

Follow-up of subjects in prospective studies based in general practice

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SUMMARY. In prospective studies of ischaemic heart disease, data on the incidence of morbidity as well as mortality are critical to the understanding of the natural history of disease. In the Regional Heart Study, 7,735 middle-aged men recruited from general practices in 24 towns in England, Wales and Scotland have been examined, and are being followed for morbidity and mortality for at least five years. This paper explains the methods used and the difficulties encountered in maintaining the flow of information on these subjects and, in particular, discusses the problems of removal and tracing. A network of enquiries, using Family Practitioner Committees, the NHS Central Register and the additional 500 doctors (to date) to whom subjects have transferred, has enabled contact to be maintained. In the first seven towns reviewed at five years from the initial examination, replies have been received from 98 per cent of the original sample still alive and living in Great Britain.

Introduction

PROSPECTIVE studies are dependent on a complete, or nearly complete, collection of data relating to the end-points under consideration. Most prospective studies have been concerned with mortality as the sole measure of outcome, as attempts to include morbidity involve a number of problems. These include removal from the area of study and failure to trace individuals to their new location. There is also the problem of obtaining cooperation from doctors not involved in the original study and the nonstandardization of reporting.

The Regional Heart Study seeks to explain the striking regional variations in cardiovascular mortality in Great Britain and to define the risk factors responsible for cardiovascular disease.¹ The study is based on a

clinical survey of middle-aged men in 24 towns in England, Wales and Scotland, which provides a cross-sectional view of the distribution of risk factors and their interrelationships.² All the men are being followed up for a period of at least five years to determine which of the many personal characteristics are most strongly associated with the development of cardiovascular events.

It is relatively straightforward to obtain information on deaths in selected men by the established system of 'tagging' used at the National Health Service (NHS) Central Register in Southport. Information on morbidity relating to nonfatal cardiovascular events is more difficult to obtain as it is not routinely available. It may come from several sources, as in the case of the Regional Heart Study involving men in 24 towns over a period of several years. A complete study of the natural history of cardiovascular disease demands that information on both morbidity and mortality should be available, and in a prospective study of this kind morbidity data improve considerably the power of the study by increasing the number of events in a given period.

This paper describes the methods used to develop a reporting system for fatal and nonfatal cardiovascular events in subjects recruited from general practices, and outlines the procedures available for tracing those who move to new areas and register with new general practitioners.

Method

Selection of towns and subjects

The selection of material for the Regional Heart Study has been described in detail in earlier publications.^{1,2} In brief, 24 towns were primarily selected from those with populations of 50,000–100,000 (1971 census). They were chosen to represent the full range of cardiovascular mortality and water hardness, and towns in all the major standard regions were included. One general

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practice in each town was selected after consultation with the District Medical Officer, who listed those practices apparently fulfilling the required criteria. These included a patient list greater than 7,500, an interested group of doctors and a social class distribution in the practice that reflected the social class distribution of the men of that town. All practices on the short-list were visited and the most suitable group selected. If there was no up-to-date age-sex register, one was established for the practice. From each age-sex register about 420 men aged 40-59 years were selected at random to produce five-year age groups of equal size. The list of names was reviewed by the doctors in the practice, who were asked to exclude those whom they considered could not participate because of severe mental or physical disability. Close scrutiny of the returned annotated lists reduced the exclusions to approximately six to 10 names per practice.

The remaining subjects were invited to take part in the study by a letter signed by their general practitioner. A response rate of 78 per cent was achieved, and 7,735 men—approximately 320 men per town—were examined over a period of two and a half years at the rate of one town per month.

The 22 per cent of nonresponders comprised men who:

1. did not reply to the invitation and one reminder, but as far as was known lived at the address supplied by the practice;
2. were not available to attend the examination in the two-week period offered because of holidays or work commitments.
3. refused, without reason.

Mortality

Mortality information is collected through the established procedures available at the NHS Central Register, in Southport³ for England and Wales and in Edinburgh for Scotland. In order to obtain death notifications, details were supplied to the two centres which enabled them to identify and tag the relevant cases. To meet Registry requirements, a card was prepared for each subject containing the NHS number (whenever it was available), full name, date of birth and last known address. A tagging charge is made on a per capita basis and the fee is increased when the NHS number is not available, or when incorrect information leads to an extensive search for the correct subject among the 52 million records held.

At three monthly intervals a batch of death notifications is received by the study centre in London. These contain identification details, place and date of death, cause of death coded to the *International Classification of Disease (9th revision)*,⁴ the name of the certifier and information as to whether a postmortem examination was performed. As reports of death are also sent in by the general practice, using the blue card system (see

below), all information is verifiable. If clarification of cause or mode of death is required, contact is made with the general practitioner, or the hospital where the death took place, to investigate any inconsistency in or between reports.

Morbidity

Practice coordinator. In each town a member of the practice staff was identified to assist with the study. In most cases this was a part-time receptionist who took responsibility for the initial Regional Heart Study survey appointments, acted as receptionist for the two-week screening period and then continued as practice coordinator for the period of follow-up. She is responsible for maintaining contact with the study centre, supervising the mailing and replacement of morbidity reports (blue card), notifying the centre of all deaths, removals and address changes, and ensuring that the general practitioners in the practice see all Regional Heart Study communications. At set intervals (18 months, three years and five years), she carries out a review of the medical records, and on completion of five years of follow-up plays a critical role in the response to the mailed questionnaire. For these tasks she receives an annual honorarium based on the estimated number of hours worked.

Blue card. On the day each man was examined, a blue card (Figure 1) was prepared with details of his identification and then placed in his medical record folder. During the two-week examination period in the town, a meeting was held for the doctors in the practice. They

Figure 1. Morbidity report (blue card).

were instructed on the procedure for completion of the card:

If any man in the study consults or is visited by a doctor for a cardiovascular event, the card should be completed and forwarded to the study centre in the prepaid envelope provided. The specific events to be reported are myocardial infarction, angina, transient ischaemic attack and stroke. A tick in the appropriate box, indicating a possible or definite episode, new or recurrent event, is all that is required, with the doctor's name and date of diagnosis. Criteria for the diagnosis of these events are printed on the back of every card.

The practice coordinator despatches the card to the centre, and a new card plus photocopy of the previous report is sent to the practice to be filed in the man's notes. Any report of nonfatal myocardial infarction is followed up by the study centre to obtain evidence of chest pain, electrocardiogram findings and enzyme levels.

Periodic review. The review of records at 18 months, three and five years, required each man's notes to be scrutinized, and discharge letters from hospitals to be reread, to ensure that all cardiovascular events had been reported. An alphabetical listing of all the men in the study, with a summary of the information received to date, was supplied to the practice and the medical records were checked against this. This procedure frequently identified some missed information, including removals and death (all causes) which had not been notified at the time of the event, and occasionally a cardiovascular event, either angina or myocardial infarction, which the doctor had recorded but failed to report at the time.

Communications. After three years of follow-up a return visit was made to each practice to present some results of the study to the general practitioners and coordinators, and to keep them informed of progress. This visit reminded them of the importance of their role, enabled any new members of the practice staff to be introduced and provided an opportunity for specific problems to be clarified. A six-monthly newsletter circulated to all collaborators in the study helps to maintain regular contact and informs them of recent progress and new publications, reprints of which are available on request. All these procedures are aimed at maintaining a high level of morbidity reporting and prompt communication of all relevant events.

Change of practice

It was anticipated that movement of patients between general practices would cause considerable loss to follow-up data. The national average of patient withdrawal from a general practitioner's list in England and Wales is around 10 per cent per annum, and theoretically in five years almost 50 per cent of the sample would have left their original general practice. It was realized, however, that an average family of four contains only one middle-aged man, and that a lower rate of mobility

could be expected from this cohort. Furthermore, middle-aged men are far less mobile than single people, young couples and the retired. Contrary to our initial beliefs, widespread unemployment does not appear to increase population mobility in this age group. As a result of this information it was decided not to accept any loss of men from follow-up, but to trace them all to their new general practitioner and to enlist the cooperation of the new doctors in morbidity reporting and in the periodic reviews.

NHS Central Register. In 1939 a door-to-door enumeration and registration took place for the purpose of issuing identity cards and ration books. This handwritten register formed the basis of the NHS Central Register in 1948 and has been kept up-to-date by the addition of all subsequent births and immigrations and the recording of all deaths and emigrations. It operates to minimize the inflation of doctors' lists, and to help the Family Practitioner Committees carry out their work of paying general practitioners on a per capita registration basis more effectively. Since 1960 the NHS Central Register has played an increasing role in certain kinds of research projects, some of which could not have developed without it.

When a patient applies to a general practitioner for registration he hands in his medical card, which is forwarded to the Family Practitioner Committee (FPC) for administrative purposes. The FPC informs the NHS Central Register of all new registrations in their area. The movement of a patient to a new FPC area is recorded on the man's record at the Central Register with a date and a symbol indicating the new area of registration. At present, FPCs retain a register of removals from their area for a year, and retain the general practice records of a deceased person or emigrant for three years. It is therefore essential to make all follow-up enquiries as promptly as possible, as information at this level is lost with time. If a late enquiry is made and no trace of the subject is found in the FPC records, the NHS Central Register are able to supply, on request, the 'last posting' from their records, which indicates the last available FPC registration of the subject.

Tracing procedures

Family Practitioner Committees receive their information from three sources: deaths and emigrations are notified by the NHS Central Register; removals outward to new areas are notified by the new FPCs calling in the notes from the previous areas of registration; local moves involving a change of doctor within the same area are dealt with internally by the local FPC. The form on which all this information is collated for each practice gives the reason for patient withdrawal and sometimes the code number of the doctor to whom the notes will be forwarded. If the notes are being sent outside the area, a cipher is given indicating the FPC area requesting the records (Figure 2). There are 100

Specimen		Suffolk Family Practitioner Committee		F.P.22	
The persons named below have been removed from your list during week ending 29.07.83 Please return the Medical Records to					
Year of Birth	Name	National Health Service Number	Reason for removal	New Area	
1	HOOPER, James RHS	SCR 17622	R	NN	
2	SAMUELS, Alfred	MZAV 143	X		
3	PHILLIPS, Jane	EEVH 149.3	X		
4	MARKS, Eileen	PQRO 112	X		
5	MARKS, Peter	EKBO 69.7	X		
6	KING, Geoffrey RHS	TCCC 203.3	R	NF	
7	ALDRICH, Christopher	DNAF 131.2	X		
8	WALTERS, David	TODJ 256	R	NF	
9	PATTERSON, Jean	MVJC 332	R	LNB	
10	PARKER, Ian	KWZK 153	R	KC	
11					
12					

Figure 2. Family Practitioner Committee recall form (FP22).

FPCs in England and Wales and 15 Primary Care Divisions in Scotland, each serving an area equivalent to the old Area Health Authority (1974–82). In the example in Figure 2, two Regional Heart Study subjects are identified, one having moved to Nottingham and one to Norfolk.

The practice coordinator informs the study centre as soon as possible of a patient's withdrawal from the practice list. She normally obtains this information from the recall form (FP 22D) sent out each week by the local Family Practitioner Committee to general practitioners in their area calling in the notes of all people who have died, emigrated or registered with a new doctor.

When notes are withdrawn from the practice, the blue card in the record folder and the Regional Heart Study stamp on the outside alert those handling the notes in the practice that information relating to this patient should be passed on to the practice coordinator, and then to the study centre. When information on removals is received by the centre, a request is sent to the appropriate FPC to supply the name of the new general practitioner and she/he will, on request, supply an interim cardiovascular morbidity report and the man's most recent address.

The transfer of records between general practitioners takes an average of three months to complete and sometimes may take much longer. Thus there is always some delay in obtaining up-to-date information on a few patients.

At the time of preparing this report (August 1983) 500 men had removed to a total of 80 different FPC areas and registered with approximately 500 new doctors. Cooperation has been gained from all but one of these general practitioners. One per cent of the sample have not yet been relocated; that is, have not registered with a new general practitioner but are known to have moved because the questionnaire has been returned unopened to the centre. The notes of these men remain with their

previous doctor until such time as they are recalled for new registration. A few of these men may have left the country but not officially emigrated. They may return, but if they should die outside Great Britain this information will be lost to the study. Nevertheless, up to the present time morbidity follow-up through the general practitioner has been maintained on 99 per cent of the original sample alive and resident in Great Britain.

Questionnaire at year 5. The fifth-year review of general practitioner records supplies up-to-date information on the current addresses of all men in the Regional Health Study and confirmation of all removals, deaths, and emigrations. Having traced all removals to their new general practitioner, permission is requested to make further contact with the men, and this is granted by the doctor supplying the man's current address and latest five-year morbidity report.

A questionnaire sent to each man five years after his initial examination enquired about morbidity during the five-year period. It included questions on angina and severe chest pain, changes in smoking and drinking habits, and economic status, with special emphasis on past and present unemployment. The questionnaire was mailed with a letter and prepaid envelope to each subject still alive and resident in Great Britain. If no reply was received within two weeks, a letter of reminder was sent with another copy of the questionnaire. If there was still no reply after a further two weeks, a third questionnaire was sent with an altered text in the letter, indicating to the men the very small number of people who had not replied. At this point the practice coordinator tried to contact nonresponders, by telephone whenever possible, to offer assistance with completion of the questionnaire if help was required. For those men who could not be reached by telephone, or who had removed to a new area, this final approach was replaced by a fourth letter and questionnaire despatched by recorded delivery.

Results

The first seven towns have completed five years follow-up and Table 1 shows some of the information arising from the study. On average, 300 men per town were examined and in five years eight men per town had died from all causes and two men per town had emigrated. In the first seven towns, a total of 166 men had registered with a new general practitioner—24 men per town, ranging from 51 in Peterborough to five in Merthyr Tydfil. This gives a removal rate of 8 per cent over five years, or 1.6 per cent per annum on average.

The first mailing of the questionnaire produced on average a 75 per cent response, ranging from 70–80 per cent (Table 2). The first reminder added a further 9–17 per cent, bringing the average response to 89 per cent. The third letter produced 3–10 per cent more replies, improving the total average response to 95 per cent. Finally, the practice coordinator and the recorded

Table 1. Regional Heart Study. Follow-up experience in seven towns* after five years.

Number of men	PET	HAR	SHR	LOW	MAN	SOU	MT	Mean
Examined	279	280	311	324	321	322	283	302
Died in five years	11	7	10	8	6	9	10	8
Emigrated in five years	1	2	1	3	0	5	1	2
Moved to new general practitioner	51	20	31	25	17	17	5	24

* Abbreviations: PET, Peterborough; HAR, Harrogate; SHR, Shrewsbury; LOW, Lowestoft; MAN, Mansfield; SOU, Southport; MT, Merthyr Tydfil.

Table 2. Regional Heart Study. Percentage response rates to fifth year questionnaires. (Number mailed per town* in parentheses.)

	PET (267)	HAR (271)	SHR (300)	LOW (313)	MAN (315)	SOU (309)	MT (272)
After 1st letter	74	70	80	78	75	78	70
Additional—after 2nd letter	11	16	13	17	14	9	17
Additional—after 3rd letter	10	7	4	3	5	8	4
Additional—after personal contact ± recorded letter	4	4	1	1	3	4	6
Final response rate	99	97	98	99	97	99	97

*Abbreviations defined in Table 1.

delivery assisted in identifying, even at this late stage, some incorrect addresses, and the tracing procedure was again put into motion. The final response ranged from 97–99 per cent, giving an overall mean of 98 per cent completed and returned questionnaires for all the men alive and living in Great Britain. The 2 per cent non-response comprises the 1 per cent not yet relocated and the 1 per cent who did not wish to complete a questionnaire although they had participated in the clinical examination five years previously.

Discussion

Many prospective studies have relied on mortality data alone from which to draw their conclusions. The addition of morbidity data, particularly in chronic diseases, is essential to the proper understanding of the development of disease. In studies of regional variation it is also critical in determining whether the incidence of the disease agrees with the official mortality patterns. This study has confirmed the feasibility of collecting morbidity data in a national prospective study, and should be of value to those planning follow-up studies.

There are many advantages to using general practice lists as a sampling frame for research. The almost complete coverage of the population registered in the Primary Care Section of the National Health Service offers an unbiased and ubiquitous register. The Family Practitioner Committees and the NHS Central Register have established procedures for tracing subjects and are willing to extend their facilities to approved research programmes.

Full collaboration with general practitioners is of fundamental importance in obtaining a high response rate. The initial letter inviting participation in the study was signed by the doctors in each practice and elicited a 78 per cent response. The request from the study centre to the participants to complete a questionnaire five years later obtained a 98 per cent response. Movement of patients between general practices, which initially seemed a factor likely to limit the full follow-up of subjects, proved to be of manageable proportions and did not affect the response rate once the patient had been located.

The design of the prospective phase of the Regional Heart Study provided two sources of information for both morbidity and mortality. The cross-checking of data supplied by the NHS Central Register and the general practices identified three cases of misreporting in 300 death notifications from one or other source, which were due to incorrect identification of the patient. No death report was received on a further five subjects, within a year of the terminal events. These notifications took from 15–41 months to reach the study centre after specific enquiries were made.

Morbidity reports are more difficult to evaluate as the review of medical records takes place in 24 towns and is carried out by at least 24 different people. However, all those responsible for this procedure are familiar with the requirements of the study and have been involved with the practice records for a considerable period of time. Based on the *Morbidity Statistics from General Practice*⁵ the observed number of reports of nonfatal myocardial infarction are slightly lower than expected. This may be due to a real decrease in ischaemic heart disease in the last 10 years or to the strict criteria required by this study for the confirmation of a definite event.

Analysis of the fifth year questionnaire will eventually supply a further source of morbidity data as recalled by the men themselves, and will be a further important method of internal validation of cardiovascular morbidity reporting.

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Prognosis of Reye's syndrome

Twenty-three sporadic cases of Reye's syndrome diagnosed according to widely accepted criteria were seen between 1979 and 1982. The patients were younger than those reported from North America (median age 9 months), girls were twice as common as boys, and the syndrome presented twice as frequently in the summer six months. The annual incidence was 1.4 cases per 100,000 among children aged less than 4 years. The prodrome consisted of upper respiratory symptoms in 61 per cent of the children and even less specific features in more than 25 per cent; two patients had varicella. Six of the 23 patients presented after a prodrome of less than 24 hours with 'acute collapse', simulating 'near miss' cot death associated with profound hypoglycaemia, and in four of these there was an unfavourable outcome. Intensive care methods including judicious fluid restriction coupled with 'prophylactic' hyperventilation (87 per cent), direct monitoring of intracranial pressure (70 per cent), and barbiturate coma (52 per cent) achieved neurologically intact survival in 74 per cent of patients. Failure to recognize the syndrome early enough or to manage it appropriately resulted in four deaths. To help reduce overall mortality in the UK paediatricians have a duty to acquaint family doctors and emergency department staff of the earliest clinical features of Reye's syndrome and of the need for immediate hospital referral.

Source: Glasgow JFT. Clinical features and prognosis of Reye's syndrome. *Arch Dis Child* 1984; 59: 230-235.