chance of observing a false positive result.[62] Pooled relative risks for subtotals are shown as open lozenges. The vertical line through unity indicates the point where there is no difference between treatments. Trials indicating an advantage for treatment A lie to the left of this line and those showing advantage to treatment B lie to the right. Individual trials indicating a statistically significant result at the p=0·01 level, lie wholly to one side of the line, such that their confidence intervals will not straddle it.

When trials had multiple treatment arms and made more than one comparison of interest the patients from the relevant arms were included in each appropriate comparison, provided that there had been a direct randomisation between the treatment categories used. Thus two trials[25] (unpublished reference (A)) are included in more than one comparison. In trials where more than one arm was of the same treatment category the patients in these arms were grouped together for analysis. For example, in the trial comparing cisplatin versus cisplatin plus cyclophosphamide versus cisplatin, cyclophosphamide, and doxorubicin[10] the patients from the two combination arms were amalgamated and compared with the patients assigned single agent treatment. Two trials stopped randomising to certain arms early,[23,24] and a further two studies employed two separate randomisation schemes[23] (unpublished reference (A)). Each of these trials was subdivided into the appropriate number of data sets, and for analysis each was treated as an independent trial and labelled *a*, *b*, etc.

Risk of fatal coronary heart disease in familial hypercholesterolaemia

Scientific Steering Committee on behalf of the Simon Broome Register Group

Abstract

***Objectives*—(*a*) To determine the excess mortality from all causes and from coronary heart disease in patients with familial hypercholesterolaemia; (*b*) to examine how useful various criteria for selective measurement of cholesterol concentration in cardiovascular screening programmes are in identifying these patients.**

***Design*—Prospective cohort study.**

***Setting*—Eleven hospital outpatient lipid clinics in the United Kingdom.**

***Patients*—282 men and 244 women aged 20-74 with heterozygous familial hypercholesterolaemia.**

***Main outcome measure*—Standardised mortality ratio, all adults in England and Wales being taken as standard (standardised mortality ratio=100 for standard population).**

***Results*—The cohort was followed up for 2234 person years during 1980-9. Fifteen of the 24 deaths were due to coronary heart disease, giving a standardised mortality ratio of 386 (95% confidence interval 210 to 639). The excess mortality from this cause was highest at age 20-39 (standardised mortality ratio 9686; 3670 to 21 800) and decreased significantly with age. The standardised mortality ratio for all causes was 183 (117 to 273) and also was highest at age 20-39 (standardised mortality ratio 902; 329 to 1950). There was no significant difference between men and women. Criteria for measurement of cholesterol concentration in cardiovascular screening programmes (family history, presence of myocardial infarction, angina, stroke, corneal arcus, xanthelasma, obesity, hypertension, diabetes, or any of these) were present in 78% of patients.**

***Conclusions*—Familial hypercholesterolaemia is associated with a substantial excess mortality from coronary heart disease in young adults but may not be associated with a substantial excess mortality in older patients. Criteria for selective measurement of cholesterol concentration in cardiovascular screening programmes identify about three quarters of patients with the clinically overt condition.**

Scientific Steering Committee of the Simon Broome Register Group
Members of the scientific steering committee and participating physicians and clinics are listed at the end of this report.

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Introduction

Familial hypercholesterolaemia is an autosomal dominant disorder of lipoprotein metabolism characterised by mutations of the low density lipoprotein receptor resulting in an accumulation of low density lipoprotein cholesterol in the plasma.[1] Heterozygous familial hypercholesterolaemia has been estimated to affect about one in 500 of the British population.[1] Most affected subjects remain undiagnosed.

It is generally accepted that patients with familial hypercholesterolaemia are at greater risk of coronary heart disease than those with polygenic hypercholesterolaemia. The first report of a substantially increased risk in heterozygous familial hypercholesterolaemia described a 51% chance of fatal or non-fatal coronary heart disease by the age of 50 in men and a corresponding risk of 12% in women.[2] That and most subsequent studies were retrospective analyses, which are subject to inherent biases. Only one study seems to have followed up a large cohort of patients (588 heterozygous familial hypercholesterolaemic patients[3]), and no life table survival analysis has been reported. Published data on morbidity and mortality relate to a time when most patients did not receive effective lipid lowering treatment. A reassessment of the mortality associated with familial hypercholesterolaemia is therefore appropriate as the widespread use of lipid lowering drugs during the past decade, especially bile acid sequestrants and fibric acid derivatives, may have reduced cardiovascular morbidity and mortality.

We have recruited a cohort of patients with definite or possible familial hypercholesterolaemia, which will allow epidemiological, clinical, genetic, and metabolic studies to be performed in a well characterised population. We report the characteristics of 526 patients with definite familial hypercholesterolaemia and their mortality during the first 10 years of follow up. We have also used the information collected at registration to examine how useful the various criteria for selective measurement of cholesterol concentration suggested for use in cardiovascular screening programmes[4] are in identifying such patients.

Patients and methods

Recruitment of patients to the Simon Broome Register of Familial Hyperlipidaemia began in 1980. Patients were registered by the participating lipid clinics, to which they had been referred by either general practitioners or hospital specialists. Three categories of patients were admitted to the register: those defined as having definite familial hypercholesterolaemia, whose families contained at least one member in whom tendon xanthomas were present; those with possible familial hypercholesterolaemia, whose families had no member affected with tendon xanthomas; and a much smaller group with severe hypertriglyceridaemia. We report on patients who were classified as having definite familial hypercholesterolaemia. This was defined as a total cholesterol concentration above 7·5 mmol/l or, when available, a low density lipoprotein cholesterol concentration

above 4·9 mmol/l together with the presence of tendon xanthomas either in the patient or in a parent, child, grandparent, sibling, uncle, or aunt.

The registration form recorded information including age, details of past medical history, family history, smoking status, alcohol consumption, and previous treatment for hyperlipoproteinaemia. The World Health Organisation's cardiovascular questionnaire[5] was used to detect angina and intermittent claudication. Supine blood pressure was measured with a standard mercury sphygmomanometer. The body mass index (weight (kg)/(height (m))^2) was calculated for 475 patients (records of height and weight were incomplete for 51 patients). The presence of tendon xanthomas, xanthelasma, arcus cornealis, and peripheral pulses was noted. A fasting venous blood specimen was taken at the registration visit and concentrations of total cholesterol, serum triglycerides, and high density lipoprotein cholesterol measured by the laboratories which were routinely used by the participating clinics. Serum low density lipoprotein cholesterol concentrations were calculated by the method of Friedewald *et al*.[6]

The completed registration forms were returned to the coordinating centre in Oxford and the data entered on computer file. The names of registered patients were sent to the NHS central register so that deaths could be notified. In the event of death a summary of the relevant hospital case notes or the postmortem report was obtained. Causes of death were coded by one investigator using the ICD ninth revision.

The demographic and clinical characteristics of the cohort were analysed by using the statistical package for the social sciences (SPSS X),[7] and results except triglyceride values are stated as the mean (SD). Triglyceride values were log transformed to normalise the data and the results stated as the geometric mean with 95% confidence intervals. Multiple comparisons between groups were performed by one way analysis of variance, and a two tailed level of significance $<0·05$ was regarded as statistically significant. A life table analysis was undertaken by using a computer program that applies standard methods for cohort studies.[8] Person years at risk were calculated within 20 year age groups and five year calendar periods. Five subjects were excluded from the life table analysis on reaching age 75.

Expected numbers of deaths from ischaemic heart disease (ICD codes 410-414) and total mortality were calculated by applying the age and calendar period specific death rates for men and women in the general population of England and Wales to the person years accumulated by men and women in our cohort. The measure of risk derived was the ratio of the number of deaths observed to the number expected. This was expressed as a percentage to give the standardised mortality ratio (=100 for the reference population). 95% Confidence intervals for the standardised mortality ratio were calculated by assuming a Poisson distribution for the observed frequency in the numerator[9] with the mean equal to the expected frequency. The test of significance used was a two sided Poisson probability of observing the number of deaths that occurred given the expected number of deaths.

Results

Between 1 January 1980 and 31 December 1989, 601 patients with definite heterozygous familial hypercholesterolaemia were registered. This analysis is confined to 526 patients aged 20-74 years at registration. Their personal and family history of cardiovascular disease is shown in table I (differences in the denominators are due to missing data). Fourteen men (5%) and four women (2%) had had coronary angioplasty or coronary artery bypass grafting. Two men (1%) and 14 women (6%) had a previous history of thyroid disease, and one had diabetes mellitus. Fifty six men (20%) and 57 women (23%) currently smoked cigarettes. Twenty six men (9%) were pipe smokers.

The presence of tendon xanthomas in a patient or first degree relative was regarded as a diagnostic feature of familial hypercholesterolaemia and used as a selection criterion for this study. Overall 454 patients (86%) had xanthomas. Nevertheless, among patients aged 20-39, 28 men (22%) and 23 women (26%) did not have xanthomas, and even among those aged 60 or more one man (3%) and five women (11%) did not have detectable xanthomas. In patients aged 20-74 the most common sites for xanthomas were the Achilles tendon (374 cases; 71%) and hand (303; 58%). Thirty five patients (7%) had elbow xanthomas, 58 (11%) pretibial xanthomas, and 32 (6%) xanthoma on the dorsum of the foot. Corneal arcus was noted in 258 patients (50%) and xanthelasma in 120 (23%) (observations were missing for six and 12 patients respectively). These two clinical signs occurred infrequently in patients who did not also have xanthomas.

The mean body mass index at registration was 24·5 (2·8) (n=282) for men and 24·0 (3·7) (n=244) for women. One hundred and two men (40%) and 62 women (28%) had a body mass index in the range 25-29·9, and nine men and 12 women had a body mass index of 30 or more. Blood pressure greater than 160/90 mm Hg was recorded at registration in six men and 19 women. The mean concentrations of total cholesterol, triglycerides, low density lipoprotein cholesterol, and high density lipoprotein cholesterol are presented in table II. There were no significant differences in mean lipid values among the age groups in either sex. The mean serum cholesterol and low density lipoprotein cholesterol concentrations exceeded the 95th centile for the general population in all participating laboratories.

Table III shows the numbers of patients meeting the criteria for cholesterol measurement that have been

TABLE I—*Personal and family history of cardiovascular disease at registration*

	Men			Women		
	Age 20-39 (n=126)	Age 40-59 (n=127)	Age 60-74 (n=29)	Age 20-39 (n=88)	Age 40-59 (n=110)	Age 60-74 (n=46)
Personal history:						
Myocardial infarction	14 (n=123)	21 (n=124)	7 (n=28)	4 (n=86)	14 (n=107)	1 (n=46)
Angina (current or before coronary artery bypass grafting)	16 (n=116)	38 (n=125)	11 (n=28)	5 (n=85)	28 (n=106)	19 (n=46)
Intermittent claudication	0 (n=117)	11 (n=125)	3 (n=26)	3 (n=86)	10 (n=103)	4 (n=46)
Stroke	0 (n=121)	1 (n=124)	0 (n=28)	0 (n=87)	0 (n=106)	1 (n=46)
Family history of myocardial infarction:						
Mother aged <60	12 (n=109)	10 (n=105)	1 (n=21)	12 (n=74)	14 (n=87)	0 (n=39)
Father aged <55	34 (n=105)	21 (n=104)	2 (n=21)	26 (n=74)	14 (n=82)	2 (n=37)

TABLE II—*Mean (SD) lipid concentrations at registration (mmol/l)*

	Men			Women		
	Age 20-39	Age 40-59	Age 60-74	Age 20-39	Age 40-59	Age 60-74
Total cholesterol	8·8 (2·2)	8·9 (2·1)	8·0 (1·9)	8·7 (2·2)	9·1 (2·8)	9·2 (2·7)
Triglycerides*	1·3 (1·2 to 1·5)	1·8 (1·6 to 2·1)	1·2 (1·0 to 1·6)	1·0 (0·9 to 1·1)	1·3 (1·2 to 1·5)	1·6 (1·4 to 1·9)
High density lipoprotein cholesterol	1·1 (0·3)	1·2 (0·5)	1·2 (0·4)	1·2 (0·4)	1·3 (0·4)	1·3 (0·4)
Low density lipoprotein cholesterol	7·3 (2·3)	6·8 (2·1)	5·7 (1·5)	6·9 (1·9)	7·6 (3·1)	6·8 (2·6)

*Values are geometric means (95% confidence interval).

suggested as useful for selective screening programmes aimed at detecting patients at high risk of cardiovascular disease. As the presence of tendon xanthomas was one of the diagnostic criteria for inclusion on the register it was excluded from this analysis.

Tables IV and V show the observed numbers of deaths from coronary heart disease and all causes during the 10 years of follow up together with the standardised mortality ratios for these causes. Coronary heart disease was present at registration in all five women and six of the 10 men who died of a myocardial infarction. It was also present at registration in five of the six patients under 40 who died of the disease. The standardised mortality ratio for coronary heart disease was 386 (95% confidence interval 210 to 639). The excess mortality from coronary heart disease was highest in the age group 20-39 (standardised mortality ratio 9686; 3670 to 21 800). It decreased significantly with age, and no excess was present in the age group 60-74 (standardised mortality ratio 44; 1 to 244). The standardised mortality ratio for all causes was 183 (117 to 273). The excess all cause mortality was highest in the age group 20-39 (standardised mortality ratio 902; 329 to 1950) but there was no excess in the age group 60-74 (standardised mortality ratio 69; 22 to 160). The median age at diagnosis for the age group 20-39 was 27 years (range 3-39), for the age group 40-59 was 42 (range 8-59), and for the age group 60-74 was 59 (range 36-71).

Discussion

The substantially increased risk of coronary heart disease associated with familial hypercholesterolaemia was recorded before lipid lowering drugs were widely prescribed.[2 10-14] Those early studies were retrospective analyses, and the only prospective report[3] did not include a life table analysis.

Our study has accumulated over 2000 person years of prospective observation and covered a period (1980-9) when lipid lowering drugs were routinely used in the participating lipid clinics. Most patients were treated with bile acid sequestrants prescribed as monotherapy or in conjunction with fibric acid derivatives, probucol, or nicotinic acid preparations. Despite this treatment life table analysis shows that patients aged 20-39 years with familial hypercholesterolaemia had about a 100-fold increase in mortality from coronary heart disease and a nearly 10-fold increase in total mortality. Although there were differences in standardised mortality ratios between men and women, the confidence intervals were wide and the differences were not statistically significant. The mortality associated with familial hypercholesterolaemia in our cohort may have been underestimated because the proportion of smokers was smaller than in the general population.

A striking finding was the reduced relative risk of death from coronary heart disease with increasing age. Patients who survived through middle age seemed no longer to be at a substantially increased risk of coronary heart disease. In both men and women aged over 60 at registration there was no increase in the standardised mortality ratio for coronary heart disease or all cause mortality. A pronounced differential mortality between younger and older patients would have considerable clinical significance if confirmed as initiating energetic treatment might be less important in older patients. Our data do not indicate which characteristics might protect some patients with familial hypercholesterolaemia against premature coronary heart disease. However, a family history of premature myocardial infarction was less common in the older age group. Higher lp(a) lipoprotein concentrations have been reported in patients with familial hypercholesterolaemia with evidence of vascular disease than in those free of complications.[15 16] This might partly explain differences in mortality between older and younger patients in our cohort, although it cannot be confirmed as lp(a) lipoprotein was not measured at registration. Future studies of participants in the register will attempt to identify factors which might influence the susceptibility to coronary heart disease.

Our results contribute to the debate about screening for hyperlipidaemia.[4 17-19] The criteria that have

TABLE III—*Number of patients with characteristics suggested for use in selective cardiovascular screening programme*

	Men			Women		
	Age 20-39 (n=126)	Age 40-59 (n=127)	Age 60-74 (n=29)	Age 20-39 (n=88)	Age 40-59 (n=110)	Age 60-74 (n=46)
Family history of myocardial infarction:						
Below age 55 in father or 60 in mother	44 (n=114)	31 (n=115)	3 (n=22)	37 (n=77)	28 (n=93)	2 (n=42)
Below age 65 in either father or mother	51 (n=114)	42 (n=115)	5 (n=22)	40 (n=77)	41 (n=93)	5 (n=42)
Other cardiovascular risk factors:						
Obesity (body mass index (kg/m^2) >30)	4 (n=112)	3 (n=119)	2 (n=26)	4 (n=78)	6 (n=100)	2 (n=40)
Hypertension (blood pressure ≥160/90 mm Hg)	1 (n=117)	2 (n=122)	3 (n=28)	2 (n=83)	9 (n=104)	8 (n=46)
Diagnosed diabetes		1 (n=123)	2 (n=28)		1 (n=107)	
Current cigarette smoker	30 (n=126)	20 (n=127)	6 (n=29)	22 (n=88)	30 (n=110)	5 (n=46)
Presence of myocardial infarction/angina/stroke/intermittent claudication	23 (n=115)	54 (n=123)	13 (n=26)	10 (n=84)	36 (n=99)	22 (n=46)
Corneal arcus	63 (n=125)	75 (n=126)	20 (n=29)	19 (n=87)	48 (n=108)	33 (n=45)
Xanthelasma	15 (n=123)	33 (n=124)	7 (n=29)	16 (n=86)	37 (n=107)	12 (n=45)
Any of above characteristics (excluding cigarette smoker and using first definition of family history)	72 (n=105)	100 (n=113)	24 (n=26)	47 (n=73)	73 (n=92)	36 (n=39)

TABLE IV—*Mortality analysis: coronary heart disease (ICD (ninth revision) codes 410-414)*

Age (years)	Person years of observation	Observed deaths	Expected deaths	Standardised mortality ratio	95% Confidence interval
			Men		
20-39	439	5	0·06	8975**	2710 to 19 400
40-59	653	4	1·28	312	85 to 800
60-74	133	1	1·34	75	2 to 416
20-74	1226	10	2·67	374***	180 to 689
			Women		
20-39	335	1	0·01	16 039*	253 to 55 700
40-59	447	4	0·26	1538***	419 to 3940
60-74	225	0	0·94		
20-74	1008	5	1·21	413*	134 to 964
			Men and women		
20-39	774	6	0·06	9686***	3670 to 21 800
40-59	1110	8	1·54	519***	224 to 1020
60-74	358	1	2·28	44	1 to 244
20-74	2234	15	3·88	386***	210 to 639

*p<0·05. **-<0·01. ***p<0·001.

TABLE V—*Mortality analysis: all causes*

Age (years)	Person years of observation	Observed deaths	Expected deaths	Standardised mortality ratio	95% Confidence interval
			Men		
20-39	439	5	0·47	1065***	345 to 2480
40-59	653	6	3·36	179	65 to 389
60-74	133	4	3.61	111	30 to 284
20-74	1226	15	7·44	202*	113 to 333
			Women		
20-39	335	1	0·20	511*	127 to 279
40-59	447	7	1·79	391**	157 to 806
60-74	225	1	3·67	27	1 to 152
20-74	1008	9	5·66	159	73 to 302
			Men and women		
20-39	774	6	0·67	902***	329 to 1950
40-59	1110	13	5·15	253**	134 to 432
60-74	358	5	7·28	69	22 to 160
20-74	2234	24	13.10	183**	117 to 273

*p<0·05. **p<0·01. ***p<0·001.

been suggested for the selective measurement of cholesterol in cardiovascular screening programmes would identify only three quarters of the patients represented here (table III). Although selective screening programmes are often thought to be more cost effective than population screening programmes, a recent British study found that using the criteria listed in table III would mean screening about 80% of the adult population.[20] Hence there seems to be little advantage in selective as opposed to population based screening. Opportunistic screening in general practice is likely to offer the most effective population based screening strategy.[21,22]

In summary, treated heterozygous familial hypercholesterolaemia was associated with a substantial excess mortality from coronary heart disease in young adults, but no significant excess was found in patients aged 60 or more. Care is needed in interpreting this finding as, although all eligible patients were included in the register, participants were not representative of all patients with familial hypercholesterolaemia in the general population, most of whom are unrecognised and untreated.[23] Most patients referred to the participating clinics were diagnosed because of xanthomas or a personal or family history of premature vascular disease, and patients without symptomatic coronary heart disease were probably underrepresented. However, the excess mortality from coronary heart disease in younger patients with familial hypercholesterolaemia was so substantial that it would persist even after the inclusion of substantial numbers of additional patients without evidence of coronary heart disease.

In future more presymptomatic patients with familial hypercholesterolaemia will be identified and included in the register as cholesterol is increasingly being measured as part of cardiovascular disease prevention programmes. This will allow the risks and age trends recorded here to be investigated further. Continued recruitment and follow up of patients already registered should allow us to determine whether newer cholesterol lowering drugs, such as HMG CoA (hydroxymethylglutaryl coenzyme A) reductase inhibitors, will reduce the mortality associated with this condition.

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ONE HUNDRED YEARS AGO

The outcry recently raised in a certain section of the public press against delay in publishing details as to the last illness of Mr Parnell has shown that the position of the medical profession is not yet fully appreciated. The details of the health and death of politicians may or may not be public property; it is a question open, perhaps, to argument, but it is, happily, not one which the medical attendant is called upon to decide. In the course of his professional duties he becomes acquainted with many facts—it would be begging the question to call them secrets—under the seal of confidence. His relation to the patient, and to his family, is a confidential relation. Acting therefore as their agent, he is only at liberty to communicate to a third party such facts as his principal authorises him to communicate. This principle guided Mr Jowers in declining to give to the press information as to the cause of his patient's death until authorised to do so by the widow. There is a great deal of human nature in man; and probably those who were loudest in finding fault with a reticence which seemed to them, in the heat of the moment, "extraordinary," would be the first to appreciate this reticence as a virtue if the case were their own. Mr Parnell's case was, in its medical history, perfectly clear: hyperpyrexia is well recognised as a most serious and not rare complication of rheumatic fever, and one which, as in his case, is frequently the determining cause of a fatal issue.

(*British Medical Journal* 1891;ii:905)