Risk factors for premature death in middle aged men

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Abstract

The causes of premature death and the associated risk factors were analysed in a cohort of 7935 middle aged men participating in a preventive population programme in Malmö. They were screened when aged 46-48 and then followed up for 3½-8 years. Two hundred and eighteen died, of whom 181 (83%) underwent necropsy. Three major causes of death were established: cancer in 61 (28%), deaths related to consumption of alcohol in 55 (25%), and coronary heart disease in 50 (23%).

Distinctly different patterns of risk factors were found to be associated with each of the three main causes of premature death. In death due to coronary heart disease smoking ($p=0.0062$), serum cholesterol concentration ($p=0.00014$), serum triglyceride concentration ($p=0.00013$), systolic blood pressure ($p=0.000012$), and diastolic blood pressure ($p=0.0021$) were the strongest single determinants but diastolic blood pressure ceased to be a predictive factor in a multivariate analysis whereas all the other variables could be combined in a highly predictive logistic model. In death related to consumption of alcohol equal or even stronger associations were found for serum γ glutamyltransferase activity ($p<0.0001$), points scored in a questionnaire screening for alcoholism ($p<0.0001$), and, inversely, serum cholesterol ($p=0.0046$) and serum creatinine ($p<0.0001$) concentrations both when applied independently and when combined in a logistic model. In death due to cancer significant associations were found for serum urate concentration ($p=0.023$) and, inversely, serum cholesterol concentration ($p=0.056-0.031$).

Malignant diseases and diseases related to consumption of alcohol were at least as prominent as cardiovascular disorders in causing premature death in the cohort of men studied. All three types of conditions are potentially avoidable and seem to be associated with significant and distinctive patterns of risk factors. These patterns should be used, as blood pressure and serum lipid concentrations already are, to predict the risk of premature death and indicate preventive measures.

Introduction

In recent years increasing confidence has been expressed in the view that "the second epidemiological revolution has provided the scientific weapons for the conquest of leading non-infectious diseases through preventive measures."¹

Knowledge of risk factors constitutes one of the most important elements in this conquest, serving as a starting point and instrument for preventive action. So far such use of risk factors has largely been confined to controlling cardiovascular disease,²

but there are other important causes of death and ill health in modern Western societies that, as evidence of analogous aetiological connections and mechanisms suggests, call for the same type of approach. The most prominent of these are disorders related to alcohol^{3,4} and neoplastic diseases.^{2,5}

In this study we attempted to analyse the causes of premature death and the associated risk factors in a cohort of middle aged men participating in the preventive medical programme in Malmö.

Subjects and methods

SUBJECTS

The Malmö preventive programme is a long term, multiphasic programme of screening and intervention directed against the most important internal medical diseases and disabilities in industrialised Western communities—for example, coronary heart disease, hypertension, cancer, diabetes mellitus, and health problems related to smoking and alcohol consumption.⁶ For the present study we followed up all the men resident in Malmö and born in 1926-32; they were allotted to seven groups according to year of birth. These men were 46-48 years old at screening, which took place from 1975 to 1979. The population comprised 10 353 men, of whom 7935 (76.7%) participated in the screening. This study deals only with those who were screened; the others have been analysed elsewhere.⁴

SCREENING INVESTIGATION

The subjects were screened as previously described.^{6,7} They answered a questionnaire that included among 260 questions nine on attitude to alcohol (the Mm-MAST^{8,9}), one on abstinence from alcohol,¹⁰ and several on smoking habit.¹¹

All laboratory analyses were performed at the department of clinical chemistry, Malmö General Hospital, according to standard methods.^{6,7,12,13} Serum γ glutamyltransferase activity was analysed according to the recommendations of the Scandinavian enzyme committee¹⁴; serum concentrations of sodium, potassium, and calcium were determined by flame photometry; triglyceride, cholesterol, urate, and glucose concentrations were measured enzymatically; and creatinine concentration was determined with Jaffe's alkaline picrate method.¹² An oral test of glucose tolerance was also done,¹⁵ and a relative weight index (actual/ideal weight) was calculated from the tables of Lindberg *et al.*^{15,16} Systolic and diastolic blood pressures at 0 and 10 minutes, standing and recumbent, were determined by standard methods.¹⁷

MORTALITY

The participants were followed up from the day after screening until the end of 1982. The longest period of follow up, for men born in 1926 and examined in 1975, was eight years, and the shortest, for men born in 1932 and examined in 1979, was three and a half years. The follow up procedure has been described previously.^{3,4,7-10} The completeness of follow up was checked up till June 1981 in a nationwide survey. By then, of the 10 353 subjects originally invited to take part, 65 (0.6%) could not be reliably classified as still living. Of these 65, 47 had emigrated to other countries. For matching we used the Swedish 10 digit personal identification numbers.

During the period of follow up 218 men died. Of these, 181 (83%) underwent necropsy, performed in 80 cases by the department of pathology and in 101 cases by the department of forensic medicine. The three major causes of death were cancer (61 (28%) deaths), diseases related to alcohol (55 (25%)), and coronary heart disease (50 (23%)). (A further 16 subjects died of other cardiovascular diseases, 32 of miscellaneous causes, and four of unknown causes.) We used a previously described definition of death due to alcohol

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related disorders.^{3,4} This required that alcohol was indicated as the sole or major underlying cause of death and included the following subgroups: death due to an accident occurring when the subject was intoxicated with alcohol; death in an alcoholic due to an organic complication associated with alcoholism—for example cirrhosis of the liver, pancreatitis, or cardiomyopathy; suicide in an alcoholic; death due to pneumonia in an alcoholic; death due to an unknown cause in an alcoholic; death in intoxication, including sudden death in an alcoholic (subjects in this subgroup were mostly found dead and all had demonstrable concentrations of alcohol in the blood, urine, or tissues at necropsy and no evidence of other specific causes of death such as cancer, haemorrhage, or myocardial infarction); and death in states related to alcohol, such as delirium tremens.

INTERVENTION

A continuing programme of intervention operated throughout the period of follow up in outpatient clinics of the department of preventive medicine.⁶ Intervention was indicated if at screening two consecutive readings showed any of the following: recumbent blood pressure after 10 minutes' rest 170/105 mm Hg (men with blood pressure of 160-170/95-105 mm Hg were checked annually at the department of preventive medicine); serum cholesterol concentration 7.7 mmol/l (298 mg/100 ml); serum triglyceride concentration 2.2 mmol/l (195 mg/100 ml); γ glutamyltransferase activity 1.4 μ kat/l; and blood glucose concentration at 120 minutes in an oral glucose tolerance test 7.0 mmol/l (126 mg/100 ml).¹⁵ Some other abnormal findings in the screening also indicated intervention. Some subjects were advised against smoking,¹⁸⁻²⁰ and others received dietary advice to help them lose weight.²¹ (Details of the results of intervention in subjects with conditions related to alcohol consumption have been reported previously.^{7,22})

STATISTICAL METHODS

For each subject who died two living controls were selected from the total population of participants and matched for date of screening and age (usually a difference of no more than two months). Statistical calculations were done by comparing all 218 subjects who had died and the various subgroups they constituted with the 436 matched controls and with all 7935 subjects originally screened.

Significances (p values) for single risk factors were assessed with two tailed Fisher's permutation tests.²³ Comparisons of predictive value of one risk factor (main or foreground variable) when a second one (background variable) had been eliminated were done with Mantel's test.^{23,24} Instead of a χ^2 approximation, however, a more accurate method was used based on the Edgeworth expansion.²⁴ The probabilities for death related to alcohol consumption, death due to coronary heart disease, and death due to cancer were estimated as functions of single risk factors under order restriction²⁵ and as functions of several factors by using a logistic model. Estimation under order restriction was also applied on the probabilities obtained by logistic model (by considering the logistic model probability to be a new variable). The distributions of some of the variables were so flat that a transformation of the original scales to interval scales was necessary to achieve satisfactory approximations of the p values.

Results

Table I shows the independent correlations of each of the variables screened for with total mortality and with the three main causes of death. Activity of γ glutamyltransferase was the variable that correlated most strongly with death due to any cause, and smoking also showed a highly significant correlation. Table II shows the results of an analysis with Mantel's test of single variables when the influence of another variable was eliminated. γ Glutamyltransferase activity and Mm-MAST score were both of independent importance in death related to alcohol consumption, but γ glutamyltransferase activity did not show any association with death due to coronary heart disease when either systolic blood pressure or serum cholesterol concentration was taken into account. Serum concentrations of cholesterol and triglyceride were, independently of each other, significantly correlated with death due to coronary heart disease. Diastolic blood pressure, however, showed no correlation with death due to coronary heart disease when systolic blood pressure was the foreground variable.

TABLE I—Results of univariate comparison, using Fisher's permutation test, of risk factors for premature death between 218 men who had died and 436 matched controls

Variable	Causes of death			
	All (n = 218)	Cancer (n = 61)	Coronary heart disease (n = 50)	Deaths related to alcohol (n = 55)
γ Glutamyltransferase	< 0.0001	NS	0.034	< 0.0001
Alcohol abstinence	NS	NS	NS	NS
Mm-MAST score	0.016	NS	NS	< 0.0001
Smoking category	0.0002	NS	0.0062	NS
Serum cholesterol	NS	0.056*†	0.00014	0.0046†
Serum triglyceride	0.022	NS	0.00013	NS
Systolic blood pressure	0.0013	NS	0.000012	NS
Diastolic blood pressure	NS	NS	0.0021	NS
Relative weight	NS	NS	NS	NS
Serum urate	NS	0.023	NS	NS
Serum creatinine	0.029†	NS	NS	< 0.0001†

*p = 0.031 when men who died were compared with all subjects screened.

†Inverse correlation.

TABLE II—Results of analysis with Mantel's test for single variables when the influence of another variable was eliminated

Cause of death	Main variable	Background variable	Two sided p value
Conditions related to alcohol	γ Glutamyltransferase	Mm-MAST score	0.00047
	γ Glutamyltransferase	Cholesterol	< 0.0001
	γ Glutamyltransferase	Creatinine	< 0.0001
	Mm-MAST score	γ Glutamyltransferase	< 0.0001
Coronary heart disease	γ Glutamyltransferase	Cholesterol	NS
	γ Glutamyltransferase	Systolic blood pressure	NS
	Cholesterol	Triglyceride	0.0056
	Triglyceride	Cholesterol	0.0024
	Systolic blood pressure	Diastolic blood pressure	0.0013
	Diastolic blood pressure	Systolic blood pressure	NS

Figure 1 shows probability of death related to alcohol consumption as a function of the three variables γ glutamyltransferase activity, Mm-MAST score, and serum creatinine concentration. Figure 2 shows the probability of death due to coronary heart disease as a function of the variables serum cholesterol concentration, triglyceride concentration, and systolic blood pressure (left) and of smoking (centre). The figures also show the probabilities of death due to cardiac heart disease and to alcohol consumption as calculated by logistic models combining the individual variables. The combination of γ glutamyltransferase activity, Mm-MAST score, and creatinine concentration gave a moderately improved prediction of death from disorders related to alcohol consumption in comparison with that

FIG 1—Probability of death related to alcohol consumption as a function of γ glutamyltransferase activity (γ GT), Mm-MAST score, and serum creatinine concentration (left) and as a function of these variables combined in a logistic model (right).

given by each of the single variables; and the combination of cholesterol concentration, triglyceride concentration, systolic blood pressure, and smoking habit gave an equally improved prediction of death due to coronary heart disease, but its predictive power and discrimination in terms of absolute numbers of deaths in the same population were lower than given by the logistic function for death related to alcohol consumption. Table III summarises this and compares the predictive power of multiple logistic functions for death due to coronary heart disease and to disorders related to alcohol with each other and with a similar function including the variables

with the non-participants.^{3,4} This makes it particularly remarkable that deaths related to alcohol consumption occurred so often and that γ glutamyltransferase activity was the single variable that correlated most strongly not only with this cause but with all the causes of death (table I).

When we analysed the major causes of death (cancer, coronary heart disease, disorders related to alcohol) separately, however, we found that γ glutamyltransferase activity was associated only with deaths related to alcohol consumption (table I) and

FIG 2—Probability of death due to coronary heart disease as a function of serum cholesterol concentration, triglyceride concentration, and systolic blood pressure (left), of smoking habit (centre), and of these variables combined in a logistic model (right).

TABLE III—Annual incidence of death due to cardiac heart disease, conditions related to alcohol intake, and cancer/100 000 men aged 48-56 in consecutive percentiles of the respective determinant functions as calculated by logistic models combining risk factors

Percentile	Causes of death			Cancer
	Coronary heart disease (excluding smoking habit)	Coronary heart disease (including smoking habit)	Conditions related to alcohol consumption	
0.05		24	8	53
0.10	39	30	14	65
0.20	50	33	21	79
0.30	60	55	30	91
0.40	72	67	43	105
0.50	86	78	60	119
0.60	103	93	77	136
0.70	120	118	116	160
0.80	145	155	173	178
0.90	204	252	369	232
0.95		340	531	264
0.97		406	646	305
(1.00)		637	1051	384

cholesterol concentration (inversely), urate concentration, and smoking habit for deaths due to cancer. The logistic model for deaths due to disorders related to alcohol consumption showed a better discrimination at both ends of its distribution than that for deaths due to coronary heart disease, in which all established risk factors for coronary heart disease in middle aged men were used. The predictive power of the logistic model for risk of death due to cancer was appreciably inferior, particularly in its ability to indicate low risk of death in malignant disease.

Discussion

Our study population comprised all those middle aged men who participated in the original screening investigation—that is, about three quarters of all the men of the same age resident in Malmö. Importantly, advanced disease related to alcohol consumption was underrepresented in the participants compared

not with deaths due to cancer, which is interesting because γ glutamyltransferase activity was introduced early as a test for malignancy of the liver.²⁶ Results from Mm-MAST, the short questionnaire to assess attitudes to alcohol that reflects habits of consumption rather than degree of individual biological complication,^{9,12} were interestingly enough also independently and almost as strongly correlated with death related to alcohol as was γ glutamyltransferase activity. The problem with Mm-MAST, however, is the high proportion of false positive results it gives in testing for disorders due to alcohol consumption. About a third of the subjects we screened answered in the affirmative to two or more of the Mm-MAST questions, which we had taken as the screening cut off point of the test.⁸⁻¹⁰ The test thus gives a high yield of patients who have to be subjected to further interrogation and investigation if it is used alone; moreover, it is hard to use a questionnaire as a therapeutic instrument in the ensuing prevention of disorders related to alcohol.⁹ In conjunction with a programme of internal medical screening and intervention Mm-MAST score is therefore most usefully applied in combination with γ glutamyltransferase activity and other variables.

The strong inverse relation between serum creatinine concentration and death related to alcohol consumption is of particular interest for several reasons. Firstly, our finding confirms similar observations in two previous studies^{27,28}; secondly, this inverse relation may be used with other indicators such as γ glutamyltransferase activity and Mm-MAST score in multivariate and multiple logistic risk factor functions (fig 1); and, finally, serum creatinine concentration tends to decrease throughout the various stages of diseases related to alcohol¹² whereas many classical markers of alcohol disorders, such as blood pressure,^{17,29-33} serum urate concentration,^{34,35} and triglyceride concentration³⁶ seem to indicate only the initial disturbances in health¹² and not the risk of death (table I). The explanation for the statistically confirmed absence of an association between markers and the later stages of diseases caused by alcohol consumption (which did occur, however, in previous health

screening studies of the same population¹²) relative to the present end point is probably that early and advanced stages of disorders related to alcohol consumption are associated with different metabolic and nutritional states.³⁷⁻⁴⁰

Tests that are disease specific are rare, and γ glutamyltransferase activity is no exception to this rule. The mechanism for the increase of γ glutamyltransferase activity with alcohol consumption is probably enzyme induction, which may be caused by other agents as well, such as drugs.⁴¹⁻⁴² Scepticism has also been expressed about the use of γ glutamyltransferase activity to determine whether subjects have a high alcohol consumption.⁴³ γ Glutamyltransferase activity relates predominantly, however, to disorders caused by alcohol consumption, in connection with which it has so far seemed to be superior to any other proposed single measurement—for example, other liver enzyme activities,⁴⁴ serum urate concentration, serum ferritin concentration,⁴⁵ mean corpuscular volume,⁴⁶⁻⁴⁷ serum glutamate dehydrogenase activity,⁴⁸ and the ratio between α amino-N-butyric acid and leucine.⁴⁹ Thus its judicious use in well controlled investigations of somatic health should be encouraged but its properties further studied. In developed⁵⁰ and developing⁵¹ countries health problems caused by alcohol consumption constitute one of the leading non-infectious epidemics. In these disorders, as in cardiovascular diseases, “the opportunities for improving health by the prevention of disease are at least as great and possibly greater”² than those afforded by curative treatment in hospital.

Although several studies have focused on risk factors for coronary heart disease, especially in middle aged men,⁵²⁻⁵⁴ the role of lipids in coronary heart disease is still controversial as far as the independent role of triglyceride concentration is concerned.⁵⁴⁻⁵⁵ In the present investigation both serum cholesterol and triglyceride concentrations were strongly significant risk factors⁵⁶ and contributed independently to the risk of death (table II, fig 2). Furthermore, systolic as well as diastolic blood pressures were significantly associated with death due to coronary heart disease (table I), but in the multivariate analysis the independent role of diastolic blood pressure disappeared (table II). This accords with the findings in the Framingham study.⁵⁷ In general, all our results regarding those who died due to coronary heart disease corresponded well with the results of earlier studies.

One of the most important aspects of risk factors in the control of diseases is discriminating in the lower end of the distribution—that is, the ability not only to identify an appreciable proportion of the subjects actually at risk but to clear as many as possible of the rest of the population from the risk of the end point in question. This was first achieved in the cardiovascular diseases.⁵⁸ In comparison, our logistic model for cancer was of inferior strength in its lower range (table III). In the men, however, the multiple logistic function of risk factors for death related to alcohol consumption was more powerful in both ends of its distribution than the corresponding logistic function of established risk factors for death due to coronary heart disease. We believe that these results support recent suggestions that these are potentially avoidable, major non-infectious diseases in Western societies that “are capable of being prevented by means that have not yet been fully implemented.”²

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Flexible induction dose regimen for warfarin and prediction of maintenance dose

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Abstract

Fifty patients with venous thromboembolic disease being treated by heparin infusion received a three day warfarin induction regimen tailored according to the prothrombin time (British comparative ratio) measured on days 2 and 3. A prediction of the final maintenance dose of warfarin was made on the basis of a prothrombin time measured on day 4. All patients were safely anticoagulated by day 6, and the prediction was accurate to within 1 mg in 46 patients. Predicted and actual maintenance doses were closely related ($r=0.867$; $n=50$; $p<0.001$).

This scheme should prove helpful in the control of anticoagulation, particularly in patients likely to be sensitive to warfarin, and should shorten hospital stay.

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Introduction

A relation between the prothrombin time after a loading dose of warfarin and the eventual maintenance dose of warfarin has been well described,¹⁻⁵ and from the derived regression equations a prediction can be made of the maintenance warfarin dose. Until recently the *British National Formulary* suggested a warfarin loading regimen of 10 mg on each of three consecutive days, but this may cause up to 35% of patients to be over anticoagulated by the fourth day.^{6,7} Patients' stay in hospital may be unnecessarily prolonged while their prothrombin time falls to within the therapeutic range and while a tentative maintenance warfarin dose is established.

The current edition of the *British National Formulary* now recommends an induction dose of 10 mg warfarin daily for three days with British comparative ratios measured before the first dose and on the second and third days, so that the subsequent warfarin dose may be modified if required.⁸ No guidelines on dose adjustment are given.

We have attempted to design a flexible three day loading dose regimen, aimed at bringing the British comparative ratio smoothly into the therapeutic range, and to predict the maintenance dose of warfarin on the basis of a British comparative ratio measured on day 4.

Method

Patients with venous thromboembolic disease presenting to physicians, surgeons, and gynaecologists at Llandough Hospital were heparinised using a continuous intravenous infusion maintaining the kaolin-cephalin clotting time (Bell and Alton platelet substitute;