PAPERS AND ORIGINALS

Mortality in two random samples of women aged 55-64 followed up for 20 years

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Summary and conclusions

Two random samples of women aged 55-64 living in the Vale of Glamorgan and the Rhondda Fach were followed up for 20 years. In each sample heights, weights, serum cholesterol concentrations, and specific causes of death were noted and the Quetelet index (weight/height²) calculated. The two samples were combined for analysis of total mortality. In the combined sample there was a strong positive association between Quetelet index and both total mortality and mortality from ischaemic heart disease. Multiple logistic regression analysis showed that both of these associations were significant, as was the strong positive association between Quetelet index and mortality from ischaemic heart disease in the samples considered separately. There was no significant association between cholesterol concentration and mortality from ischaemic heart disease in each sample. There was a small negative association between cholesterol concentration and both total mortality in the combined sample and ischaemic heart disease in the Rhondda Fach sample.

These results suggest that the Quetelet index is important for prognosis, whereas the serum cholesterol concentration is not.

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Introduction

There are few prospective studies on mortality in women. In the Framingham study¹ the risk of developing ischaemic heart disease in women was shown to rise rapidly with serum cholesterol concentrations of 6.2 mmol/l (240 mg/100 ml) or more, but in a study at Tecumseh² the incidence of this disease was poorly related to serum cholesterol concentrations in women of all ages. There have been no comparable studies on women in the United Kingdom. We therefore report a study of mortality in women from two areas of Britain conducted over 20 years.

Subjects and methods

Samples of women aged 55-64 living in the Vale of Glamorgan in 1956³ and in the Rhondda Fach in 1958⁴ were selected at random from private censuses and examined by the epidemiological section of the Medical Research Council's pneumoconiosis unit. The Rhondda Fach is a coal-mining valley, and the Vale of Glamorgan an adjacent, wealthier, agricultural area. Both population samples were followed up for exactly 20 years. We are confident that we knew who was then alive and received copies of the death certificates of all those who died during follow-up.

For this study we used the heights and weights of the women as the Quetelet index (weight/height²); the serum cholesterol values, measured by Dr Tudor Morris using Trinder's method,⁵ which is closely similar to Anderson and Key's modification of Abell's method; and the specific causes of death grouped according to the "B" list of the International Classification of Diseases (eighth revision). Information on smoking was available only for the Rhondda Fach sample and was not included in the analysis. Interestingly, 83% of these women were non-smokers, and only 2% smoked 15 or more cigarettes daily.

TABLE 1—Deaths in 20 years and characteristics of two samples of women

Area of sample	Total in sample	Total No (%) seen	No (%) of deaths in 20 years	Characteristics (mean $\pm$ SD)*		
				Age (years)	Quetelet index (kg/m ²)	Serum cholesterol concentration (mmol/l)
Vale of Glamorgan	100	86 (86)	39 (45)	59.7 $\pm$ 3.0 (n = 84)	26.9 $\pm$ 6.0 (n = 84)	6.5 $\pm$ 1.3 (n = 78)
Rhondda Fach	193	173 (90)	97 (56)	59.7 $\pm$ 3.0 (n = 169)	27.7 $\pm$ 6.1 (n = 169)	6.9 $\pm$ 1.7 (n = 162)

*Excludes six women who died in first two years.

Conversion: SI to traditional units—Serum cholesterol: 1 mmol/l $\approx$ 38.7 mg/100 ml.

Results

Table I shows that the mortality rate from all causes was considerably higher in the Rhondda Fach sample than in the Vale of Glamorgan sample. The higher death rate in the first area was due mainly to circulatory disorders (figure). Six women who died in the first two years of the study are excluded from the analysis, since terminal illnesses might have affected weights and serum cholesterol concentrations. The Rhondda Fach women had higher mean Quetelet indices and cholesterol concentrations.

Cause-specific percentage mortality (ICD, 8th revision, "B" list) in samples of women aged 55-64 living in Rhondda Fach and Vale of Glamorgan.

Causes of death: B19=malignant neoplasms; B28=ischaemic heart disease; B30=cerebrovascular disease; B26, 27, and 29=chronic rheumatic and other heart disease and hypertensive disease; B31, 32, and 33=respiratory disease excluding tuberculosis.

Before relating age, Quetelet index, and cholesterol concentration to mortality we calculated the correlation coefficients for each variable with the others. The results ruled out the possibility of significant interactions. The results for total mortality in the two population samples were closely similar and are therefore combined. Table II shows the strong positive association between the Quetelet index and mortality from all causes and also the positive relation between the Quetelet index and mortality from ischaemic heart disease in the combined population sample.

Table III shows the slight negative relation between total mortality and cholesterol concentrations. The relation between cholesterol

TABLE II—Quetelet index (weight/height²), total mortality, and mortality from ischaemic heart disease (IHD) in combined population sample

Quetelet index tertiles	No of women	No (%) of deaths from:	
		All causes	IHD
T1	87	36 (41)	7 (8)
T2	87	44 (51)	14 (16)
T3	79	50 (63)	19 (24)
Total	253	130 (51)	40 (16)

TABLE III—Serum cholesterol concentration, total mortality in combined population sample, and mortality from ischaemic heart disease in separate population samples

Cholesterol tertiles*	Total mortality		Mortality from ischaemic heart disease			
	No in tertile	No (%) of deaths	Rhondda Fach		Vale of Glamorgan	
			No in tertile	No (%) of deaths	No in tertile	No (%) of deaths
T1	81	47 (58)	55	11 (20)	26	3 (12)
T2	80	41 (51)	54	10 (19)	26	4 (15)
T3	79	35 (44)	53	8 (15)	26	3 (12)
Total	240	123 (51)	162	29 (18)	78	10 (13)

*Values not known in 13 women.

concentrations and mortality from ischaemic heart disease was different in the two population samples. In the Rhondda Fach sample there was a negative relation, whereas in the Vale of Glamorgan sample the results were not consistent.

Multiple logistic regression analysis with the General Linear Interactive Modelling (GLIM) package⁶ was performed to determine the independent effects of age, Quetelet index, and cholesterol concentration on mortality from all causes and ischaemic heart disease. There was a highly significant ($p < 0.01$) positive association between the Quetelet index and mortality from all causes in the combined population sample, and a significant positive association ($p < 0.05$) in the Rhondda Fach sample alone. In each population sample there was a significant ($p < 0.05$) positive association of the Quetelet index with mortality from ischaemic heart disease, but no significant relation between the cholesterol concentration and mortality from the disease.

Table IV shows the observed numbers of deaths and numbers predicted with the multiple logistic model. The results of the multiple

TABLE IV—Predicted and observed mortality by age, Quetelet index, and serum cholesterol concentration in combined population sample

Predicted risk of death	Total mortality		Mortality from IHD	
	No in sample	Observed No of deaths	No in sample	Observed No of deaths
Above median	120	78	78	29
Below median	120	45	78	10
Total	240	123	156	39

IHD = Ischaemic heart disease.

logistic regression analysis for the combined population sample were confirmed for deaths from all causes and from ischaemic heart disease with Cox's regression and life-table model.⁷ The small difference in mortality rates between the two samples was not significant and had no appreciable influence on regression estimates obtained from either the multiple logistic model or the Cox model. Combining the two population samples for analysis was therefore acceptable.

Discussion

Our findings—namely, the unimportance of the serum cholesterol concentration as a prognostic factor and the importance of the Quetelet index—are interesting. The first finding might have been expected. Our results are based on mortality, while most of the Framingham and Tecumseh data are based on incidence of ischaemic heart disease. Because of the clofibrate trial,⁸ we know that non-fatal and fatal attacks of ischaemic heart disease may have different aetiologies. Thus our results may be reconciled with the others.

Our findings relating to the Quetelet index are more important and are supported by those of Garrow,⁹ who reviewed American evidence linking excess body weight with increased total mortality and mortality from ischaemic heart disease in men and women. Reducing weight may therefore have preventive possibilities.

Some limitations of our data should be emphasised: numbers were relatively small, and neither blood pressure nor electrocardiograms were recorded. Nevertheless, the predictive value of our model based on age, Quetelet index, and cholesterol concentration and derived from the multiple logistic regression analysis was reasonably good (table IV). The ratio of 2.9:1 for mortality from ischaemic heart disease compares reasonably well with the 3.3:1 found for the incidence of this disease in Framingham¹⁰ in women aged 50-62 followed up for 12 years, using the additional variables of blood pressure, smoking history, and electrocardiograms.

The difference in mortality between women in the Rhondda Fach and the Vale of Glamorgan apparently relates more to body shape than to cholesterol concentration.

Requests for reprints should be sent to Dr A L Cochrane.

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Event recording in a clinical trial of a new medicine

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Summary and conclusions

In a double-blind trial of the effect of zimelidine on weight and appetite 24 obese patients were allocated at random to receive either zimelidine or placebo for eight weeks followed by the alternative treatment for eight weeks. Possible adverse effects were elicited by asking patients at weekly intervals whether they had experienced any symptoms or ailments and recording all such "events" on a special form. A conventional checklist of symptoms was also used. Among 19 patients who completed the trial the two methods of recording yielded similar patterns of events. Of symptoms not on the checklist, insomnia was more common during treatment with zimelidine.

Event recording was found to be a practicable and convenient method of detecting possible adverse effects.

Introduction

The traditional method of detecting unwanted effects of drugs in clinical trials is to use checklists of predictable side effects or ask clinicians to report adverse reactions. In 1977 it was pointed out that unexpected side effects could be detected more reliably if doctors recorded all adverse events experienced by patients and not just those regarded as adverse reactions to drugs.¹ The purpose of event recording would be not to replace clinical suspicion by "blind data-gathering"² but to supplement it. Although no one has advanced cogent arguments against using this procedure (which might also show unexpected benefits of drugs), it remains the exception rather than the rule in Britain. Since the practicability of the method has been questioned, we report here our experience of event recording in

a trial of the effect of a new bicyclic antidepressant, zimelidine, on body weight and appetite. This trial was carried out after preliminary studies in depressed patients had suggested that zimelidine might reduce appetite.

Patients and methods

The patients, who were not suffering from psychiatric illness, were adults attending a general-practice clinic for obesity. They consented to take part in a double-blind clinical trial. One week after an initial examination they were allocated at random to receive either zimelidine 100 mg twice daily or matching placebo tablets. After eight weeks the treatments were reversed for a second period of eight weeks.

We report here only our assessment of possible adverse effects in patients who completed the trial; details of the weight changes and of patients who dropped out will be reported elsewhere. The patients were seen weekly and asked whether they had experienced any symptoms or ailments, including changes in chronic conditions. All such events were recorded on a special form, irrespective of whether a link with zimelidine was suspected. Every fourth week a conventional checklist of 21 symptoms was also used, but only after the patients had been asked to mention anything that had been bothering them.

The incidences of symptoms during the periods of treatment with zimelidine and placebo were compared by analysis of discordant pairs with McNemar's test.³

Results

Out of 24 patients who entered the trial, 19 (all women) completed the two eight-week periods; their mean age was 35 years.

The symptom checklist suggested that dry mouth and possibly constipation were associated with zimelidine treatment. The table gives the results of event recording, showing all symptoms mentioned by at least two women. An excess of insomnia occurred during treatment with zimelidine ($p < 0.05$). Six patients mentioned difficulty in sleeping only during the zimelidine period. Of these, four reported the symptom only during the first week of zimelidine treatment, and the others during the first two and three weeks respectively. Another woman reported insomnia during both treatment periods but mentioned it only once during the first period (placebo) and six times during the second (zimelidine). No other symptom was significantly more common during either period, although there was a tendency for dry mouth, constipation, and nausea to occur more often during treatment with zimelidine. The incidence of headache, which has been suspected as a side effect of zimelidine,⁴ was similar during the two periods.

Among 27 events mentioned by only one woman during either period were dysmenorrhoea, toothache, measles, sore eyes, and "feeling hungry."

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