Depression as a risk factor for ischaemic heart disease in men: population based case-control study

Julia Hippisley-Cox, Katherine Fielding, Mike Pringle

Department of General Practice, The Medical School, Queen's Medical Centre, Nottingham NG7 2UH

Julia Hippisley-Cox *lecturer in general practice*

Mike Pringle *professor of general practice*

Trent Institute for Health Services Research, The Medical School, Queen's Medical Centre

Katherine Fielding *lecturer in medical statistics*

Correspondence to: Dr Hippisley-Cox julia.h-cox@nottingham.ac.uk

BMJ 1998;316:1714–9

Abstract

Objective: To determine the relation between depression, anxiety, and use of antidepressants and the onset of ischaemic heart disease.
Design: Population based case-control study.
Setting: All 5623 patients registered with one general practice.
Subjects: 188 male cases with ischaemic heart disease matched by age to 485 male controls without ischaemic heart disease; 139 female cases with ischaemic heart disease matched by age to 412 female controls.
Main outcome measure: Adjusted odds ratios calculated by conditional logistic regression.
Results: The risk of ischaemic heart disease was three times higher among men with a recorded diagnosis of depression than among controls of the same age (odds ratio 3.09; 95% confidence interval 1.33 to 7.21; P = 0.009). This association persisted when smoking status, diabetes, hypertension, and underprivileged area (UPA(8)) score were included in a multivariate model (adjusted 2.75; 1.13 to 6.69; P = 0.03). Men with depression within the preceding 10 years were three times more likely to develop ischaemic heart disease than were the controls (3.13; 1.27 to 7.70; P = 0.01). Men with ischaemic heart disease had a higher risk of subsequent ischaemic heart disease than men without ischaemic heart disease (adjusted 2.34; 1.34 to 4.10; P = 0.003). Depression was not a risk factor for ischaemic heart disease in women on multivariate analysis (adjusted 1.34; 0.70 to 2.56; P = 0.38). Anxiety and subsequent ischaemic heart disease were not significantly associated in men or women.
Conclusion: Depression may be an independent risk factor for ischaemic heart disease in men, but not in women.

Introduction

Depression is present in over 45% of patients admitted to hospital after a myocardial infarction[1] and is an independent risk factor for increased mortality[2–4] and increased morbidity[5 6] after myocardial infarction. Depression may precede myocardial infarction,[7] although this is not certain.[8 9] Research in this area has been limited to studies of small numbers of highly selected hospital patients, often without any control group.[10]

Furthermore, the overall relation between depression, ischaemic heart disease, and cholesterol concentration is unclear. Some evidence shows that low cholesterol concentration may be related to depression[11] and increased risk of suicide.[12–15] Other evidence shows that no relation exists between low and declining cholesterol concentration and depression[16–18] or suicide.[19 20] If ischaemic heart disease is associated with hyperlipidaemia, and depression is associated with low cholesterol concentration, then a lower prevalence of depression in patients who subsequently develop ischaemic heart disease would be expected.

We aimed to determine whether *(a)* an association exists between ischaemic heart disease and depression, *(b)* depression occurs before or after the onset of ischaemic heart disease, and *(c)* the relation between depression and ischaemic heart disease differs between men and women. We included diagnoses of anxiety as well as of depression, as the two conditions often coexist.

Method

Selection of cases and controls

We conducted this case-control study in a rural dispensing training practice with 5623 patients on the borders of Nottinghamshire and Lincolnshire. Cases were male and female patients who have or have had ischaemic heart disease. Cases were identified from the practice computer; we selected those who either had a recorded diagnosis of ischaemic heart disease (including angina, myocardial infarction, coronary artery surgery) or were receiving repeat prescriptions of nitrates. The written records of all cases were reviewed to confirm the diagnosis, the date of onset, the first presenting illness (angina or myocardial infarction), and the results of supporting diagnostic investigations—that is, resting and exercise electrocardiography, and angiography.

We needed 299 matched case-control sets (one case to two controls) to show a relative risk of 2 for the onset of depression before the onset of ischaemic heart disease. This is based on a 20% prevalence of prior depression in cases compared with a 10% prevalence in controls. This sample size would give 95% power at the 5% significance level. Altogether, 327 patients with ischaemic heart disease were registered with the practice on 1 January 1996. There were insufficient patients aged over 80 for us to match two controls per case in that age group. To maintain the power of the study,

Table 1 Baseline characteristics of cases and controls*

	Male cases (n=188)	Male controls (n=485)	Female cases (n=139)	Female controls (n=412)
Mean (SD; No with data) age in 1996 (years)	69 (11; 188)	65 (10; 485)	74 (11; 139)	71 (10; 412)
Mean (SD; No with data) body mass index (kg/m^2)	26.9 (3.6; 174)	26.6 (3.7; 400)	27.1 (5.4; 129)	26.0 (4.9; 361)
Mean (SD; No with data) deprivation score	–9.5 (9.2; 188)	–10.0 (9.7; 485)	–9.3 (8.3; 139)	–8.5 (7.9; 412)
Mean No (%) with diabetes	19 (10)	13 (3)	11 (8)	12 (3)
Mean No (%) with hypertension	51 (27)	65 (13)	48 (35)	66 (16)
Mean No (%) of current or former smokers	57 (30)	148 (31)	30 (22)	74 (18)

*The number of controls per case varied according to the age of the case (see Methods section); hence the mean age of controls is weighted towards the younger age group.

therefore, we allocated between one and four age matched and sex matched controls according to the number of patients in each 10 year age band (four controls to each case under 60 years, three to each case aged 60-69, two to each case aged 70-79, and one to each case aged over 80 years). The controls were selected from an alphabetical list of patients currently registered with the practice. The next patient of exactly the same age in years, but with a different surname (to avoid family members), was chosen. Patients who had died were not included in the analysis as their manual records were no longer available.

Data collection

Every control was given a "pseudodiagnosis" date, the date on which he or she was the same age as the matching case was at diagnosis of ischaemic heart disease. For cases and controls, Read codes that related to depression or anxiety were identified from the computer database, and the dates of first diagnoses of depression and the first diagnoses of anxiety were recorded. Diagnoses of postnatal depression or manic depression were excluded. Computerised data for the use of antidepressants—that is, tricyclic drugs, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors—during five years preceding the diagnosis or pseudodiagnosis date were also recorded, together with the date of first prescription. We searched a random sample of 30 manual records to validate the computer data and found no discrepancy. We also collected the following data on all subjects: age; sex; body mass index; underprivileged area (UPA(8)) score, which is a measure of deprivation on the basis of the subjects' postcode; date of onset of ischaemic heart disease; age at diagnosis of ischaemic heart disease; and most recently recorded smoking status (current or former smoker or non-smoker). The presence or absence of prior diabetes mellitus and hypertension were recorded.

Statistical methods

The statistical analyses generally used were conditional multiple logistic regression analysis for individually matched case-control studies. The statistical package used was STATA (version 5.0). The dependent variable was the presence of ischaemic heart disease, and the principal variable was depression before the diagnosis or pseudodiagnosis date. When depression occurred in the same year as the onset of ischaemic heart disease, it was assumed to have occurred after onset. This was done because only the year of onset was recorded for some cases and controls. Such an assumption would tend to underestimate rather than overestimate the odds ratio. The univariate and multivariate associations for body mass index, deprivation score, anxiety, depression, use of antidepressants, diabetes, hypertension, and smoking status were determined. A case-control set was excluded if the information either for the case or for all the controls was not known for the variable in question. The multivariate models presented here comprise smoking status, hypertension, diabetes, and deprivation score. Body mass index was not included in the final model owing to the number of missing data points that would have greatly reduced the eventual sample size and therefore the power of the study.

Results

Characteristics of study population

Of the 5623 patients registered with the practice, 327 patients had ischaemic heart disease; of these, 205 first presented with angina, 122 first presented with a myocardial infarction, and 23 had had previous coronary artery surgery. Altogether, 188 male cases (105 with angina, 83 with a myocardial infarction) were age matched to 485 male controls; 139 female cases (100 with angina, 39 with a myocardial infarction) were age matched to 412 female controls. Table 1 shows the baseline characteristics, and table 2 shows the Read codes used for the diagnoses of depression.

Men

Depression as risk factor for ischaemic heart disease

Table 3 shows the results of the univariate and multivariate analysis for men with and without ischaemic heart disease. On univariate analysis, men with a recorded diagnosis of depression were three times more likely than controls of the same age to develop ischaemic heart disease (odds ratio 3.09; 95% confidence interval 1.33 to 7.21; P = 0.009). The risk of ischaemic heart disease persisted when smoking status, diabetes, hypertension, and deprivation score were included in the calculations (adjusted 2.75; 1.13 to 6.69; P = 0.03).

The data were reanalysed by comparing the mean values for each group of controls with the value for their respective case by using the Wilcoxon signed rank test. Men with ischaemic heart disease had a higher

Table 2 Computer codes used to record depression for cases and controls

Depression	Computer code	Total No with code		Total
		Cases	Controls	
Single major depressive episode	E112	3	2	5
Recurrent major depression	E1131	1	1	2
Neurotic depression (reactive type)	E204	5	4	9
Depressive disorder	E2B	42	78	120
Depressed	1B17	13	21	34
On examination depressed	2257	3	1	4
Total		67	107	174

Table 3 Univariate and multivariate associations for 188 males with ischaemic heart disease compared with 485 age matched controls without ischaemic heart disease

	Unadjusted		Adjusted	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)*	P value
First diagnosis of anxiety or depression before diagnosis of heart disease				
Depression†	3.09 (1.33 to 7.21)	0.009	2.75 (1.13 to 6.69)	0.03
Anxiety‡	1.62 (0.46 to 5.63)	0.45	1.40 (0.37 to 5.25)	0.62
Duration of depression (years)§:				
⩽10	3.13 (1.27 to 7.70)	0.01	3.12 (1.23 to 7.93)	0.02
>10	2.18 (0.61 to 7.77)	0.23	1.63 (0.41 to 6.44)	0.048
Tricyclic antidepressants¶	3.49 (0.95 to 12.85)	0.06	3.55 (0.89 to 14.21)	0.07
Mean daily dose of tricyclic antidepressant¶:				
<75 mg	2.92 (0.61 to 13.91)	0.18	2.97 (0.58 to 15.11)	0.19
⩾75 mg	4.71 (0.70 to 31.77)	0.11	5.02 (0.62 to 40.56)	0.13
Duration of tricyclic antidepressants (months)¶:				
⩽4	5.07 (0.88 to 29.15)	0.07	5.47 (0.84 to 35.50)	0.08
>4	2.27 (0.36 to 14.50)	0.39	2.19 (0.31 to 15.49)	0.43
First diagnosis of anxiety or depression after diagnosis of heart disease				
Depression†	2.20 (1.28 to 3.79)	0.005	2.34 (1.34 to 4.10)	0.003
Anxiety‡	1.61 (0.75 to 3.48)	0.220	1.62 (0.73 to 3.59)	0.23
Tricyclic antidepressants¶	1.83 (1.00 to 3.37)	0.05	1.82 (0.97 to 3.41)	0.06
Selective serotonin reuptake inhibitors**	4.01 (1.41 to 11.44)	0.009	4.68 (1.61 to 13.60)	0.005

*Model adjusted for smoking status, hypertension, diabetes, and depression score.
†Relative to subjects without depression. ‡Relative to subjects without anxiety. §Relative to a baseline of no depression. ¶Relative to subjects who had not had tricyclic antidepressants. **Relative to subjects who had not had selective serotonin reuptake inhibitors.

score for depression than the controls did (P = 0.01). This is consistent with the results of the conditional logistic regression analysis.

Duration of depression

Duration of depression before ischaemic heart disease was categorised as "no depression," "duration ⩽10 years," or "duration >10 years." These categories were used because of the distribution of the data. Duration of depression was associated with risk of heart disease on univariate analysis (table 3). Men who had a recorded diagnosis of depression within the preceding 10 years had a risk of ischaemic heart disease three times as high as both the controls (3.13; 1.27 to 7.70; P = 0.01) and the patients who had depression for more than 10 years before the onset of ischaemic heart disease. When smoking status, hypertension, diabetes, and underprivileged score were included in the calculations, the risk was essentially unaltered (adjusted 3.12; 1.23 to 7.93; P = 0.02).

Tricyclic antidepressants before ischaemic heart disease

Only six male cases and six male controls were taking tricyclic antidepressants before the onset of ischaemic heart disease. Of these, three cases were taking dothiepin and three amitriptyline; five controls were taking dothiepin and one amitriptyline. The mean dose for cases was 68.8 (SD 24.7) mg and for controls was 54.2 (SD 40.1) mg. The median duration of use for cases was 3 (range 1-7) months and for controls was 10 (2-16) months.

The results in table 3 suggest that men who had been prescribed tricyclic antidepressants in the recent past have a risk of ischaemic heart disease three times as high as controls but with a wide confidence interval owing to small numbers (adjusted 3.55; 0.89 to 14.21; P = 0.07). When the doses of tricyclic antidepressants were included as a categorical variable in the logistic regression model, increased doses seemed to be associated with increased risk of heart disease (table 3). However, these results were also not significant owing to the small sample size. The study was not designed to determine the particular effect of tricyclic antidepressants on risk of heart disease.

Depression after onset of ischaemic heart disease

Men with ischaemic heart disease are twice as likely to have a recorded diagnosis of depression after the onset of ischaemic heart disease as men without ischaemic heart disease (2.20; 1.28 to 3.79; P = 0.005). When smoking, deprivation score, hypertension, and diabetes were included the increased risk of depression persisted (adjusted 2.34; 1.33 to 4.10; P = 0.003).

Depression after ischaemic heart disease: effect of prior depression

The risk of any subsequent depression was related more to prior ischaemic heart disease (adjusted 2.42; 1.39 to 4.21; P = 0.002) than to prior depression (adjusted 0.70; 0.15 to 3.16, P = 0.64).

Women

Depression and risk of ischaemic heart disease

Table 4 shows the results for the univariate and multivariate analysis for women. Depression was not associated with an increased risk of subsequent ischaemic heart disease on either univariate or multivariate analysis. When the use, dose, and duration of tricyclic antidepressants were examined in women, no significant associations were found (table 4). The odds ratios for antidepressants, however, were in the opposite direction to that found for men.

Depression after onset of ischaemic heart disease

On multivariate analysis women with ischaemic heart disease had twice the risk of having a recorded diagnosis of depression compared with women of the same age without ischaemic heart disease (adjusted 1.86; 1.10 to 3.16; P = 0.02).

Table 4 Univariate and multivariate associations for 139 females with ischaemic heart disease compared with 412 age matched controls without ischaemic heart disease

	Unadjusted		Adjusted	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)*	P value
First diagnosis of anxiety or depression before diagnosis of heart disease				
Depression†	1.20 (0.64 to 2.25)	0.58	1.34 (0.70 to 2.56)	0.38
Anxiety‡	1.77 (0.67 to 4.68)	0.25	1.70 (0.63 to 4.61)	0.29
Duration of depression (years)§:				
⩽10	1.06 (0.47 to 2.39)	0.89	1.18 (0.51 to 2.71)	0.70
>10	1.46 (0.70 to 3.06)	0.32	1.55 (0.73 to 3.31)	0.26
Tricyclic antidepressants¶	0.80 (0.32 to 1.99)	0.64	0.94 (0.37 to 2.35)	0.90
Mean daily dose of tricyclic antidepressant¶:				
<75 mg	0.81 (0.27 to 2.42)	0.71	1.08 (0.36 to 3.31)	0.87
⩾75 mg	0.78 (0.16 to 3.89)	0.76	0.70 (0.12 to 3.77)	0.67
Duration of tricyclic antidepressants (months)¶:				
⩽4	0.70 (0.20 to 2.48)	0.58	0.88 (0.24 to 3.26)	0.85
>4	0.93 (0.27 to 3.26)	0.91	1.01 (0.29 to 3.56)	0.99
Firat diagnosis of anxiety or depression after diagnosis of heart disease				
Depression†	1.83 (1.01 to 3.04)	0.02	1.86 (1.10 to 3.16)	0.02
Anxiety‡	1.80 (0.80 to 4.03)	0.15	2.11 (0.92 to 4.87)	0.08
Tricyclic antidepressants¶	1.83 (1.00 to 3.37)	0.05	2.14 (1.18 to 3.87)	0.01
Selective serotonin reuptake inhibitors*	2.12 (0.89 to 5.09)	0.09	2.21 (0.90 to 5.45)	0.08

* Model adjusted for smoking status, hypertension, diabetes, and depression score.
†Relative to subjects without depression. ‡Relative to subjects without anxiety. §Relative to a baseline of no depression. ¶Relative to subjects who had not had tricyclic antidepressants. **Relative to subjects who had not had selective serotonin reuptake inhibitors.

Anxiety

Anxiety before and after onset of ischaemic heart disease—Anxiety was not found to be a risk factor for ischaemic heart disease for men or women, on either univariate or multivariate analysis. Similarly, men and women with ischaemic heart disease were not at increased risk of having a recorded diagnosis of anxiety.

Dead patients

Although dead patients were not formally included in the case-control study, we had identified on the database 69 dead patients who had had ischaemic heart disease. These dead patients were no more likely than the 327 study patients with ischaemic heart diseases to have been depressed before or after the diagnosis of ischaemic heart disease. The two groups were similar for the baseline characteristics.

Discussion

To our knowledge this is the first controlled study to show that depression is likely to be an independent risk factor for ischaemic heart disease for men in primary care. This risk persists regardless of smoking status, deprivation score, and presence of diabetes or hypertension. Previous studies have shown that certain personality traits predict increased cardiovascular risk—for example, type A personality[21] and hostility.[20 22]

Strengths and weaknesses of this study

This study used a larger sample of cases and controls than previous studies, and subjects were selected from the community. As such, the population is more representative of the population with ischaemic heart disease than the populations in studies that selected cases and controls from secondary care. This study has used routinely collected data from a general practice database which has been validated and found to have a high standard of data completeness and accuracy.[23] General practice databases do not seem to have undue bias in epidemiological studies of patient morbidity.[24] As this study is a case-control study, any minor limitations of the routinely collected data will apply to both cases and controls and are therefore unlikely to cause significant bias. Although this study has been conducted on a single practice population, we have no reason to believe that the patients studied are different from any other practice population.[23]

Validity of diagnosis

For the past year the practice has had a protocol for diagnosing and treating depression. This specifies diagnostic criteria and suggests which Read codes and antidepressant drugs to use. Only the doctors enter diagnoses of depression on the computer. When new patients register with the practice, the general practitioner reviews all their past records in order and enters diagnoses of depression and ischaemic heart disease (and dates of onset) on the computer. However, as the diagnoses had been made over a 30 year period, the protocol was not operational for most of the study period. We used diagnosis of depression rather than a numerical rating score. We think that depression of sufficient character and severity to warrant assessment by a general practitioner probably has greater validity than a score that assesses mood on one occasion. The pragmatic nature of this study is likely to have increased the generalisability of its results, particularly as most depressed patients are managed entirely in general practice. The diagnoses of depression in general practice are consistent with psychiatric criteria, although the disorder tends to be less severe.[25 26]

Depression, ischaemic heart disease, and cholesterol

Although we did not include cholesterol concentrations, our results provide indirect evidence supporting other studies that have found no association between low or declining concentration of cholesterol and depression.[16–18] If low cholesterol concentration was related to low mood then we would have expected that a population with a high predicted cholesterol

Key messages

- So far, research into whether depression precedes myocardial infarction has been limited
- This case-control study examined the relation between ischaemic heart disease and depression and the differences in this relation between men and women
- Depression may be a risk factor for ischaemic heart disease in men but not women
- This is independent of diabetes, hypertension, deprivation score, and smoking status

concentration—that is, patients with ischaemic heart disease—would have a lower prevalence of depression. This is clearly not the case for men with ischaemic heart disease.

Plausibility of depression as cause for ischaemic heart disease

At least six possible explanations exist for why depression could be an aetiological factor for ischaemic heart disease. Firstly, depression may lead to coronary events directly or indirectly via poorer health behaviours, such as increased smoking or decreased activity.[5] This has been shown in patients who are depressed after myocardial infarction,[6] and the same mechanism could operate before infarction. Such behaviour changes may lead to a poorer cardiovascular risk profile—for example, higher cholesterol concentration or blood pressure. Secondly, the association between depression and risk of heart disease may be due to an effect of tricyclic antidepressant drugs. Our study did not have adequate power to detect the risk associated specifically with antidepressants. Thirdly, depression has been shown to be proarrhythmogenic in patients with established ischaemic heart disease.[2 3] This is thought to be due to changes in the balance between sympathetic and parasympathetic nerve activity—for example, an increase in sympathetic nerve activity or a decrease in parasympathetic nerve activity, or both of these. This mechanism might operate in depressed patients without established ischaemic heart disease, increasing their risk of developing it or accelerating its onset. Fourthly, depression might result in an unfavourable lipid profile resulting from an interaction between the catecholamine and steroid axes.[3] Fifthly, depression might be confused with "vital exhaustion"—the prodromal symptoms of tiredness, apathetic mood, and sadness—which can occur immediately before a myocardial infarction. We do not think that this explains our findings as we took the year of onset of both depression and ischaemic heart disease. When both years were identical, we assumed that depression occurred after ischaemic heart disease. Finally, there may be a separate, and yet unidentified, aetiological factor that causes both depression and ischaemic heart disease in men.

Men versus women

None of the above factors has so far explained why depressed men seem to be at a higher risk of ischaemic heart disease than women, but several possible explanations exist. Firstly, men, who are at higher absolute risk of ischaemic heart disease, are more susceptible than women to changes in autonomic nerve activity or changes in the operation of the catecholamine and steroid axes. Secondly, depression may lead to an increase in smoking and a decrease in physical activity that is more pronounced in men than women. Thirdly, the discrepancy in risk might be due to the variation in prevalence of both diseases in men and women. Fourthly, men's higher risk might result from a difference in general practitioners' ability or opportunity to make diagnoses of depression in men and women. It might reflect differences in severity of depression and illness behaviour between the sexes—for example, men may be diagnosed with depression only if it is of a certain severity. If depression is a risk factor for cardiovascular disease then there could be a "dose response" relation whereby patients with severe depression have a higher coronary risk. If men with a recorded diagnosis of depression have a more severe illness than women, then we would expect men to have a higher coronary risk. We had intended to use secondary care referral as a marker for the severity of depression, although data were insufficient to allow such an analysis.

We thank Collingham Medical Centre for providing us with access to the data for this study, Lynne Wright for extracting some of the computerised data, and Professor Clair Chilvers for her helpful comments on this manuscript.

Contributors: JH-C conceived the idea, contributed to the study design, reviewed the literature, collected the data, did the statistical analysis, interpreted the results, drafted the paper, and is the guarantor for the paper. KF designed the study and advised on the statistical analysis. MP advised on the design and on the interpretation of the results and contributed to the writing of the paper. Dr Hutton and partners, of Collingham Medical Centre, allowed access to the centre's high quality database. Ms Lynne Wright assisted with some of the data collection. Ms April McCambridge collected the references for the literature review. Professor Clair Chilvers commented on a final draft of the manuscript.

Conflict of interest: None.

Funding: None.

1 Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, et al. The nature and course of depression following myocardial infarction. *Arch Intern Med* 1989;149:1785-9.
2 Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995;91:999-1005.
3 Wassertheil-Smoller S, Applegate WB, Berge K, Chang CJ, Davis BR, Grimm R Jr, et al. Change in depression as a precursor of cardiovascular events. *Arch Intern Med* 1996;156:553-61.
4 Lesperance F, Frasure-Smith N, Talajic M, Cameron O. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996;58:99-112.
5 Carney RM, Rich MW, Freedland KE, Saini J, TeVelde A, Simeone C, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 1988;50:627-33.
6 Ladwig KH, Roll G, Breithardt G, Budde T, Borggrefe M. Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet* 1994;343:20-3.
7 Appels A. Mental precursors of myocardial infarction. *Br J Psychiatry* 1990;156:465-71.
8 Fielding R. Depression and acute myocardial infarction: a review and reinterpretation. *Soc Sci Med* 1991;32:1017-27.
9 Thomas C, Kelman GJ, Ahn C, Yang C. Depressive symptoms and mortality in elderly persons. *J Gerontol* 1992;47:S80-7.
10 Carney RM, Freedland KE, Jaffe AS. Insomnia and depression prior to myocardial infarction. *Psychosom Med* 1990;52:603-9.
11 Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. *Lancet* 1993;341:75-9.
12 Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. *BMJ* 1990;301:309-14.
13 Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, et al. Serum cholesterol level and mortality findings for men screened in the multiple risk factor intervention trial. *Arch Intern Med* 1992;152:1490-500.

14 Lindberg G, Rastam L, Gullberg B, Eklund GA. Low serum cholesterol concentration and short term mortality from injuries in men and women. *BMJ* 1992;305:277-9.
15 Zureik M, Courbon D, Ducimetiere P. Serum cholesterol concentration and death from suicide in men: Paris prospective study I. *BMJ* 1996;313:649-51.
16 Brown SL, Salive ME, Harris TB, Simonsick EM, Guralnik JM, Kohout FJ. Low cholesterol concentrations and severe depressive symptoms in elderly people. *BMJ* 1994;308:1328-32.
17 Keech A, Collins R, MacMahon S, Armitage J, Lawson A, Wallendszus K, et al. Three-year follow-up of the Oxford cholesterol study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J* 1994;15:255-69.
18 Wardle J, Armitage J, Collins R, Wallendszus K, Keech A, Lawson A for the Oxford Cholesterol Study Group. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996;313:75-8.
19 Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. *BMJ* 1994;308:373-9.
20 Wysowski DK, Gross TP. Deaths due to accidents and violence in two recent trials of cholesterol-lowering drugs. *Arch Intern Med* 1990;150:2169-72.
21 O'Connor NJ, Manson JE, O'Connor GT, Buring JE. Psychosocial risk factors and nonfatal myocardial infarction. *Circulation* 1995;92:1458-64.
22 Siegler IC, Peterson BL, Barefoot JC, Williams RB. Hostility during late adolescence predicts coronary risk factors at mid-life. *Am J Epidemiol* 1992;136:146-54.
23 Pringle M, Ward P, Chilvers C. Assessment of the completeness and accuracy of computer medical records in four practices committed to recording data on computer. *Br J Gen Pract* 1995;399:537-41.
24 Tilyard MW, Dovey SM, Spears GF. Biases in estimates from the RNZCGP computer research group. *N Z Med J* 1995;108:118-21.
25 Sireling LI, Paykel ES, Freeling P, Rao BM, Patel SP. Depression in general practice: clinical features and comparison with out-patients. *Br J Psychiatry* 1985;147:119-26.
26 Sireling LI, Paykel ES, Freeling P, Rao BM, Patel SP. Depression in general practice: case thresholds and diagnosis. *Br J Psychiatry* 1985;147:113-8.

(Accepted 2 February 1998)

Understanding controlled trials

Crossover trials

Bonnie Sibbald, Chris Roberts

This is the fifth of an occasional series on the methods of randomised controlled trials

National Primary Care Research and Development Centre, University of Manchester, Manchester M13 9PL
Bonnie Sibbald *reader in health services research*
Chris Roberts *senior research fellow in statistics*
Correspondence to: Dr Sibbald.

BMJ 1998;316:1719

In a crossover trial subjects are randomly allocated to study arms where each arm consists of a sequence of two or more treatments given consecutively. The simplest model is the AB/BA study. Subjects allocated to the AB study arm receive treatment A first, followed by treatment B, and vice versa in the BA arm. Crossover trials allow the response of a subject to treatment A to be contrasted with the same subject's response to treatment B. Removing patient variation in this way makes crossover trials potentially more efficient than similar sized, parallel group trials in which each subject is exposed to only one treatment. In theory treatment effects can be estimated with greater precision given the same number of subjects.

Crossover trials are generally restricted to the study of short term outcomes in chronic diseases or processes because the disease or process needs to persist long enough for the investigator to expose the subject to each of the experimental treatments and measure the response. Also the treatment must be one that does not permanently alter the disease or process under study.

The principal drawback of the crossover trial is that the effects of one treatment may "carry over" and alter the response to subsequent treatments. The usual approach to preventing this is to introduce a washout (no treatment) period between consecutive treatments which is long enough to allow the effects of a treatment to wear off. A variation is to restrict outcome measurement to the latter part of each treatment period. Investigators then need to understand the likely duration of action of a given treatment and its potential for interaction with other treatments.

For example, Chisholm et al used a crossover design to examine the effects of replacing butter with margarine on the lipoprotein profile of subjects with hypercholesterolaemia.[1] Patients were randomised to a six week butter diet followed by a six week margarine diet, or the reverse sequence. Treatment periods were separated by five weeks' washout in which patients returned to their usual diet. The impact on lipoprotein profiles was measured from blood specimens taken in the last week of each experimental period. The assumptions are that six weeks is long enough for an experimental diet to affect lipoprotein profile and that five weeks is long enough for the effects to dissipate.

In the analysis of crossover trials it is conventional to pretest the data for evidence of carry over. If carry over is present the outcome on a given treatment will vary according to its position in the sequence of treatments. This approach is based on the questionable assumption that no carry over is present when a statistical test fails to find one. For example, Chisholm et al's hypercholesterolaemia study concluded that there was no carry over when an analysis of variance found no statistically significant interaction between treatment sequence and outcome.[1] However such tests have limited power and cannot rule out a type II error (wrongly concluding there is no carry over effect).[2]

If carry over is detected convention suggests this may be dealt with in the analysis in one of two ways. The usual approach is to treat the study as though it were a parallel group trial and confine analysis to the first period alone. The advantages of the crossover are lost, with the wasted expense of discarding the data from the second period. More importantly, the significance test comparing the first periods may be invalid.[3] A second approach, applicable only to studies with at least three treatment periods (ABB/BAA), is to model the carry over effect and use it to adjust the treatment estimate. Such approaches, while statistically elegant, are based on assumptions which can rarely be justified in practice.[2]

The best advice is therefore to avoid using a crossover design if there is any good reason to suppose that carry over effects are likely to occur. A readable approach to the problems of designing and analysing crossover trials is provided by Senn.[2]

1 Chisholm A, Mann J, Sutherland W, Duncan A, Skeaff M, Frampton C. Effect on lipoprotein profile of replacing butter with margarine in a low fat diet: randomised crossover study with hypercholesterolaemic subjects. *BMJ* 1996;312:931-4.
2 Senn SJ. *Cross-over trials in clinical research.* Chichester: John Wiley, 1993.
3 Freeman PR. The performance of the two-stage analysis of two-treatment, two-period crossover trials. *Stats Med* 1989;8:1421-32.