Caerphilly and Speedwell collaborative heart disease studies

THE CAERPHILLY AND SPEEDWELL COLLABORATIVE GROUP*

SUMMARY   The Caerphilly and Speedwell studies are based on representative samples of over 3000 subjects in South Wales and over 2000 in Bristol. They include cross sectional studies of risk factors for prevalent ischaemic heart disease (IHD) and of determinants of those risk factors. Prospective studies based on over 2000 men aged 45–59 in each area have been set up. In addition to the examination of lipid and thrombosis factors of possible relevance to IHD, the studies also focus on possible dietary, hormonal, and psychological risk factors, both as possible "risk factors" for IHD and also as possible "determinants" of risk factors.

The Caerphilly and Speedwell studies comprise an integrated research programme based on Caerphilly, a small town in south Wales (population 45 000), and Speedwell, a district of Bristol, a major English city. All the classic research techniques are being used—cross sectional surveys, case-control comparisons, prospective studies, and, in separate population samples, intervention studies including randomised controlled dietary trials.

In common with other similar studies the aims include the examination of known risk factors for ischaemic heart diseae (IHD) and the identification of new risk factors, and the identification of possible determinants of those risk factors. Some of the more particular aims of the work are:

The examination of high density lipoprotein (HDL) cholesterol as a risk factor for IHD.

The examination of certain thrombosis related tests and IHD.

A detailed examination of dietary factors of possible relevance to IHD.

The examination of several hormones (oestradiol, testosterone, and cortisol) in relation to IHD.

The method we are using to examine possible risk factors is the longitudinal or prospective study in which the predictive power of the various factors for

incident IHD is measured. For the identification and evaluation of possible determinants of those risk factors we have chosen to use cross sectional studies of random samples of the populations followed by randomised controlled intervention trials in population samples remote from Caerphilly and Speedwell.

The power of a prospective study depends ultimately on the number of events occurring during the period of follow up and this, in turn, is determined by the size of the population sample, the incidence of IHD, and the duration of follow up. It was decided to base both the Caerphilly and the Speedwell cohort studies on men aged 45–59, and in such subjects an initial incidence of IHD events (including IHD deaths) of around 1·0 per 100 a year might be expected.[1-3] Nevertheless, because conclusions drawn from a cohort study should be based on subjects who were disease free at the start, a lower figure, say 0·5 per 100 a year initially, might be reasonable. As the rate will rise as the cohort ages, a yield of, say, 70 to 80 events per 1000 men over the following ten years would seem to be reasonable. We therefore planned to base the Caerphilly and the Speedwell prospective studies each on about 2300 men, of whom about 2000 would be likely to be free of historical or ECG evidence of IHD.

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Method

In Caerphilly the electoral rolls for the town and for several adjacent villages were used as a sampling frame. Random samples were drawn, and for those studies in which a limited age range was required, younger and older subjects were later rejected. Several population samples have been drawn and studied in Caerphilly, as follows.

A random sample of men with a wide age range, 30–69. The objectives relevant to this sample were cross sectional, in particular the examination of the dietary, hormonal, and other determinants of known risk factors for IHD, including the lipoproteins and certain thrombosis factors such as fibrinogen.

A total population of men aged 45–59 in the town, including subjects of these ages already drawn in the wide age range sample above. The main objectives relevant to this sample are prospective—namely, the examination of the predictive power of factors for incident IHD.

The examination of men in the above samples enabled us to define a further population sample in Caerphilly—namely, a population of subjects with prevalent IHD. These subjects have been the basis of "case-control" studies, but in most such studies only cases of "silent" IHD have been included (ECG evidence of ischaemia but no history of myocardial infarct or angina) in order to limit the extent to which the known occurrence of an IHD event would have led a subject to change his diet or his way of life.

A small random sample of women has also been studied in Caerphilly to obtain evidence on male-female differences in the various risk factors and determinants. This has a similar age range to the main male cohort, though because of interest in the possible effects of the menopause the lower age limit is 40 years. A preliminary cross sectional survey of a random sample of women in Caerphilly in which the aims were limited to an examination of dietary and other determinants of lipoproteins has already been reported.[4][5] That population sample is not considered further in the present report.

In Speedwell, Bristol, the population sample consisted of all men aged 45–59 who were registered with 16 general practitioners in two health centres. The study has a common core protocol with the Caerphilly cohort study. Identical survey methods were used and for many of the tests the same laboratories were used as for the Caerphilly studies. When different laboratories had to be used comparability studies were conducted. A pilot study was conducted in Speedwell and the results of this have been published.[6][7]

Subjects drawn in these samples were written to and then visited. They attended an evening clinic for questioning and for measurement of a variety of clinical and other factors. They then attended a clinic between about 5 am and 9 am, in a fasting state, for venepuncture. After this several subsamples of the Caerphilly subjects were drawn for further investigations: three in every ten were asked to do a seven day weighed dietary intake study: a sample of cases of IHD together with matched controls were asked to attend a special clinic for adipose tissue sampling and a random sample of men had measurements of noise exposure at home and at work.

The data collected so far are listed below. To indicate the population samples for which each item is available, "Caerphilly," "All," or "Speedwell" subjects is stated.

General medical and social information (all subjects)—Questionnaires were used to obtain data on general health, medical history, smoking history, family history, and social class.

Anthropometry (all subjects)—Height and sitting height were measured on a Holtain stadiometer, skinfold thickness was measured at three sites, frame size was estimated from several skeletal measurements, and body weight was taken on a beam balance.

Lung function (Caerphilly subjects)—Forced expiratory volume in one second and forced vital capacity were measured with a McDermott spirometer.

Prevalent IHD (all subjects)—An ECG was taken with chest and limb leads and the London School of Hygiene and Tropical Medicine chest pain questionnaire was administered.

Blood pressure (all subjects) was measured on a Hawksley random zero muddler sphygmomanometer.

Haematology (all subjects)—Blood samples were sent for routine haematology and for whole blood viscosity.

Biochemistry (Caerphilly subjects)—Factors thought to be of possible relevance to HDL cholesterol concentrations include thyroid, liver, and renal function. In order to get some information on these the following were measured: T_4 and T_3 uptake by radioimmunoassay, total protein, albumen, bilirubin, alkaline phosphatase, and aspartic transaminase together with creatinine and uric acid.

Plasma lipids (all subjects)—Total serum cholesterol and triglyceride, and HDL cholesterol, together with its sub-fractions HDL_2 and HDL_3 were measured. Because the evaluation of HDL cholesterol was one of the main objectives, and because there were several methods of estimation, one of which was relatively new, two lipid laboratories were asked to accept samples from every

subject in Caerphilly. One laboratory used the heparin-manganese precipitation method, the other used precipitation with phosphotungstate-magnesium solution followed by micro-ultracentrifugation.

Thrombosis factors (all subjects)—Fibrinogen was estimated by both a biological and a chemical method. The platelet related test heparin thrombin clotting time[8] was done. Antithrombin III was estimated both by radial immunodiffusion and by the use of a chromogenic substrate.

Plasma hormones (Caerphilly subjects)—Testosterone, oestradiol and corisol, were measured by specific radioimmunoassay.

Immunology (Speedwell subjects)—Serum immunoglobulins IgA, IgM, and IgG were measured by radial immunodiffusion. Antibodies to reconstituted dried whole bovine milk were estimated. In the Caerphilly subjects C_3 genotype was identified.

Arterial stiffness (Speedwell subjects)—Using an ultrasound technique the pulse wave in the posterior tibial artery at the ankle was measured to give evidence on the compliance of the wall of the arterial tree.[9]

Dietary data (Caerphilly subjects)—The collection of detailed dietary data is one of the main aims of the study. Every subject in Caerphilly was asked to complete a detailed dietary questionnaire and a 30% sample of subjects was asked to conduct a seven day weighed dietary intake record.

Psychological factors (Caerphilly subjects)—The Framingham scale[10] was used to measure type A behaviour.

After the initial examination of men in Caerphilly, subjects with ECG evidence of ischaemia but with no history of angina or infarction—that is, men with IHD who are unlikely to have changed their diet as a result of the disease—together with control subjects with no evidence of ischaemia had a sample of subcutaneous adipose tissue taken from the left illiac fossa for fatty acid estimation by gas liquid chromatography. Also after the analyses of the data collected at the initial examinations we have set up several randomised controlled trials to test associations shown in the cross sectional data. In order not to disturb the main prospective study these are all conducted in subjects remote from Caerphilly. So far, these have included trials of the effect of fatty fish consumption on plasma lipoproteins,[11] the effect of alcohol intake on serum lipids and on plasma fibrinogen, and the effect of ascorbic acid intake on plasma lipids and cereal fibre consumption, blood pressure, and plasma fibrinogen.

Several quality control procedures have been conducted throughout. About one in every 20 samples submitted to each of the laboratories was a blind split-sample duplicate. A subsample of subjects was asked to give a second sample of blood after an interval that varied from a few weeks to several years. The first of these procedures examines variability introduced by the laboratory together with transport to the laboratories, the second gives evidence on the stability of the tests within subjects. A further quality control procedure was necessitated by the fact that while the same questionnaires, the same ECG coders, and the same biochemical and haematological laboratories were used, no single laboratory could accept blood for lipid estimations from all the Caerphilly and the Speedwell subjects. A few duplicate blood samples from one survey were therefore added on occasions to batches of samples from the other survey. This "cross over" will enable comparability between laboratories to be examined, and it should be possible to pool the data from the two population samples.

All the information collected from the subjects has been checked, coded, and entered into data files on a local Honeywell Multics computer. Data have then been subjected to range and compatability checks.

Results

The table lists the numbers of subjects in the various population samples and the numbers seen. The numbers who cooperated in the various subsidiary studies, such as the weighed dietary intake recording and the adipose tissue sampling, are not given but a high response rate has been maintained throughout all the work.

Numbers in the Caerphilly and Speedwell samples, the numbers seen, and the response rates

	Random sample	*Examined (%)*
Caerphilly men aged:		
30–69	797	711 (89%)
45–59	2703	2442 (90%)
Speedwell men aged:		
45–59	2550*	2348* (90%)
Caerphilly women aged:		
40–59	270*	212* (79%)

*Provisional estimates.

Discussion

The choice of the size of a population sample for the examination of cross sectional data is fairly easy. In the wide age range sample in Caerphilly the numbers were chosen to give a reasonable power in the detection of associations as statistically significant.

For example, it requires a sample size of 650 or above for a correlation coefficient of 0·1 to be statistically significantly different from zero at the 1% level. This indicates that our cross sectional studies will be very sensitive indeed, particularly when the data from the two cohorts are considered. We are also interested in associations between factors, and in particular betwen dietary, hormonal, and personality factors.

On the other hand, a danger in studies in which numerous factors are measured is that many spurious associations will be found at conventional levels of statistical significance. It is here that the value of the male and female Caerphilly samples and of the two cohorts will become apparent, as consistency between them will constitute valuable evidence of validity. More dependable evidence of association, however, will come from the intervention randomised controlled trials.

In analyses of the cross sectional data we propose to use definitions of prevalent IHD that closely follow those used in the Whitehall study.[12] Evidence of IHD, is: angina (assessed by the London School of Hygiene and Tropical Medicine chest pain questionnaire), myocardinal ischaemia (judged from the ECG), or a history of mycardial infarction (judged from the chest pain questionnaire and other medical history), or a combination of these. In particular we define:

Possible IHD—Minor Q waves, T wave and ST change, and L bundle branch block—that is, Minnesota code items 1–3, 4–1 to 4–4, 5–1 to 5–3, and 7–1.

Probable IHD—Angina or a history of myocardial infarction, or major Q waves on the ECG, or a combination of these—that is, Minnesota code items 1–1 or 1–2.

Many prospective studies are in progress throughout the world. To our knowledge, however, none in the United Kingdom is attempting to explore dietary, hormonal, and personality factors, or the interactions between these, and their associations with known risk factors such as lipoproteins, fibrinogen, blood pressure, etc. In any case as laboratory technology advances there is a continuing need for further epidemiological work, and especially prospective studies. In particular, the recent preventive trials of aspirin[13–15] have focused interest on platelet function in ischaemic heart disease. We have therefore conducted several platelet related tests in both cohorts and very shortly we hope to extend the range of these tests on the Caerphilly subjects.

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