountered a risk of 1 in 90.

The risks observed in our 'younger' series (to the nearest whole number) for male relatives of male index patients are 1 in 12, for male relatives of female index patients 1 in 10, for female relatives of male patients 1 in 36 and for female relatives of female patients 1 in 12. This represents an approximately 5-, 6½-, 2½-, and 7-fold increase over the general population, as seen in Table VI. There has been a substantial increase in risk in the general population during the period under review, but the series is not large enough to see if the relative increase in risk remains constant. There is, however, a suggestion that as the general risk increases the relative risk drops. Taking all relatives together, between 1930 and 1945 there were 7 deaths when 0·6 would have been expected, whereas from 1945 to 1964, 27 deaths occurred when 4·9 would have been expected.

The female relatives of male patients show substantially less increase in risk of death from ischaemic heart disease than the other three classes of relatives. There is no indication that this is due to a reluctance to diagnose death from 'coronary artery disease' in young women, since there is no surplus of deaths of female relatives in categories 421, 422, and 93. This suggests that the familial causes (whether genetic or common family environment) of ischaemic heart disease in many men are not such as to cause ischaemic heart disease in women; the causes in women, however, can certainly affect their brothers and fathers.

The increased deaths from cerebral haemorrhage and thrombosis in the sum of the 4 classes of 'younger' relatives show that some aetiological factors are common in this group of disorders and in ischaemic heart disease. We were not, however, able to confirm Rose's observation (1964) that relatives of patients with ischaemic heart disease tend to die earlier from 'all causes', but, unlike Rose's, our observations are restricted to adult life.

Familial concentrations may be due to genetic resemblance between relatives, to common family environment or, as is probably the case here, a mixture of both. Members of a family will tend to share environmental factors such as occupational class, diet, smoking, and exercise habits which have been shown to be related to the incidence of ischaemic heart disease. This will perhaps be true of sibs rather more than of parent and child. It is not easy to compare risks between parents and sibs of patients in this series, because deaths occurring a generation apart are subject to differences in both risks and classification. It seems likely, however,

TABLE XII

COMPARISON OF RISKS OF DEATH IN R.G.'S CATEGORIES 420 AND 94 OF RELATIVES OF 'YOUNGER' FEMALE PATIENTS OF TOTAL GROUP (A) WITH THIS GROUP LESS RELATIVES OF 7 PATIENTS WITH HYPERCHOLESTEROLAEMIC XANTHOMATOSIS (B)

Age at Death From Ischaemic Heart Disease	A Total Group of Female Patients			B Female Patients with Hypercholesterolaemic Xanthomatosis			C A minus B		
	Age of Patient at Onset of Ischaemic Heart Disease, 35–64								
	O	E	O/E	O	E	O/E	O	E	O/E
Male relatives									
35–54	13	2·02	6·44**	2	0·15	13·33**	11	1·87	5·88**
55 and over	18	7·87	2·29*	1	0·30	3·33	17	7·57	2·25
Female relatives									
35–64	9	1·30	6·92**	3	0·13	23·08**	6	1·17	5·13*
65 and over	4	3·31	1·21	0	0·26	—	4	3·05	1·31

From the Poisson distribution (Pearson and Hartley, 1954) $p < 0.01$ shown * $p < 0.001$ shown **.

that the causes of the differences in risk to the female relatives of the male patients compared with female relatives of female patients are more likely to be genetic than environmental. A real distinction between common genes and common environment is perhaps best established by twin studies, and it would be of much interest to see the further results of the Danish twin study (Harvald and Hauge, 1963), particularly for deaths from ischaemic heart disease in the 'younger' age-group. Meanwhile, if Falconer's method of analysis of heritability (1965) is applied to this survey the risks to men would be compatible with a heritability of 60% and for women of 70%; though, as Falconer notes, the true heritability would be lower than this to the extent that the family concentrations are due to the common environment.

The index patients in this series were an unselected group with ischaemic heart disease and the familial concentrations might well vary according to the underlying causes. Exceptional familial concentrations of ischaemic heart disease are noted more frequently amongst families of the female than of the male patients (see Appendix II). There were only two striking familial concentrations among the families of the male patients (see Appendix IIA, families 40 and 120). In both, the mother was affected, and in family 40 the index patient has hypertriglyceridaemia. Familial concentrations appear more frequently amongst the female patients (see Appendix IIB, families 1, 51, 83, 84, and 93). In families 1, 51, and 84 the index patients and one or more relatives have hypercholesterolaemic xanthomatosis; in family 84, twin brothers of the index patient are reported, one died at 38 of ischaemic heart disease and the other at the same age was found to have ischaemic heart disease and hypercholesterolaemic xanthomatosis; family 83 has 4 family members with diabetes mellitus while in family 93 no special factors were found.

Index patients with hypercholesterolameic xanthomatosis form one specific subgroup worth special study. In this series hypercholesterolaemic xanthomatosis was diagnosed in 7 women patients; however, no systematic search was made for this condition so it may have been present in more. Tables of risk constructed for the family members of the 7 female index patients diagnosed as having hypercholesterolaemic xanthomatosis (see Table XII) showed a 13-fold increase in risk to their 'young' male relatives and a 23-fold increase in risk to the 'younger' female relatives, indicating a specially high risk to the 'younger' relatives in these families. When the life experience of the relatives of these 7 hypercholesterolaemic families is subtracted from the total series very little reduction in risk is shown amongst the male relatives over the general population; the female relatives show rather more reduction in the increased risk over the unselected series.

Summary

The health experience of all adult first degree relatives of 121 men and 96 women with ischaemic heart disease and 104 men and 105 women controls is reported. The causes of death and morbidity of both groups of relatives have been documented, and causes of death (from death certificates) have been

classified by the Registrar General's staff using the criteria current at the date of death. A comparison has been made of deaths from ischaemic heart disease in the relatives of controls and the general population for England and Wales with the relatives of patients with ischaemic heart disease. When deaths under 55 years in men and 65 years in women are considered the relatives of both sexes of female patients with onset under 65 years show a nearly 7-fold increase compared with the general population and the male relatives of the male patients with onset under 55 years show an increase of risk of death which is 5 times that in the general population. The female relatives of the male patients experience an increased risk which is $2\frac{1}{2}$ times that of the women in the general population.

Family concentrations of ischaemic heart disease are noted especially in the families of the female patients and are most marked in the families of patients with hypercholesterolaemic xanthomatosis or amongst families containing members with diabetes. Two pairs of twins with ischaemic heart disease are mentioned.

The evidence points to an increased risk of ischaemic heart disease to relatives and suggests that the increased risk may be in part due to genetic factors.

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Appendix I

Definitions of Categories used on Life Tables from Registrar General's Statistical Review

Year	Category	Definition
Before 1920		
1908	B111	Diseases of particular organs Heart
1910	79	*Organic disease of the heart*
	79b	Fatty degeneration of heart
1917	64c	Cerebral haemorrhage
1921–1930		
Table 17	89	*Angina pectoris*
	90	*Other diseases of the heart*
	90·7	Other or unspecified myocardial disease
	90·9	Heart disease undefined
	91	*Diseases of the arteries*
	74	*Cerebral haemorrhage, apoplexy, etc.*
	74a1	Cerebral haemorrhage so returned
1931–1939		
Table 21	93	*Diseases of the myocardium*
	93b	Myocardial degeneration
	93b2	Cardiovascular degeneration
	93b3	Other diseases included under 93b
	94	*Diseases of the coronary arteries, angina pectoris*
	82	*Cerebral haemorrhage, apoplexy, etc.*
	82a1	Cerebral haemorrhage so returned
	82b	Cerebral thrombosis
	97	*Arteriosclerosis*
	97·1	Arteriosclerosis with cerebral haemorrhage
1940–1949		
Table 21	93	*Diseases of the myocardium*
	93c	Myocardial degeneration, infarction, and sclerosis and other chronic myocarditis
	93c·1	Cardiovascular degeneration
	93c·3	Other myocardial degeneration
	93d	Myocarditis, not distinguished as acute or chronic
	94	*Diseases of the coronary arteries, angina pectoris*
	94a	Diseases of the coronary arteries

Appendix I—*continued*

Year	Category	Definition
	94b	Angina pectoris without mention of coronary disease
	83	*Intracranial lesions of vascular origin*
	83a	Cerebral haemorrhage
	83bc	Cerebral embolism, thrombosis, and softening
1950–present day		
Table 17	420–422	*Arteriosclerotic and degenerative heart disease*
	420	*Arteriosclerotic heart disease, including coronary disease*
	420·1	Heart disease specified as involving coronary arteries
	421	*Chronic endocarditis not specified as rheumatic*
	422	*Other myocardial degeneration*
	422·1	Myocardial degeneration with arteriosclerosis
	422·2	Other diseases included under 422
	331	*Cerebral haemorrhage*
	332	*Cerebral embolism and thrombosis*

Appendix II

Details of families of index patients with ischaemic heart disease

Male and female 1st degree relatives are shown M F; male and female half-sibs m f; italics show relative affected with ischaemic heart disease, when followed by SP indicates affected relative diagnosed since pedigree was taken and not used in tables; *indicates diabetes; † hypercholesterolaemic xanthoma; CVD cerebrovascular disorder; ND death not documented; RG's category following date of death shows classification by RG's staff (see Appendix I); Mx indicates male died at x years; round brackets indicate sibs under 20 years and half-sibs who do not appear on tables; square brackets indicate twins; IE indicates insufficient evidence for use in tables; W indicates war death.

Family No.	Propositi		Parents		Sibs and half-sibs	Children
	Year of Birth	Age at Onset IHD	Mothers	Fathers		
A—MALE PATIENTS						
One-child families						
1	1907	46	1881–1918	1879–1962ND		M1950
2	1930	34	1905	1903		M1957; M1959
3	1911	50	1887	*1886–1955* *420.1*		F1940; M1945; M1948
4	1906	57	1878–1935	1874–1910		M1933
5	1914	47	1878–1960	*1869–1947* *94a*		M1942; M1945; F1949
6	1912	48	1881–1943 83a	*1881–1953* *422.2*		

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
One-child families (continued)						
7	1913	50	*1890–1956* *420.1*	1887		M1940; F1942; M1946
8	1911	49	1878–1948 83a	1872–1916		M1947; M1952; (Mo; Fo)
9	1912	48	1871–1947	1877–1915W		F1936
10	1906–1965	54	1967–1940ND	1872–1931	(Mat. ½ sibs f, f, f, f, m, m, m, 1891–1944)	F1927; F1937
11	1904	56	1870–1937	1868–1944		F1936; M1940; M1943; (Mo; Mo; Fo)
12	1906	57	1878–1955 331	1877–1942 83a		M1935
Two-child families						
13	1913	49	1882–1960ND	1881–1941	F1915	F1941
14	1911	44	1889	*1878–1944* *94a*	M1920	M1940
15	1903	59	1875–1946	*1873–1947* *94a*	F1908	
16	1901	56	1875–1941	1873–1963ND	*M1902*	
17	1912	49	1880–1957	IE	F1911	F1934; M1936
18	1902	58	1875–1923	1869–1927	F1909	
19	1916	48	*1882–1942* *94a*	1869–1928	M1920	
20	1910	54	1873	1871–1926	M1903	M1942; F1944
21	1904	59	*1880–1941* *93c.3*	*1879–1947* *94a*	F1905	
22	1929	35	1899	1898	M1927	M1954; F1957
23	1928	33	1900–1930ND	1893–1960	M1927	M1961
24	1905	58	*1876–1961* *420.1*	1880–1952	F1902	
25	1905	51	1880–1923	IE	F1917	F1932; [F1943; F1943]; (M3; Fo)
26	1904	60	*1871–1947* *94a*	1871–1952	M1910	
27	1901	58	1872–1942W	1872–1942W	*M1895–1963* *422.2*	
28	1902	59	*1865–1960* *420.1*	1854–1938	M1909; (Mo)	
29	1926	35	1897–1963	*1881–1941* *94a*	M1930	F1951; F1957
30	1904	58	1873–1907	1879–1954ND	F1900; (Fo) (Pat. ½ sib m, 1913; f, 1917–1961 f, 1915) 331	F1929; F1935
31	1914	47	1883	1883	M1910–1933W	M1946
32	1904	58	1875–1944	*1873–1959* *422.2*	M1913	
33	1904	59	*1873–1934* *93b.3*	1878–1959	F1910	
Three-child families						
34	1911	52	1878–1931	IE	M1903; F1906	F1942; F1944; F1946
35	1909	44	1880*	1880–1928	*M1906–1962*; F1911 *420.1*	F1948; F1949
36	1904	58	1883–1951	1875–1937	*M1903–1957*; F1904 *420.1*	M1937; F1943
37	1906	57	1877–1925	1874–1947	F1902; M1912; (F15; F15)	M1929; M1934; M1940; M1948
38	1908	44	1879–1963	1878–1960ND	M1907; F1912	F1932; M1933; F1937
39	1906	57	1885–1945	1878–1951 332	F1909; F1912; (M1)	F1945
40	1903	57	*1875–1956* *422.2*	*1874–1946* *93c.1*	M1899; *M1914–1965 SP* *420.1*	
41	1905	55	1871–1960	1880–1939	M1903–1962; M1910	F1930; F1932
42	1908	51	1884–1950	1881–1919	F1908; M1914; (Mat. ½ sib m23)	M1938
43	1915	48	1881	1858–1932	M1905; M1927	M1939; M1942
44	1910	53	1888–1923	1885–1935 97.1	F1916; F1921–1941; (M1, M5)	M1940; F1942; F1946; F1955
45	1913	49	1878	1880–1916	M1912; M1916; (Mat. ½ sibs m1896; f1900; m1904)	F1942
46	1929	34	1900	*1903–1960* *420.1*	M1926; F1927	F1955; F1956; F1958
47	1904	57	1869–1942ND	1850–1909	M1898; F1906; (Mat ½ sib m1915)	F1930; F1932
48	1902	57	1886–1953	1883–1961	F1905; M1907	F1927; F1932; F1940; (Mo)
49	1901–1964	59	1878–1949ND	1876–1918	F1908–1947; F1909	
50	1906	57	*1880–1942** *94a*	1879	M1904; M1914	M1928; M1932; F1933; F1936; F1945

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
Three-child families (continued)						
51	1916	46	1887–1960	*1894–1960* *420.1*	M1914; M1927	M1947
52	1923	40	1894	1892–1927	F1923; M1928	M1951; M1955; F1957; F1961
53	1910	49	1880–1957	1883–1950	M1908; M1912	F1945; M1951
54	1913	48	1884–1951	1884–1914W	F1909; F1910	
55	1906	54	1878–1918	1872–1931	*M1902*; F1914	(M2; Fo)
56	1910	49	1880–1962	*1869–1934* *93b.3*	*M1901–1963 SP*; M1903–1961 *420.1*	M1947
57	1900	63	IE	1867–1944	F1888; F1891*; (F)	M1941; M1943; M1946; F1948
58	1908	50	*1877–1929* *90.7*	1875–1943	F1899–1951; M1902; (M15) 331	
59	1906	57	1884–1960	*1884–1949* *94a*	M1905; M1914; (Fo)	[F1957; F1957]
Four-child families						
60	1902	55	1873–1933 82a·1	1865–1924	M1908; M1912; F1914	F1938
61	1921	41	1884–1932	1882	M1908; M1913; F1918	M1946; M1948
62	1906	56	1880–1956ND	1885–1912	F1904; M1910; F1912	F1940; M1942
63	1906	57	*1877–1947* *94a*	1873–1958	F1899; M1901; M1912	F1946
64	1912	51	1890	1873–1918W	M1913; F1923; F1926	F1945; M1954
65	1908	56	1875–1955	*1878–1963* *420.1*	F1905; F1908; F1912; (Mo)	F1937; M1948
66	1902	61	1875–1962ND	1873–1939 82b·2	F1906; M1915–1940W; F1916	F1925; F1930; F1932
67	1904	52	IE	1882–1910	F1901–1935; M1907; M1910	
68	1916	45	1882–1933	1878–1931	M1909–1958; F1912; M1914	M1944
69	1914	49	1886–1954	1883	*M1910–1962*; F1922; M1927 *420.1*	M1941; M1943
70	1906	57	*1871–1947* *94a*	1872–1913	F1896; M1900; *M1909–1955* *420·1*	M1935; F1939; F1941
71	1910	54	1884*ND	*1885–1941* *94a*	F1907–1950; F1914; F1918 331	M1942; M1951
72	1914	49	1881–1955	1876	M1901; F1904; F1908	M1943; M1951
73	1905	52	*1878–1950** *420.1*	1875–1957	M1903; M1910; F1914	M1935; M1944; M1947
74	1912	52	1867–1958	*1865–1929* *89*	F1887–1964ND; F1894; F1904; (F2; F8)	
75	1902	61	1876–1962	1874–1956	M1900; M1907; M1913	M1938; M1942; M1946
Five-child families						
76	1903	54	1885–1947 83bc	1884–1926ND	F1904; M1916; F1918; M1920	F1929; M1933
77	1920	40	1893–1954	*1891–1962* *420.1*	M1917; F1923; F1925; F1933	M1943; M1946; M1948; M1952; F1955
78	1901	63	*1874–1963* *420.1*	IE	M1898; M1909–1963; M1914–1934ND; M1919	F1929
79	1921	42	*1884–1958* *420.1*	*1887–1943* *94a*	M1908; F1910; F1912; F1914	
80	1904	59	1872–1943ND	IE	M1902; M1907; M1909–1945; M1917	
81	1922	42	1889	1888–1927	F1916; F1918; F1924; M1926	M1958
82	1908	54	IE	IE	F1903; *F1906*; M1910–1930ND; F1919; (Fo; Fo)	F1936; F1941; F1945
83	1900	63	1868–1939 82a.1	*1865–1938* *93b.3*	F1898CVD; M1902; F1908; M1911	M1937; F1942
84	1910	49	*1883–1943* *94a*	1881–1916W	*M1903*; M1909–1958; [M1914 (Fo)]; [F1916 (Mo)]	F1936; M1938
85	1918	46	1895–1953 331	1890	F1912; M1914; M1915; F1921	M1952
86	1911	51	1878–1954	1865–1938ND	F1897; F1902; M1903; F1908	M1936; F1937; M1945
87	1916	47	1880	1875–1947 83bc	F1905; F1908–1958ND; M1910; F1913	M1951; M1954; M1957; F1962
88	1910	53	1867	1866–1946ND	F1903; F1907; M1908; F1915	F1940; M1948
89	1903	57	1866–1934	1865–1936	M1894; F1897–1918; *M1900*; M1907	M1937
90	1908	53	1885–1951 332	1881–1941	M1903; F1905; M1913–1961; F1915; (F7; M1)	F1936; F1933
Six-child families						
91	1901	58	1859–1942 83bc	1856–1924	M1883; *M1884–1954*; M1887–1955; *420.1* M1889; F1897–1954	F1954; F1959; M1963

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
Six-child families (continued)						
92	1904	50	1874	1877–1944	M1898–1950; M1900; M1904; M1909; F1917	M1934; F1939
93	1913	50	1883–1951 331	1883–1918	*M1901–1955*; M1903; F1904; *420.1* M1907–1940; *M1910–1964 SP* *420.1*	F1934; F1938
94	1904	55	1879	*1873–1934* *94*	F1900; M1902; M1908; F1910; F1914	M1925; F1930; F1943; F1945
95	1918	46	1890–1958	1891–1956 332	M1910; F1916; M1920; M1922; M1923	M1942; M1946
96	1909	54	1876–1921	1867–1937 97.3	M1905–1959; F1906; F1907; F1916; F1918	F1941
97	1914	49	1874–1940 83bc	1873–1927	F1897; M1899; F1905; M1906–1939; M1910	
98	1921	42	1887	1888–1939ND	M1909; F1912; M1918–1940W; F1926; M1932	(M3)
99	1916	45	1889–1957 332	*1886–1952* *420.1*	F1914; F1918; M1920; F1922; F1924	M1946
100	1912	46	1876–1949	1876–1929	*M1902–1951*; F1903; F1905; F1907; *420.1* M1910; *M1914*	M1938
Seven-child families						
101	1929	35	1895–1939 97.1	1895	M1916; M1918; *M1920–1964*; F1921*; *420.1* M1924; F1928	M1950; F1953
102	1906	52	1865–1944	1860–1929	F1884; M1890–1961; F1899; M1902; M1905–1963; [*M1906 SP* propositor]	
103	1910	37	1868–1959ND	1858–1921	M1890; F1894; *M1894–1961*; F1899; *420.1* F1904; F1910; (F4; M0)	M1940; M1943
104	1904	59	1880	1878–1951	*M1896*; M1901; F1908; F1916; M1910; F1920; (F2)	M1944; M1948
105	1907	57	1885–1961 331	*1873–1961* *420.1*	M1904; M1909; M1914; M1916; M1927; M1929; (M19)	M1950; F1952
106	1894	63	1860–1941ND	1855–1911	F1877; F1880; F1883; M1885; M1891; F1900–1960	*M1914–1962*; M1917; *420.1* M1921–1942; F1923; M1925; M1931
107	1909	56	1883	*1876–1961** *420.1*	F1909; F1911; M1913; M1915; F1916; F1926–1954	
108	1911	52	1882	*1885–1953* *422.2*	F1910; M1918; F1922; F1924; M1926; F1928	F1940; F1948
109	1919	45	*1880–1951* *422·2*	1869–1940	F1906; F1908; F1910; F1913; M1914; F1916	(M3)
Eight-child families						
110	1916	47	1889	*1883–1941* *94a*	M1912; M1919; F1924; M1932; F1938; F1940; F1942	M1946–1963; M1948; F1953
111	1918	43	1880–1948	1879–1955	F1906; M1907; F1910; F1912–1953ND F1913; F1916; [F1918; propositor]	F1945; F1948
112	1909	52	1877–1948	1878	M1901; F1902; M1904; F1906; M1907; F1908; F1911	M1933; M1935; M1937; M1939; M1941; F1943
113	1899–1963	52	1870–1945	1869–1939ND	M1894; M1897–1917W; F1901; M1903–1923; F1905; M1907; M1909	F1927
114	1911	48	1889	1885–1936 97.1	M1913; M1915; M1917; F1919; M1921–1954; F1922; F1924	F1938; M1944
Nine-child families						
115	1902	61	*1866–1938* *93b.2*	1866–1934	F1889; F1891; F1894; M1895–1927; M1898; M1900; M1904; M1908	F1938
116	1909	49	1868–1915	1862–1929	M1890; F1891; M1893; M1897; M1899; M1902; F1903; F1906	
Ten-child families						
117	1920	42	1879–1958	1878–1945	*M1899–1952*; F1900; F1905–1927; *420·1* M1907; M1909; M1911; *M1914*; F1916; FIE	M1947; M1949

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
Eleven-child families						
118	1928	37	*1885–1944* *93c.3*	1874–1932	*M1909–1951*; F1913; M1914; F1916; *420·1* F1918–1936; F1920; M1921; F1922; M1924; M1927	
119	1907	54	1876–1960ND	1860–1919ND	F1899; F1900–1928ND; F1901; F1902; F1905; *F1906–1959*; M1911; M1916; *420.1* F1920; MIE	
120	1918	46	*1881–1950* *420.1*	1873–1926	F1901; F1905; *M1906–1961*; F1908; *420.1* *M1909–1963*; F1910; *M1913–1957*; *420.1* *420·1* M1915; M1919; M1921–1941W; (F1)	
121	1904	60	*1867–1948* *93c.1*	*1868–1931* *94*	M1888; *F1890–1956*; M1891–1962; *420.1* F1892; F1897; M1898–1918W; F1899; F1902; M1906; F1908	M1942; F1946; F1947
B—FEMALE PATIENTS						
One-child families						
1	1897†	58	IE	IE		M1917; *M1920*; *F1921*; *M1923*; *M1925–1963*† *420·1*
2	1899	65	1872–1939	1868–1938*		M1926; (M16)
3	1900*	64	*1873–1945* *93c.1*	1878–1931		F1934
4	1900	61	1875*	1871–1904		M1921; M1923; F1927; M1931
5	1905	59	1883–1946	1884–1915W		M1925; F1928
6	1901	57	*1871–1957* *420.1*	1859–1931 82a.1	(Mat. ½ sib *m62**) *422.2*	
Two-child families						
7	1900	59	1872–1955 331	1870–1937	F1911–1957	M1926
8	1910	54	1878	*1881–1949* *94a*	M1908*ND	F1933; F1936–1960
9	1886	68	*1860–1939** *93b*	1859–1938 82a.1	F1898–1923	M1911; M1913
10	1919	41	1892	1879	M1908	M1952; F1960
11	1926†	38	*1900–1950* *420.1*	1900	M1931	
12	1903	61	1865–1949 83bc	1865–1922	FIE; (Mat. ½ sibs f60, m50)	M1925
13	1898	61	1865–1931	1860–1902	F1892–1920	M1918; M1928
14	1917	47	1895–1963*	*1888–1940* *94b*	F1921	M1943
15	1897	62	*1863–1949* *93c.1*	1854–1910	F1903–1949; (F4)	
16	1902	62	1869–1951	*1861–1926* *90.7*	M1898–1952	F1930
17	1901	51	1876–1950 331	1875–1947 83a	M1902CVD	(Mo)
18	1899	48	1861–1915	*1868–1954* *420.1*	F1893–1920	F1928; M1937
19	1923	41	*1897*	1889	M1921–1942ND	F1944; F1946
20	1900	62	1868–1911	IE	MIE; (M19)	M1920; M1923; M1925; F1931; F1934; M1938; (Mo)
21	1912	52	1887	*1880–1950* *422.1*	*M1910–1963* *420.1*	
22	1911	53	1869–1945 83bc	*1862–1922* *89*	M1908	
Three-child families						
23	1905	53	1876–1944*	IE	M1901; M1903	F1927
24	1892	65	IE	IE	F1890; M1892*	F1919; F1923
25	1898	63	1878–1909	1870–1939	F1897CVD; *M1899–1954*; *420.1* (Mo; Mo; Fo; M14)	*M1922*; F1931

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
Three-child families (continued)						
26	1899	55	1877–1933	1876–1930	M1904; M1910–1940W; (M1; Fo)	M1923; F1925
27	1902	62	1868–1931*	*1857–1910* 79b	M1896–1929; F1902–1932	
28	1913	51	1887–1950*	1879–1949	*M1905*; M1910-1942	
29	1925	39	1900	*1880–1929* 90.7	M1921; M1923	
30	1896	54	*1865–1948* 93c.1	*1869–1944* 93c.3	F1897–1957; F1908	F1916; M1923; F1928; M1933; M1937
31	1911	41	1882	1878–1917	*M1905–1959*; F1909; (F19) 420.1	M1937
32	1905	56	1881–1947	1879–1954	*M1911–1962*; M1920 420.1	
33	1909	55	1882–1935	*1882–1955* 420.1	F1904; M1913	
34	1921	36	1890	*1889–1947* 93c.3	*M1911*; F1926	F1944
35	1911	53	1893–1956 332	IE	F1913; M1914	F1934; F1948
36	1906	58	1879–1918	IE	M1908; F1910	M1931
37	1902	59	*1866–1944* 93c.3	1871–1955 332	M1899; M1916; (F6*)	F1928; M1940
38	1901	63	1866–1918	1862–1925	F1895; M1899–1957; (Mo; Mo)	M1930; M1933
39	1905	59	1882–1930	1878–1930	M1905; M1907	M1936; M1938; F1944
40	1903	61	1870–1962* 332	*1869–1908* B3	*F1895–1951*; M1898* 420.1	
41	1905†	59	*1884–1941* 94a	1879–1944	*M1909*; F1922	
Four-child families						
42	1904	58	*1874–1946* 93d	1869–1929	M1899; M1909; F1916; (M18W)	M1932; F1937
43	1897*	67	1870	1870–1923	M1900; M1902; F1907	M1915
44	1898	57	*1866–1929* 90.7	1865–1909	*M1895–1951*; F1905; M1906 420.1	
45	1916	48	*1889–1962* 420.1	1889–1938 82a.1	*M1914–1960*; F1920; F1929 420.1	M1933; F1936; F1952; F1954
46	1909	50	IE	1878–1931*	F1904; *M1905–1963*; F1906 420.1	
47	1903	56	*1869–1954* 422.2	1872–1956	F1896; M1898; M1901; (F17*)	
48	1912	49	1890–1954*	*1886–1963* 420.1	M1913; M1915; F1924; (M14)	M1947
49	1918	45	*1893–1955* 420.1	1895–1964	M1917; M1920; F1923	F1945
50	1908	54	*1876–1953* 422.1	1874–1935	M1902; F1903; M1905–1936	
51	1897†	57	*1873–1942* 93c.3	1871–1944†	*F1900–1960*†; M1902†; *F1914* 420.1	F1923; F1924†; F1926; M1931; F1939
52	1911	53	*1873–1947* 93c.3	1869–1914	M1900; F1904; FIE	
53	1907	57	1872–1961 331	1866–1916	F1910; F1914; F1918; (M7)	
54	1911	53	1882–1962 332	1880–1925	M1909; M1915; F1918	F1944; M1949
55	1903	54	1878–1938	1874–1956	*M1900*; M1905; *M1907–1949*; (Mo) 94a	
56	1913	50	1891–1954 331	1887–1924	F1908; M1910; M1912; (M19)	M1931
Five-child families						
57	1910*	53	1886	1884–1960	M1912–1936; F1914; F1918; F1922	
58	1903	61	1866–1934	*1852–1927* 90.9	F1889–1959; M1900; M1904; F1907 331	M1942
59	1905	56	*1877–1936* 420.1	*1875–1950* 420.1	*M1901–1961*; M1902–1942W; F1908; 420.1 M1915; (Pat. ½ sib m1948)	M1927; M1932; F1940
60	1900	60	1866–1915	1863–1932 82a.1	M1897; M1899CVD; F1913; F1923	
61	1920	44	1886–1950	1886–1952 332	*M1907–1958*; F1913; M1924*; F1930 420.1	F1940
62	1903*	61	1874–1942* 83a	1874–1942	F1897; M1898*; *M1900*; F1907*	M1926; M1929
63	1899	62	1884–1954	1877–1930	M1900; M1903; M1905; F1909	F1926; M1933
64	1921	41	1894	*1889–1947* 94a	M1914; M1916; M1926; F1927–1962	

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
Five-child families (continued)						
65	1896	63	*1867–1939* 94a	1867–1914	M1893; *M1894–1957* 420.1; M1898; F1903*	F1915; M1917; M1920; F1923
66	1892	64	1850–1930 74a.1	1845–1921	F1871; *F1879–1955* 422.2; *F1880–1949* 93c.1; *M1889–1956* 420.1; (M17)	
67	1901	63	1874	1874–1952 332	F1899; F1903; M1907; M1909	F1923; F1926; F1927; M1931; M1933
68	1923	41	1883–1939	1884–1942	F1908; F1910; F1915; M1916; (F1; Fo)	M1946; M1948; F1956
69	1907	47	1877–1945*	1873–1930	F1899; *M1902ND*; F1905; F1918	M1930; M1936
70	1905	59	*1875–1950* 420.1	1867–1930 74a	M1897; M1899; F1901; F1907	M1936
71	1904	53	1859–1955ND	1865–1919	M1889; M1893; M1898; M1910; (M19W; M9)	F1926; M1930
72	1895	53	1865–1952	1870–1943 83a	*F1899–1962*; F1902; M1907; 420.1 M1915–1963; (Mo; Mo; Fo) 332	M1913; M1919; M1921
Six-child families						
73	1894	57	1866–1938	1872–1926	F1885; M1888; F1890; *F1891*; M1893–1948; M1900–1941 83a	F1921
74	1912	52	1885–1939*	1884–1949	M1911–1959; F1914; F1917; [M1926; M1926]	
75	1915	41	*1891*	*1885–1938* 93b.3	F1918; M1920–1941W; F1922; M1924; F1928	F1936; M1940; M1947
76	1897	62	1865–1917 64e	1860–1905	M1888–1915ND; M1890–1939; F1891–1958*; M1896–1918W; F1900	F1920; F1927; M1928
77	1892	65	1855–1917	1855–1924 74a.1	M1879–1938; *M1880–1936* 93b.3; *F1881–1962* 420.1; F1883–1961; F1886–1961 331	
78	1907	53	*1885–1955* 422.1	1875–1949	F1904; M1909; F1911; F1916*; F1922; (F3)	M1936
79	1901	61	1868–1927	1863–1915	F1890; F1894–1958; *F1897–1962* 420.1; F1904–1960; M1906; (M18W) 331	
80	1903	49	1885–1934	1884–1933	M1905–1962; F1908; M1910–1932; *M1913–1964*; M1916 420.1	F1921; F1923; F1926; F1930; M1935; M1940; (Mo; Mo; Mo)
81	1901	60	*1881–1941** 94a	1878–1931	M1904; *M1906–1962*; F1910; F1918; 420.1 F1921	F1923; M1925
82	1902*	60	1862–1947ND	1862–1914W	M1898; F1904–1944W; [F1911; (Fo)]; M1913; F1914	F1930; M1936; (M2)
83	1913	50	1873–1950 332	*1870–1934** 94	F1903*; *M1905–1944**; M1907; 94a *M1910–1947**; *M1921* 93c	F1944; F1948
84	1920†	44	1893–1963	*1889–1957* 420.1	M1912–1961; F1914; M1915; *M1923*†; [*M1926*†; *M1926–1962*] 420.1	M1943; M1945; M1950
85	1897	67	1876–1944 83a	*1868–1934* 94	F1908–1940W; F1909; F1910; *F1912*; F1914; (M1)	(M17)
Seven-child families						
86	1910	54	1879–1957	*1875–1960* 422.1	F1900; M1900; M1901–1961; M1903; M1904; M1905; (M6)	F1940; F1950
87	1900	56	1863–1945ND	1851–1920	F1886; M1890; F1892; M1896–1960; M1899–1958; F1913–1964ND	
88	1910	50	1875–1962ND	1881–1935	M1903; F1907; F1909; M1909; M1912; M1915	
89	1906†	50	1874–1929	1871–1923	F1894; F1899; F1901; M1903–1962; F1910; M1914	M1942
90	1923	40	1892	1890–1938ND	F1910; M1911; F1913; M1919; F1924; F1929; (F1)	F1946
Eight-child families						
91	1906	57	1882	*1883–1956ND*	F1907; M1913; M1914; F1916; F1917; F1920; F1922	F1927

Appendix II—*continued*

Family No.	Propositi: Year of Birth	Propositi: Age at Onset IHD	Parents: Mothers	Parents: Fathers	Sibs and half-sibs	Children
Eight-child families (continued)						
92	1895	60	1871–1940	1868–1945 93c.1	F1894; F1897; M1899; M1901; F1903; F1904; M1906	F1922; M1932
Nine-child families						
93	1895	63	1865–1945 83bc	1862–1932 93b.3	M1890–1960; M1891–1957; M1892; F1894–1953; M1897–1946; F1899–1933; M1904; M1908	M1928; F1931
Ten-child families						
94	1914†	50	1877–1959	1874–1950	F1902; F1904; F1906; M1910; M1916; F1917–1947; F1918; F1919; M1920–1962†; (M18)	
95	1901	62	1873–1950ND	1873–1939 94	M1888; M1892; F1895; M1898; F1900; F1902; F1903; F1904CVD; F1905	F1938
Eleven-child families						
96	1910	53	1887–1957*	1885–1937 82a.1	M1909; M1911; M1913; M1915; M1917; M1919; M1921; M1925; F1926; F1927; (F10)	F1933